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Editorial

Health Benefits of Exercise

Belle M Hegde

The Journal of the Science of Healing Outcomes, State College, Pennsylvania, USA and Mangalore, India*
Manipal University, Manipal, India**
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“Better to hunt in the fields, for health unsought
Than fee the doctor for a nauseous draught.
The wise, for cure, on exercise depend;
God never made his work for man to mend.

John Drydon[1]

How true! God never meant his machine to be mended by ordinary mortals. It was made with built-in mechanisms needed for rescue measures. Modern living has robbed most of the “civilised” world of the many benefits of an active life style. Man has become sedentary, what with all the gadgets for assisting him in every walk of life. Even housewives have become more or less sedentary. This is a curse on human health and longevity.

The intensity of exercise needed for physical fitness and bodybuilding is often confused with that needed for health benefits and longevity. The two are totally different. Physical fitness may not be the same as a healthy life without physical illnesses. The emphasis is changing from encouraging an increase in fitness to encouraging an increase in total energy expenditure. This new approach comes from the recognition that there is a genetic component to fitness and that health benefits are achieved by activities that do not necessarily produce large gains in fitness[2].

Regular physical activity decreases the likelihood of premature deaths[3]. Very heavy physical exercise is sometimes associated with sudden death, but regular exercise, not of the vigorous type, more than compensates for this extra risk by the overall reduced risk at all other times[4].

Routine exercise does confer many benefits like better exercise tolerance, lower body weight, lower blood pressure-both systolic and diastolic, better control of blood sugar and cholesterol, lowered cardiovascular morbidity and mortality, lowered stroke risk, diminished accident rates, better social acceptability, strengthened bones in postmenopausal women, significantly reduced cancer risk of all types, better respiratory reserve, lesser incidence of viral infections, lowered risk of depression and most of all, a good night’s rest at the end of the day. There are reports of well-controlled studies that even show longer life expectancy in those that are active compared to couch potatoes[5].

Although sudden death is more common during or immediately after a bout of vigorous exercise, it is not seen in people who regularly exercise. Regular exercise programs do protect one from the risks of an acute exertional episode, which might be a necessity in an emergency[6]. The question that would be asked by many patients and lay people is: at what age does the exercise regime benefit most? Recent work has clearly shown that exercise started even in those past the middle age would bestow its benefits, irrespective of the previous state of health.

A small number of young men (five) aged 20 years in 1966, were studied extensively for their aerobic power, i.e. body’s ability to use oxygen. They were then given 3 weeks of complete bed rest. At the end of the bed rest, they were again tested to show that their aerobic capacity had declined significantly at the end of three weeks of bed rest. Now in their late 50s, they were completely re-examined to see the effect of

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ageing on their systems. They had lost their aerobic power by 11%, their body fat had almost doubled and their muscle mass was reduced significantly. Their cardiovascular capacity had declined significantly.

They were then given a period of exercise, none of which was vigorous, and there were no weight exercises. Most of the exercises were walking, bike riding or swimming. All of them started gradually and built up slowly to achieve, at the end of the month, moderate exercise for forty minutes a day for at least five days in a week. Six months later, a repeat assessment showed that all the men had regained their aerobic capacity by 15%, their cardiovascular health had returned to normal, and they had less fat and bulkier muscles. They were fitter in every respect and felt a lot better. Three weeks of bed rest at the age of 20 had made them much worse than at their age of 56 years. Six months of moderate exercise got them back to the physical health of their younger days at age 20. “It is never too late to get back to shape” said the author of the paper[7].

Health-related articles in lay press give mostly misleading ideas about the health benefits of exercise while goading the population to do vigorous exercise to get into shape. The exercise outfits industry is a multi-billion dollar industry, anyway. It would have its say through these write-ups and advertisements! Vigorous exercise is not only unnecessary, as the benefits gained by mild-to-moderate exercise are as good, if not better, than that gained by vigorous exercise; but moderate exercise avoids the possible risk of sudden death during or immediately after a bout of exercise, more so in the elderly. I have written at length about that in the past. It is worth repeating that physical fitness and good health are two different cups of tea, although both could be simultaneously present in an occasional lucky individual[8].

Various types of exercise have been scientifically studied in the past, including walking, running, cycle ergometer, callisthenics, and restrictive exercises. Although all of them do good to the human system, the best of the lot seems to be walking. The latter does not need any special sports gears, could be done in any place and weather, and most importantly, by any body at any age. Even the very old have been shown to benefit by walking, the added advantage being the mental alertness in that age group, in addition to all other benefits of other age groups.

Standard advice has been to recommend exercise durations ranging from 20 - 40 minutes a day for at least four to five days in a week. If done daily, it is still better. Physical activity needs to be continuous. Studies have shown that the benefit of lowered blood pressure due to exercise disappears if one stops the activity for more than two weeks[9].

Industrialised countries could benefit a lot by making regular exercise popular among all their sedentary people. The benefits by way of deaths avoided and premature morbidity could be very substantial, both from the economic point of view and that of manpower conservation. People with even modest motivation should be encouraged to gain important benefits of increasing their physical capacity. Avoiding premature death seems to be the single most important bonus of increased physical activity in the population. Although the physiological mechanisms of many of the good effects of exercise are not clearly understood, the benefits are very well studied and documented by now. The latest study, reported earlier, gives the right message for the elderly who missed out on being active during their younger days. They could catch up at any time and get back to good health and avoid physical disability and premature mortality. In addition to the regular exercise mentioned above, people should also be encouraged to be as mobile as possible, even in their work places.

“Catch them young” would be the best way to do this. Started early in life, the benefits could be life-long and longevity could be enhanced significantly. The byproduct of this would be to distract adolescents from the bad effects of drug abuse, television obsession, and many other criminal activities. Physical exercise confers the added bonus of a tranquil mind that reduces hatred, jealousy, and anger-the three devils that have been shown to be most important risk factors for major killers like heart attacks, brain attacks and cancer[10].

One bad habit that delays starting of an exercise habit at any age is the temptation to postpone. People put it off to the next day and that tomorrow might never come!

T'Morra, t'morra,
Lookin' for t'morra,
My aunt became a spinster that way.

E.Y.Harburg 1898-1981: T'morra (1944)

REFERENCES


Review Article

Recent Advances in Proper Management of Multidrug-resistant Tuberculosis

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ABSTRACT

Widespread occurrence of multidrug-resistant tuberculosis (MDR-TB) is a serious threat to the success of TB control worldwide. Based on current evidence, the World Health Organization (WHO) has recently revised the classification of anti-TB drugs to help clinicians build an appropriate regimen for effective treatment of MDR-TB. A shorter (9 to 12 month) regimen has also shown promise in effective treatment of MDR-TB. Accurate drug susceptibility testing (DST) of Mycobacterium tuberculosis to anti-TB drugs is also crucial for diagnosis and management of MDR-TB. Phenotypic DST of M. tuberculosis by solid medium-based methods is slow, requiring 4 - 6 weeks to report results. Liquid broth-based automated Mycobacteria Growth Indicator Tube (MGIT) 960 system reporting results within 10 - 14 days have been developed and endorsed by WHO. Although performance of MGIT 960 system was excellent in early proficiency studies for first-line drugs except pyrazinamide, recent studies have shown poor performance for M. tuberculosis isolates with low-level resistance to rifampicin and ethambutol. Performance of MGIT 960 system for second-line drugs is also sub-optimal. Molecular DST methods rapidly detect resistance to first-line and important second-line drugs. Whole-genome sequencing is a newer alternative capable of providing rapid drug resistance profiles to inform treatment and strain information for global surveillance.

KEY WORDS: anti-TB drugs, multidrug-resistance diagnosis, recent developments, re-classification, tuberculosis

INTRODUCTION

Tuberculosis (TB) is a major infectious disease of global proportions and the widespread occurrence of drug-resistant (DR)-TB is a serious threat to global TB control success. The natural history of TB is unique. Most active TB disease cases in humans are caused by Mycobacterium tuberculosis. Some disease cases are also caused by Mycobacterium africanum (mainly in Africa) and Mycobacterium bovis (due to consumption of unpasteurized milk), two other species belonging to the M. tuberculosis complex[1]. The infection is acquired by individuals mainly by inhalation of droplet nuclei containing few bacilli expectorated by sputum smear-positive pulmonary TB patients (open TB) during close human contact[2,3]. The infection is acquired by individuals mainly by inhalation of droplet nuclei containing few bacilli expectorated by sputum smear-positive pulmonary TB patients (open TB) during close human contact[2,3]. Primary infection with M. tuberculosis either leads to clinically active TB disease (in ~10% of exposed individuals) or the effective immune response mounted by the host arrests multiplication of tubercle bacilli; however, complete sterilization is achieved in only a sub-set of individuals[2,3]. In the remaining subjects, infection is only contained but not eradicated, as some bacilli escape killing and persist in granulomatous lesions (latent TB infection). The latent infection may remain dormant for a long-time; however, M. tuberculosis retains the ability to resuscitate and cause active TB, years to decades later, often due to waning of the immune response[2,3]. Current estimates suggest that nearly 25% of the world population is latently infected with tubercle bacilli and 5 - 10% of the infected individuals will eventually develop active TB disease during their life-time[4]. The risk of reactivation of latent infection is much higher in human subjects with underlying immunodeficiencies, diabetes or co-infection with human immunodeficiency virus (HIV) [2,3]. Most active TB disease cases in low TB incidence/ high income countries occur in foreign-born individuals due to reactivation of latent infection,

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while recent infection/re-infection is also common in TB endemic countries[8-7]. Pulmonary TB accounts for > 85% of active TB cases in high TB incidence countries, while extrapulmonary TB is more common in low TB incidence countries[8-7].

METHODS
In this article, recent advances in the diagnosis and proper management of patients with DR-TB were critically reviewed. For this purpose, the latest data on the global epidemiology of TB and DR-TB were obtained from the annual TB report published in 2017 by the World Health Organization (WHO). The current literature on re-classification of anti-TB drugs, new treatment approaches and recent developments in rapid diagnosis of DR-TB were extensively researched and critically evaluated. The main findings are described below.

LITERATURE REVIEW
Global epidemiology of TB, drug-resistant TB and multidrug-resistant TB
Despite declining trends in the worldwide incidence of active TB disease by about 2% and reduction in TB deaths by nearly 3% in the last several years, the global burden of TB continues to remain high. According to the latest annual survey conducted by the WHO, there were an estimated 10.4 million active TB disease cases (including 1 million patients co-infected with HIV) in 2016[8]. Most of the estimated TB cases in 2016 occurred in the WHO regions of South-East Asia (45%), Africa (25%) and the Western Pacific (17%) while only 7%, 3% and 3% of cases occurred in the Eastern Mediterranean region, the WHO European region and the region of the Americas, respectively[8]. Nearly 56% of the 10.4 million TB cases occurred in only five (China, India, Indonesia, the Philippines and Pakistan) countries[8]. The annual number of incident TB cases varied widely among individual countries, ranging from less than 10 per 100,000 people in most high-income countries to 150 - 300 per 100,000 people in most of the 30 high TB burden countries[8]. The incidence of more than 500 cases per 100,000 people was also recorded in some countries (such as Lesotho, Mozambique, the Philippines and South Africa). An estimated 1.3 million people not infected with HIV (HIV-negative) and an additional 0.374 million HIV-coinfected individuals died from TB in 2016, making TB the ninth leading cause of death worldwide and the leading cause of death from a single infectious agent[8]. Most of the global TB deaths in recent years have been attributed to the resistance of M. tuberculosis strains to an increasing number of anti-TB drugs.

The increasing incidence of DR-TB, multidrug-resistant (MDR)-TB (M. tuberculosis resistant at least to rifampicin and isoniazid, the two most effective first-line drugs) and extensively drug-resistant (XDR)-TB (MDR-TB strains additionally resistant to a fluoroquinolone plus injectable agent, kanamycin, amikacin or capreomycin) pose a major threat to global TB control efforts[8]. In 2016, an estimated 600,000 new TB cases were resistant to rifampicin (RR-TB) and 490,000 of these RR-TB cases were additionally resistant to isoniazid (MDR-TB)[8]. Patients infected with RR-TB also require the same treatment approaches as MDR-TB. Worldwide, an estimated 4% of all new TB cases and 19% of previously treated cases had MDR-TB and nearly half (47%) of these cases occurred in only three (India, China and the Russian Federation) countries[8]. The WHO has further categorized infection with M. tuberculosis strains resistant only to rifampicin and isoniazid without additional resistance to other first-line drugs as uncomplicated MDR-TB. Successful treatment of uncomplicated MDR-TB is higher compared to treatment of MDR-TB resistant to additional first-line drugs[8-10]. Nearly 10% of all MDR-TB cases are now estimated to have XDR-TB[8-11]. Several countries including India, Iran, Italy and South Africa have also reported totally drug-resistant (TDR) (or extremely drug-resistant)-TB, active disease caused by M. tuberculosis strains resistant to all tested anti-TB drugs[12-16]. The definition of TDR-TB, however, is currently vague and not endorsed by WHO, since drug susceptibility testing (DST) results for many second-line and other drugs are poorly reproducible (ranging from 50-80%) and the number of drugs tested varies widely among reference mycobacteriology laboratories around the world[17]. The WHO expert committee has recently concluded that defining total drug resistance in M. tuberculosis is challenging and controversial and the existing category of XDR-TB already encompasses extensive drug resistance to the most active anti-TB drugs[9,17].

Treatment of fully drug-susceptible-TB is highly efficacious[18,19]. On the contrary, treatment of patients with DR-TB, particularly MDR/XDR-TB, is much more difficult due to lengthy (12 - 24 months), more expensive and more toxic drug regimens and the patients often experience clinical failure or disease relapse[10,11,16]. Worldwide, treatment success rates for drug-susceptible TB, MDR-TB and XDR-TB have been recorded as 83%, 54%, and 30%, respectively[8]. Thirty-five countries in Asia and Africa have also introduced short-course (9 - 12 months) drug regimens (known as Bangladesh regimen) for the treatment of RR-TB/ MDR-TB patients, with treatment success rates of
nearly 90%.[8,20,21] Two new anti-TB drugs (bedaquiline and delamanid) have recently been approved to treat MDR-TB under defined programmatic conditions[22]. Furthermore, in an effort to improve treatment outcome, more than 80 countries have started using bedaquiline and more than 50 countries have started including delamanid in treatment regimens for MDR/XDR-TB[8].


The anti-TB drugs were previously categorized into 5 groups (Group 1 to 5) based on decreasing efficacy and increasing toxicity. Group 1 included highly efficacious, relatively less toxic and mostly bactericidal first-line (rifampicin, isoniazid (INH), ethambutol and pyrazinamide (PZA)) oral drugs suitable for combination therapy.[18,19] Streptomycin, previously used as a first-line drug, is not used routinely anymore for the treatment of fully drug-susceptible (pansusceptible) TB due to higher frequency of resistance of M. tuberculosis isolates to streptomycin across the world and the availability of other active drugs that can be easily incorporated in oral regimens.[18,23] Group 2 included injectable aminoglycosides (kanamycin and amikacin) and capreomycin (cyclic polypeptide).[10,19] Group 3 included fluoroquinolones, particularly bactericidal agents such as levofloxacin (at high dose), gatifloxacin and moxifloxacin.[24,25] Group 4 included oral agents that are mainly bacteriostatic, less efficacious, expensive and more toxic than other second-line drugs and were used in therapy regimens only for treatment of MDR-TB and XDR-TB.[10,18,19,26] High dose INH and rifabutin (RBU) were also used as second-line oral agents for some patients with drug-resistant TB.[10,26] Group 5 included third-line (reinforcing agents of unchanged efficacy) agents that were used only occasionally for the treatment of MDR/XDR-TB but were not recommended for routine use due to variable efficacy and serious side effects, and some of these drugs (e.g. thioacetazone) are contraindicated for HIV-coinfected TB patients.[10,27] These drug classifications are now considered inadequate for the proper management of MDR/XDR-TB patients. Recent estimates have shown that management of MDR-TB by conventional approaches requiring the use of multiple, highly toxic and expensive drugs for 18 - 24 months actually amplifies the antimicrobial resistance further, since successful outcome is achieved in only about 50% of treated patients.[8,22,26] The availability of two new anti-TB drugs, bedaquiline and delamanid, to treat MDR-TB has renewed hope for improved outcome of MDR-TB and to prevent development of XDR-TB[28-31]. To improve the outcome of MDR-TB treatment, WHO has now re-classified anti-TB drugs with the aim of developing a more effective (more efficacious and better tolerated) regimen for RR-TB and MDR-TB cases.[32-34] It should be emphasized here that according to the revised scheme, the currently available drugs, including bedaquiline and delamanid, are classified into four groups (Group A to Group D) specifically for the treatment of RR-TB cases, particularly MDR-TB[32-34]. Furthermore, the remaining first-line drugs (PZA, ethambutol and possibly high-dose isoniazid and rifabutin) have been relegated to a minor role as a subclass of Group D agents. The newly described anti-TB drug groups are shown in Table 1.

Group A now includes moxifloxacin, gatifloxacin or high-dose levofloxacin (fluoroquinolones with bactericidal and sterilizing activity and excellent safety profile) as the best agents for the treatment of MDR-TB. These agents are now placed ahead of injectable agents, since their use is associated with a favourable outcome.[32-34] Group B includes second-line injectable (amikacin, kanamycin and capreomycin) drugs which are bactericidal but lack sterilizing activity.[32-34] It has also been suggested that Group B may, in future, include three oral drugs; linezolid (or sutezolid or tedizolid), bedaquiline and delamanid, if they prove to be more effective and less toxic than the injectables.[32-34] Group C currently includes second-line oral drugs; linezolid, clofazimine, ethionamide/prothionamide and cycloserine/terizidone.[32-34] Linezolid is bactericidal with sterilizing action. Although linezolid at regular dose is toxic, the toxicity can be mitigated by reducing the dose.[35] Ethionamide and prothionamide have moderate bactericidal activity but also exhibit higher toxicity, while clofazimine has some sterilizing activity and good tolerability.[32-34]

Group D drugs have been further divided into three sub-groups; D1, D2 and D3. Group D1 includes PZA and other first-line drugs (ethambutol and high-dose isoniazid), provided they are likely to be effective.[32-34,36] Rifabutin may also be considered for M. tuberculosis isolates with specific rpoB mutations which confer resistance to rifampicin but not to rifabutin.[37,38] Group D2 includes two new drugs; bedaquiline and delamanid that have recently been approved to treat MDR/XDR-TB cases when no other options are available or tolerated to complete at least four active drug-regimen.[32,29-31]. Both drugs are bactericidal with sterilizing activity as they target actively replicating and dormant bacilli.[39-41] Recent studies have also shown safe and effective use of bedaquiline for up to 18 months as well as concomitant
Table 1: Re-classification of anti-TB drugs for proper management of multidrug-resistant tuberculosis

<table>
<thead>
<tr>
<th>Category and drug</th>
<th>Chemical description</th>
<th>Cellular process inhibited</th>
<th>Efficacy</th>
</tr>
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<tbody>
<tr>
<td>Group A: Fluoroquinolones</td>
<td>Levofloxacin</td>
<td>Fluoroquinolone</td>
<td>DNA replication</td>
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<td></td>
<td>Gatifloxacin</td>
<td>8-Methoxy-fluoroquinolone</td>
<td>DNA replication</td>
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<td></td>
<td>Moxifloxacin</td>
<td>8-Methoxy-fluoroquinolone</td>
<td>DNA replication</td>
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<tr>
<td>Group B: Second-line, injectable agents</td>
<td>Amikacin</td>
<td>Aminoglycoside</td>
<td>Protein synthesis</td>
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<tr>
<td></td>
<td>Kanamycin</td>
<td>Aminoglycoside</td>
<td>Protein synthesis</td>
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<tr>
<td></td>
<td>Capreomycin</td>
<td>Polypeptide</td>
<td>Protein synthesis</td>
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<tr>
<td></td>
<td>Streptomycin</td>
<td>Aminoglycoside</td>
<td>Protein synthesis</td>
</tr>
<tr>
<td>Group C: Other core second-line agents</td>
<td>Thiacetazone</td>
<td>Oxazolidione derivative</td>
<td>Protein synthesis</td>
</tr>
<tr>
<td></td>
<td>Delamanid (OPC-67683)</td>
<td>8-Methoxy-fluoroquinolone</td>
<td>DNA replication</td>
</tr>
<tr>
<td>Group D: Add-on agents</td>
<td>Pyrazinamide</td>
<td>Nicotinamide derivative</td>
<td>Membrane energetics</td>
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<tr>
<td></td>
<td>Ethambutol</td>
<td>Ethylene diimino di-l-butanol</td>
<td>Lipid/cell wall synthesis</td>
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<tr>
<td></td>
<td>High-dose isoniazid</td>
<td>Nicotinic acid hydraizde</td>
<td>Mycolic acid synthesis</td>
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<tr>
<td></td>
<td>Rifabutin</td>
<td>Rifamycin derivative</td>
<td>Protein synthesis</td>
</tr>
<tr>
<td>Group D2</td>
<td>Bedaquiline (TMC207)</td>
<td>Diarylquinolone</td>
<td>ATP synthesis</td>
</tr>
<tr>
<td></td>
<td>Delamanid (OPC-67683)</td>
<td>Nitroimidazo-oxazole</td>
<td>Mycolic acid synthesis</td>
</tr>
<tr>
<td>Group D3</td>
<td>Para-amino salicylic acid</td>
<td>Para-amino salicylic acid</td>
<td>Folic acid synthesis</td>
</tr>
<tr>
<td></td>
<td>Amoxycillin-clavulanate</td>
<td>Carbapenem with b-lactamase inhibitor</td>
<td>Cell wall synthesis</td>
</tr>
<tr>
<td></td>
<td>Imipenem-clavulanate</td>
<td>Carbapenem with b-lactamase inhibitor</td>
<td>Cell wall synthesis</td>
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<tr>
<td></td>
<td>Meropenem-clavulanate</td>
<td>b-lactam with b-lactamase inhibitor</td>
<td>Cell wall synthesis</td>
</tr>
<tr>
<td></td>
<td>Thiacetazone</td>
<td>Thiacetazone</td>
<td>Mycolic acid synthesis</td>
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$^a$Levofloxacin is bactericidal at high-dose
$^b$Thiacetazone is not recommended for HIV-infected patients

use of both these agents$^{[31,42]}$. These findings suggest the possibility of using these new agents for the entire duration of treatment as well as their use in patients with resistance patterns beyond MDR-TB such as pre-XDR-TB (MDR-TB strains additionally resistant either to fluoroquinolones or second-line injectable agents) and XDR-TB patients. Group D3 includes p-aminosalicylic acid, thiacetazone, amoxycillin-clavulanate, imipenem-clavulanate and meropenem-clavulanate, some of which require greater attention for toxicity$^{[32-34]}$. Importantly, the meropenem/clavulanate was found to be more active than imipenem/clavulanate and is bactericidal$^{[42-45]}$. Thus, meropenem/clavulanate may be used as a core drug for pre-XDR/XDR-TB cases with resistance to second-line injectables (Table 1).

According to this new drug classification proposed by WHO (Table 1), patients with RR-TB or MDR-TB should be treated with at least five effective anti-TB drugs during the intensive phase and should include PZA and four core second-line drugs, including one each from Group A and B and at least 2 drugs from Group C$^{[32-34]}$. The remaining first-line drugs (ethambutol, high-dose isoniazid and/or rifabutin) are to be used only if they are likely to be beneficial based on drug resistance profile$^{[32-34]}$. If a sufficient number of effective drugs are not available, an agent from Group D2 and other agents from Group D3 may be added. The new guidelines for effective treatment of RR-TB and MDR-TB also advocate that if PZA is compromised due to resistance (based on molecular analyses as phenotypic susceptibility testing is unreliable, see below) or can not be used, the regimen may be reinforced with a drug from Group C or D2, and if not possible, then from Group D3$^{[32-34]}$. The total number of drugs included in the regimen should be carefully considered, keeping in mind the expected benefits and the risk of adverse reactions and non-adherence. According to WHO, recognizing and promptly managing adverse drug reactions in the treatment of MDR-TB should be considered as a priority$^{[8,32-34]}$. Other important factors contributing to the success of a given anti-TB drug in the management of MDR-TB cases include easy availability of the
drug at an affordable price and reliable laboratory tests for confirming susceptibility or resistance of *M. tuberculosis* to the drug. Accordingly, high-dose isoniazid can be added to an MDR-TB regimen when a mutation in the *katG* gene is absent, however, it should not be counted as one of the four active drugs. Similarly, rifabutin should be considered if susceptibility is confirmed or is suggested by a favorable rpoB mutation profile, but it should not be counted as one of the four active drugs.

Another important development in the treatment of MDR-TB is the introduction of the shorter ‘Bangladesh regimen’ of 9-months duration. This regimen included an intensive phase of 4 months with high-dose gatifloxacin, PZA, ethambutol, clofazimine, kanamycin, prothionamide and isoniazid, followed by 5 months of continuation phase with high-dose gatifloxacin, PZA, ethambutol, clofazimine and reported treatment success rate of nearly 90%[20,46]. This regimen is much cheaper than the longer regimens that require treatment for 18 - 24 months. However, gatifloxacin, which likely played a critical role in its success, was withdrawn from the market due to the association of this drug with dysglycaemia, depriving resource-poor countries of an efficacious, effective and inexpensive drug.[47] The WHO has also recommended this shorter MDR-TB regimen in its new guidelines with moxifloxacin replacing gatifloxacin[33]. The revised shorter regimen now includes an initial phase of 4 - 6 months of treatment with PZA, kanamycin, moxifloxacin, prothionamide, clofazimine, high-dose isoniazid and ethambutol followed by 5 months of continuation phase with PZA, kanamycin, moxifloxacin and ethambutol[21,33,48]. The shorter regimen is suitable for adults and children with RR-TB and MDR-TB who have not been previously treated with second-line drugs and the *M. tuberculosis* strain has either been shown to be susceptible to fluoroquinolones and second-line injectable agents or the resistance to these agents is considered highly unlikely.[53]. The WHO guidelines also recommend rapid diagnosis of drug resistance detection by molecular testing to ensure appropriate selection of patients who can truly benefit from the shorter MDR-TB regimen[33]. Rapid diagnosis will also reduce the duration of the infectious period by rapid initiation of treatment with an adequate regimen, further transmission of MDR-TB within the community and development of additional resistance leading to pre-XDR-TB and XDR-TB[21,33,48].

Drug susceptibility testing of *M. tuberculosis* to anti-TB drugs

Accurate DST of *M. tuberculosis* in clinical specimens and culture isolates to all first-line (rifampin, isoniazid, ethambutol and PZA) and important second-line (fluoroquinolones, particularly new generation fluoroquinolones, levofloxacin, gatifloxacin and moxifloxacin and injectable agents; kanamycin, amikacin or capreomycin) drugs is crucial for the diagnosis of DR-TB/MDR-TB for proper management of MDR-TB patients[49-52]. Effective treatment with sufficient number of active drugs for the appropriately required duration will also limit transmission of MDR-TB and development of XDR-TB[10,53]. Recent modelling studies have suggested that improper treatment of patients with DR-TB and MDR-TB may lead to replacement of pan-susceptible TB by MDR-TB as the dominant *M. tuberculosis* phenotype across the world[54,55].

Phenotypic DST is usually considered as the most reliable laboratory approach to determine susceptibility or resistance of *M. tuberculosis* to anti-TB drugs due to good clinical correlation and quality control. Phenotypic DST of *M. tuberculosis* by solid (Lowenstein-Jensen or 7H10 agar) medium-based critical proportion method is considered as the gold standard for first-line (except PZA) and important second-line drugs. However, the method requires 4 - 6 weeks to report results[50,56,57] (Table 2). Commercial liquid culture systems and molecular assays have been developed and endorsed by WHO and Centers for Disease Control and Prevention (CDC) for more rapid detection of drug resistance in *M. tuberculosis*[50,51,58]. The liquid-broth-based semiautomated, radiometric BACTEC 460TB system accurately performed DST of *M. tuberculosis* for both first-line (including PZA) and important second-line drugs for more than two decades, reporting results within 14 days (Table 2) and was considered as an accurate and reliable alternative to the solid medium-based method[23,51,57]. The concerns for safe disposal of radioactivity, however, led to the development of fully automated culture systems such as Bectec Mycobacteria Growth Indicator Tube (MGIT) 960 system, MB/BacT system and Versa TREK system with similar turnaround time, which subsequently replaced BACTEC 460TB system in clinical microbiology laboratories[23,51,57]. Consistent results were obtained in early proficiency testing studies between BACTEC 460TB system versus MGIT 960 system or other automated systems for first-line and bactericidal second-line (fluoroquinolones and injectable aminoglycosides/cyclic peptides) drugs[51,57]. The diagnostic accuracy and reproducibility of phenotypic DST methods for less active second-line and other drugs are also inadequate as these methods have not been standardized internationally. This is reflected in the wide variability of practices among
supranational reference laboratories. Consequently, phenotypic DST for second-line and third-line drugs is not completely reliable\cite{37-40,60}. Phenotypic DST by rapid liquid culture-based methods such as MGIT 960 system has been studied extensively for first-line drugs (isoniazid, rifampicin, ethambutol and PZA) with a general consensus regarding critical concentrations\cite{38,50,57,60}. As stated above, streptomycin is now used as a second-line drug. Although the performance of MGIT 960 system has been excellent for isoniazid, recent studies have shown poor performance of this method for \emph{M. tuberculosis} isolates for the other three (rifampicin, PZA and ethambutol) first-line drugs for different reasons\cite{61-65} as described below.

**Limitations of DST of \emph{M. tuberculosis} by MGIT 960 system for first-line drugs**

Resistance of \emph{M. tuberculosis} to rifampicin in ~97% isolates is due to mutations in an 81-base pair (bp) rifampicin resistance determining region (RRDR) of the \emph{rpoB} gene\cite{66}. The resistance in the remaining 3% isolates is due to mutations in N-terminal or cluster II regions of the \emph{rpoB} gene or in other genes\cite{66,67}. The solid medium-based proportion method with shorter (4 weeks) turnaround time and rapid liquid culture-based MGIT 960 system fail to detect rifampicin resistance in \emph{M. tuberculosis} strains exhibiting low-level (minimum inhibitory concentration, MIC of 0.5-2.0 µg/ml) resistance\cite{68-71}. These low-level rifampicin-resistant strains with increased MICs below the critical concentration mostly contain mutations within RRDR, particularly at codons 511, 516, 526 and 533 or at codon 572 within cluster II region of the \emph{rpoB} gene\cite{63,68-71}. It should be pointed out here that 1572F mutation in cluster II region of the \emph{rpoB} gene which confers low-level resistance to rifampicin was accurately detected by the radiometric BACTEC 460TB system which has now been discontinued\cite{69,70,72}. In one study carried out in Bangladesh and Democratic Republic of Congo, these disputed mutations accounted for >10% of all \emph{rpoB} mutations in \emph{M. tuberculosis} strains cultured from patients with failing therapy or experiencing relapse\cite{70}. Furthermore, the significance of some (such as D516Y and I572F) of these disputed mutations in conferring resistance to rifampicin is indicated by gene replacement studies\cite{73}. The patients infected with \emph{M. tuberculosis} strains with disputed \emph{rpoB} mutations often fail treatment or relapse, suggesting that rifampicin resistance due to disputed \emph{rpoB} mutations is clinically and epidemiologically relevant\cite{74-77}. These findings call for modification of the standard phenotypic DST by MGIT 960 system for greater accuracy of rifampicin resistance detection and suggest that a susceptible result should be confirmed by molecular testing when the suspicion for rifampicin resistance (such as previous history of anti-TB therapy, failing therapy, relapse or history of close contact with a patient with RR-TB and MDR-TB) is high. Molecular testing for rifampicin resistance is also important since some mutations (such as H526Y/D, S531L, etc.) confer cross resistance to rifabutin, while strains with other \emph{rpoB} mutations (particularly at codon 511, 516, 533 and some mutations at codon 526) are resistant to rifampicin but remain susceptible to rifabutin\cite{37,38,78,79}. Hence, rifabutin may be used as an alternative second-line drug in treatment regimens of some MDR-TB patients.

PZA is used for the treatment of pan-susceptible
TB as well as DR-TB and MDR/XDR-TB, as the drug is active against 'persister' bacilli that are sequestered within macrophages and are not killed by other drugs\(^{[18,80]}\). The drug also improves outcome in fluoroquinolone-containing regimens for the treatment of MDR-TB and new drug regimens proposed for the treatment of various forms of DR-TB also show improved outcome when combined with PZA\(^{[19-41,85,82]}\). Unfortunately, resistance to PZA is found frequently in MDR-TB strains, as nearly 50% of MDR-TB strains at some geographical locations are also resistant to PZA\(^{[83]}\). Despite these observations, PZA is still included in treatment regimens since DST for PZA is not applied in routine testing and even if applied, it often yields unreliable results\(^{[84,85]}\). Phenotypic DST is not applied in routine testing and even if applied, still included in treatment regimens since DST for PZA is not applied in routine testing and even if applied, it often yields unreliable results\(^{[84,85]}\). Phenotypic DST of \(M.\) \(tuberculosis\) for PZA (most effective at pH 5.6) requires precise acidic conditions which prevent the growth of about 20% of the isolates\(^{[84]}\). Furthermore, the inoculum size also has profound effects on DST results as larger inoculum may lead to alkalization of the medium, causing false PZA resistance\(^{[83]}\). Nearly 90% of PZA-resistant \(M.\) \(tuberculosis\) isolates contain mutations in \(pncA\) encoding pyrazinamidase, the enzyme that converts the pro-drug PZA into its active form, pyrazinoic acid\(^{[86-88]}\). The \(pncA\) mutations are scattered across the entire length of the gene and the mutations linked with resistance have been thoroughly investigated\(^{[86-89]}\). Although nearly 10% of PZA-resistant \(M.\) \(tuberculosis\) isolates do not contain \(pncA\) mutation, the contribution of other genes (\(rpsA\) and \(panD\)) that have been analyzed so far appears minor, suggesting the involvement of other gene(s)\(^{[97-99]}\). Due to difficulties in accurate phenotypic DST for PZA, WHO is currently considering \(pncA\)-based methods as the recommended approach for molecular diagnosis of PZA resistance in \(M.\) \(tuberculosis\)\(^{[99]}\).

Ethambutol is a slow-acting, bacteriostatic anti-TB drug and the problems associated with accurate phenotypic DST for ethambutol have been recognized for quite some time, particularly with rapid liquid culture-based methods\(^{[90,91]}\). Ethambutol interferes with \(M.\) \(tuberculosis\) growth by inhibition of one of three arabinosyltransferases (encoded by \(embCAB\) operon) which participate in the synthesis of arabinogalactan, a component of the mycobacterial cell wall\(^{[92]}\). Mutations in \(embCAB\) operon are the first step in the evolution of ethambutol resistance but only modestly (3 - 8 fold) increase its MIC\(^{[73,93,94]}\). These mutations occur most frequently (pooled sensitivity of 0.76) in \(embB\) gene, particularly at codons 306, 406 and 497\(^{[95]}\). High-level resistance, however, develops subsequently due to acquisition of additional mutations in \(embCAB\) operon or in other genes\(^{[86,97]}\). Conventional solid medium-based phenotypic DST for ethambutol is time-consuming, while DST by MGIT 960 system often reports false susceptibility of \(M.\) \(tuberculosis\) mainly due to mutations in ethambutol resistance conferring genes (particularly \(embB\)) that increase MIC close to the critical concentration of the drug\(^{[50-52,73,93,94]}\). The radiometric BACTEC 460TB system which has now been discontinued was much more accurate compared to MGIT 960 system for ethambutol DST, particularly for \(M.\) \(tuberculosis\) isolates containing \(embB\) mutations that confer low-level but clinically significant resistance to ethambutol\(^{[64,93,94,98]}\). Current evidence shows that patients infected with \(embB\) mutants should be considered as having EMB-resistant TB even if the isolates appear to be EMB-susceptible by phenotypic DST methods to avoid evolution of secondary mutations and selection of fully drug-resistant strains\(^{[93-97]}\). False susceptibility to ethambutol is not very critical for the treatment of pansusceptible TB since ethambutol is used only in the initiation phase of treatment and can even be omitted from treatment regimens if the susceptibility of \(M.\) \(tuberculosis\) isolate to rifampicin and isoniazid has been documented\(^{[18,80]}\). However, false susceptibility to ethambutol is of considerable importance for the successful treatment of RR-TB and MDR/XDR-TB as drug regimens (including shorter regimens) for these conditions should include all active first-line drugs for improved outcome\(^{[10,11,28,33,66]}\).

**Limitations of phenotypic DST methods for second-line drugs**

Fluoroquinolones, particularly newer bactericidal fluoroquinolones (\(e.g\). high-dose levofloxacin, moxifloxacin and gatifloxacin) and second-line injectable drugs (aminoglycosides, kanamycin and amikacin and cyclic peptides, capreomycin and viomycin) are the backbone of treatment regimens for MDR-TB, and resistance to these drugs in MDR-TB strains defines XDR-TB\(^{[8,10,32-34]}\). Streptomycin, another aminoglycoside which was used earlier as a first-line agent, is now used as second-line drug due to higher rates of resistance of \(M.\) \(tuberculosis\) strains to this agent\(^{[10,32-34]}\). The MGIT 960 system has also been evaluated for fluoroquinolones and injectable agents; aminoglycosides (amikacin and kanamycin) and cyclic peptides (\(e.g\). capreomycin) yielding excellent agreement with the reference proportion method or with BACTEC 460TB system\(^{[50-52,59,60,99]}\). However, these studies have mainly been carried out with \(M.\) \(tuberculosis\) strains exhibiting high-level resistance to bactericidal second-line drugs. Recent studies on rifampicin-resistant and ethambutol-resistant strains indicate that \(M.\) \(tuberculosis\) isolates...
with low-level resistance to second-line drugs may also yield discordant results more frequently with rapid liquid culture-based methods such as MGIT 960 system compared to the proportion method. The performance of MGIT 960 system for less active (mainly bacteriostatic) second-line drugs has been sub-optimal, mainly because the critical concentrations for these agents are not well-defined[50-52,99]. The problems associated with slow and/or inaccurate DST of *M. tuberculosis* by phenotypic methods have been overcome by developing molecular methods.

**Molecular methods for DST of M. tuberculosis**

Molecular methods detect genetic mutations associated with drug resistance rapidly (within 1 - 2 days) and shorten the time between MDR/XDR-TB diagnosis and appropriate treatment[100-102]. To ensure that mutations associated with drug resistance are differentiated from other mutations, specific mutations are validated by gene replacement studies[73,93,94]. Another advantage associated with this approach are the findings that different mutations confer different levels of phenotypic resistance to anti-TB drugs and some mutations are significantly associated with higher odds of patient mortality[103-106]. Based on the methodology, molecular methods are grouped into three main categories: hybridization-based assays including real-time polymerase chain reaction (PCR) assays and line probe assays, PCR-sequencing of select panel of target genes and whole-genome sequencing (WGS) of *M. tuberculosis* in clinical specimens and culture isolates[107,108] (Table 2).

**Hybridization-based molecular diagnostic assays for DR-TB, MDR-TB and XDR-TB**

Hybridization-based assays mainly include GeneXpert MTB/RIF assay (Xpert), reverse-hybridization-based line probe assays and various formats of DNA microarrays for detecting resistance to various combinations of first-line and/or second-line drugs. Xpert is a fully automated, cartridge-based, real-time PCR assay that detects active TB disease and resistance of *M. tuberculosis* to rifampicin[109-111]. Since nearly 85% of rifampicin-resistant *M. tuberculosis* isolates are also additionally resistant to isoniazid, the method also detects the majority of MDR-TB cases[8,23]. Another cartridge-based, fully-automated assay that simultaneously detects resistance of *M. tuberculosis* to isoniazid, fluoroquinolones and second-line injectable agents directly in clinical specimens has recently been developed as another point-of-care test[115,116]. Thus, combining this test with Xpert will not only detect MDR-TB more specifically, but will also help in the diagnosis of XDR-TB. One disadvantage of the Xpert (and other hybridization-based assays) is the recent findings of silent mutations in the rpoB gene that lead to false rifampicin resistance by Xpert[77,113]. This has resulted in revised WHO recommendations regarding the use of Xpert. The WHO guidelines now state that Xpert may be used as the initial diagnostic test, and treatment for MDR-TB should be started if rifampicin resistance result is expected or, if unexpected, Xpert testing should be repeated on another sputum sample, particularly for settings where the prevalence of rifampicin-resistant TB is <15%[114]. Treatment, however, should be optimized following phenotypic testing or DST by another genotypic test and resolution of any discordant rifampicin susceptibility results by sequencing of the rpoB gene[114].

Reverse hybridization-based line probe assays that are commercially available mainly include GenoType MTBDRplus assay that detects resistance of *M. tuberculosis* to rifampicin and isoniazid for the diagnosis of MDR-TB and GenoType MTBDRsl assay that detects resistance to fluoroquinolones (levofloxacin, gatifloxacin and moxifloxacin) and injectable agents (kanamycin, amikacin and capreomycin) in MDR-TB strains for the diagnosis of XDR-TB[115,116]. Compared to other molecular assays (such as PCR-sequencing), line probe assays (and PCR-restriction fragment length polymorphism) are more suitable for the detection of developing resistance or infection with two strains, one susceptible and one drug-resistant (heteroresistance) strain as they are more easily detected by differential hybridization with wild-type and mutant probes[117,118]. However, similar to Xpert assay, line probe assays are also prone to report false resistance due to synonymous point mutations in target region[98,71,119]. Line probe assays have also been developed for pncA gene for the detection of resistance to pyrazinamide[120,123].

DNA microarrays have also been developed for detecting resistance to various combinations of first-line and/or second-line drugs (Table 2). A DNA microarray (GeneChip) has been developed for detection of MDR-TB and is commercially available[122]. A simplified microarray test has also been developed for detecting and identifying mutations in rpoB, katG + inhA, embB, and rpsL for reporting resistance to rifampicin, isoniazid, ethambutol and streptomycin with sensitivities (relative to phenotypic DST) of 100%, 90%, 70% and 35%, respectively. The sensitivity for MDR-TB was 89% relative to phenotypic DST[125]. However, many isolates yielded false-susceptible results due to DNA mutations that were not represented by a specific microarray probe[123]. An integrated microfluidic card with TaqMan probes
and high-resolution melting curve analysis has also been developed for detecting mutations in critical regions of rpoB, katG + inhA, embB, rpsL + rrs + eis, gyrA + gyrB, and pncA genes for detecting resistance to rifampicin, isoniazid, ethambutol, aminoglycosides (streptomycin, kanamycin and amikacin) + cyclic peptides (capreomycin and viomycin), fluoroquinolones and pyrazinamide, respectively. The test reported an accuracy of 96.1% in comparison to that of Sanger sequencing and 87% accuracy compared to phenotypic DST.[124]

**PCR-sequencing-based molecular diagnostic assays for DR-TB, MDR-TB and XDR-TB**

PCR amplification followed by DNA sequencing (PCR-sequencing) has been used for detecting resistance to one or several first-line and second-line drugs by targeting appropriate number and regions of loci conferring resistance to different anti-TB drugs.[64,72,100,125] The sensitivity of PCR-sequencing for first-line and second-line drugs varies considerably according to the number and regions of drug resistance associated loci included for each drug. The sensitivity is also affected by the frequency of specific mutations in these loci at different geographical locations/ethnic groups of TB patients.[72-74,118,126-128] Furthermore, this approach is time consuming and technologically demanding and is rapidly being replaced by WGS.[101,102]

**Whole-genome sequence-based assays for DR-TB, MDR-TB and XDR-TB**

The problem of lower sensitivity of drug resistance detection due to limited genome coverage by hybridization-based assays and PCR-sequencing of selected panel of gene loci are overcome by WGS.[101,102] WGS characterizes both common and rare mutations predicting drug resistance, or consistency with susceptibility, for all first-line and second-line anti-TB drugs. With the advent of next generation sequencing technologies, use of WGS is increasingly being applied for routine mycobacterial species identification, detection of drug resistance and strain typing of *M. tuberculosis*.[101,129-132] The coverage of the entire genome also makes WGS a rapidly scalable method for determination of drug resistance caused by any chromosomal mutation to any first-line and second-line drug as well as newer anti-TB agents (Table 2). Recent studies have also demonstrated the applicability of WGS for tracking transmission and outbreaks of DR-TB and deciphering novel mechanisms of drug resistance.[138,139,140] Novel methods for DNA extraction from MGIT 960 cultures, optimization of library preparation, and bioinformatics pipeline have been introduced to reduce the turnaround time for obtaining WGS data.[131,132] Recent studies have also shown that WGS of *M. tuberculosis* can be performed directly from patient samples to rapidly generate antibiotic susceptibility profiles for same-day diagnosis.[135,136] England is the first country that has already started using WGS on a national scale to realize its full potential for the diagnosis of tuberculosis, detection of drug resistance, and typing of *M. tuberculosis* for epidemiological purpose.[137] However, the high cost of equipment and reagents, requirement of technical expertise and bioinformatic support make this method difficult to implement, at least at present, in resource-poor developing countries where DR-TB and MDR/XDR-TB are endemic. In this regard, it is pertinent to mention that the introduction of Xpert assay few years ago revolutionized the diagnosis of active TB and its resistance to rifampicin.[109-111] This test is currently provided at reduced cost by WHO to poor developing countries for rapid diagnosis of TB, RR-TB and MDR-TB. Similar action is urgently needed to simplify WGS data acquisition and analysis on a cost-effective basis to make it suitable for poor developing countries, if the WHO’s target of ‘End TB by 2035’ is going to be realized.

**CONCLUSION**

Widespread occurrence of DR-TB and MDR-TB is mainly responsible for most of the global TB deaths. Nearly 600,000 cases of RR-TB and MDR-TB are estimated to have occurred in 2016 that resulted in the death of 240,000 patients. Accurate DST of *Mycobacterium tuberculosis* in clinical specimens and culture isolates to first-line and second-line drugs is crucial for rapid diagnosis and effective management of MDR-TB. Phenotypic DST of *M. tuberculosis* by solid medium-based proportion method is considered as the gold standard; however, the method requires 4 - 6 weeks to report results. The liquid medium-based fully automated culture systems (e.g. MGIT 960 system) report results within 10 - 14 days; however, their performance for *M. tuberculosis* isolates carrying specific resistance conferring mutations in target genes for some first-line drugs (e.g. rifampicin and ethambutol) and many second-line drugs is sub-optimal. To overcome these limitations, molecular methods have been developed for rapid (within 1 - 2 days) detection of drug resistance for all first-line and important second-line drugs. Whole-genome sequencing is a newer alternative that has the potential of providing rapid drug resistance profiles for all anti-TB drugs to inform treatment. The method additionally provides strain information for global
epidemiological surveillance. However, the cost of equipment and reagents is prohibitively high for resource-poor developing countries where DR-TB and MDR-TB are endemic. The method also requires expert technical and bioinformatic support, which makes this method difficult to implement in resource-poor and developing countries. Efforts are urgently needed to simplify WGS data acquisition and analysis on a cost-effective basis to make it suitable for poor developing countries to meet WHO’s target of ‘End TB by 2035’ across the world.

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Original Article

Frequency of Short Term Complications of Second Trimester Amniocentesis in Pregnant Women referred to Perinatology Clinic of Azzahra Hospital, Rasht, 2012 - 2014

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ABSTRACT

Objective: To investigate the frequency of short term complications of second trimester amniocentesis

Design: An analytical cross-sectional study

Setting: Perinatology clinic of Azzahra Hospital, Rasht, Iran

Subjects: Eight hundred and thirty-four pregnant women referred to perinatology clinic

Intervention(s): Amniocentesis at 15 - 22 weeks of gestation by convenient sampling

Main outcome measure(s): Patients were followed up for 4 weeks until receipt of amniocentesis results. Abortion rate, intrauterine fetal death, chorioamnionitis, vaginal bleeding and premature rupture of membranes were registered during this period.

Results: Eleven cases (1.3%) showed short-term complications, including 4 with abdominal pain (0.5%), 4 with vaginal bleeding (0.5%), 2 had abortions (0.2%) and 1 with amniotic fluid leakage (0.1%). The outcome of pregnancy showed 22 fetal losses, of which 20 had legal abortion due to abnormal karyotype and 2 (0.2%) had spontaneous abortion. The most prevalent karyotype was trisomy 21. The history of abnormal child and first trimester vaginal bleeding were significantly associated with fetal loss (p = 0.014 and p = 0.0001, respectively). According to the regression analysis, the history of having an abnormal child and first trimester vaginal bleeding increased the chance of fetal loss which were 4.7 and 12.6 times, respectively. Furthermore, sonography as a screening test for diagnosing abnormalities had 21.2% sensitivity and 96.4% specificity.

Conclusion: Our study showed that the frequency of short-term complications from amniocentesis was low and sonography did not have enough sensitivity to diagnose fetal abnormalities; therefore, although amniocentesis may be a safe procedure in the second trimester, in high risk women, physicians should inform them regarding probable complications.

KEYWORDS: amniocentesis, amniotic fluid, congenital malformations

INTRODUCTION

Birth defect is the most leading cause of infant mortality and 21% of neonatal death is caused by these defects1,2. So far, more than a thousand human abnormalities in the number and structure of the chromosomes have been identified and reported. Chromosomal abnormalities may cause mental retardation, heart defects and other congenital malformations. Prenatal screening and termination of pregnancy with permission and consent of the family is obviously the only way to prevent these outcomes. Recently, the screening at the first trimester of pregnancy followed by the amniocentesis at 15 - 18 weeks of gestation are considered as standard methods of assessment regarding the high diagnostic accuracy and low risk for fetuses and mothers1,3. The indications for amniocentesis during pregnancy include maternal age (35 years or older), chromosomal abnormality or neural tube defects in previous
pregnancies, abnormal screening result at the first or second trimester of pregnancy, positive family history of chromosomal or genetic disorders, and history of intrauterine infections or RH incompatibility. Despite the increased rate of amniocentesis, this method may cause complications. The risk of abortion and pregnancy loss are the main concerns for pregnant women undergoing amniocentesis. Overall, fetal loss occurred in 1 out of 200 cases (or 0.5%). However, by using techniques such as ultrasound, the mortality rate decreased and occurred in 1 out of 300 - 500 cases. In a study by Tabor et al, the rate of abortion after amniocentesis was 1.4%, while it was 1.9% after chorionic villus sampling.

Eddleman et al compared abortion in amniocentesis and control groups and mentioned 1% and 0.94% of amniocentesis and control groups had abortion, respectively. In another study, 1.66% of fetal deaths were related to amniocentesis. In addition to abortion, preterm rupture of membrane, chorioamnionitis and hemorrhage after amniocentesis were also the complications of amniocentesis.

As amniocentesis is accepted as a gold standard for fetal assessment, identifying the precise assessment regarding the mortality rate and short-term complications after amniocentesis is mandatory. This estimation may help to decrease complications. As there is no definite estimation in our country regarding this issue and based on the common screening tests and increased maternal age, we aimed to assess the frequency of some short-term complications of second trimester amniocentesis in pregnant women referred to perinatology clinic of Azzahra hospital.

SUBJECTS AND METHODS

This is an analytical, cross-sectional study which was conducted from May 2012 to March 2014 in perinatology clinic of Azzahra hospital. Ethical approval was obtained from Guilan University of Medical Sciences Ethics Committee (Number: 1930382807, dated 18 December 2014).

All pregnant women referred to perinatology clinic for amniocentesis at 15 - 22 weeks of gestation participated in this study. Exclusion criteria were second amniocentesis, twin pregnancy and lack of access to patient’s history and their laboratory results. Written consents were obtained from all participants before enrollment. Before the procedure, the same perinatologist performed an ultrasound to check the abnormalities and anomalies, placental location, the best puncture site, the largest liquid pocket and the cord place. Also during the ultrasound, to reduce the risk, layers of amnion and chorion were assessed to perform amniocentesis at >16 weeks of gestation in the absence of fusion.

All procedures of amniocentesis were performed under ultrasound guidance with a 22 gauge needle. For sampling, 1 ml of amniotic fluid was discarded to prevent contamination with mother cells and next 20 ml was sent to the cytology and genetics laboratory. Patients were monitored for 30 minutes and if no complication such as leakage of amniotic fluid, bleeding and abdominal pain was noted, they were discharged and rested for 2 - 3 days at home. Patients were followed up for 4 weeks to receive its outcome. Abortion rates, intrauterine fetal death (IUFD), chorioamnionitis, vaginal bleeding and premature rupture of membrane (PROM) during this period were recorded. Samples were packed with ice box and sent to a laboratory in less than 12 hours.

All of the above procedures were carried out by the same perinatologist. For karyotyping, the culture was done on the acquired cells. Data were collected by means of a form including two parts: 1) demographic and medical characteristics including age, occupation, education level, number of live births and the number of pregnancy, abortion, history of stillbirth, history of abnormal child, age during pregnancy, amniocentesis, culture, karyotype result as predisposing factors and 2) short-term complications of amniocentesis including pain, bleeding, abortion, vaginal bleeding, IUFD, leakage of amniotic fluid, PROM and chorioamnionitis during the 4 weeks after amniocentesis.

Statistical analysis

Data were analyzed by SPSS version 19 and were reported by frequency, percentage, mean and standard deviation. Data were analyzed for normal distribution. Quantitative data were analyzed by ANOVA and Post hoc tests and qualitative data were analyzed using logistic regression, chi-square, and Fisher exact test. Variables with non-normal distribution were assessed by non-parametric Mann Whitney test. P-value < 0.05 was considered significant and 95% confidence interval was noted.

RESULTS

In this study, 877 patients were enrolled. Forty-three cases were excluded due to lack of contact numbers, twin pregnancies or second amniocentesis. The remaining 834 patients were analyzed. The highest percentage of subjects was aged 18 - 35 years, had a diploma and were housewives. Table 1 shows the demographic characteristics.

The highest percentage of women in the study had normal serum levels of alpha-fetoprotein (82.1%). The percentage of women who had decreased and increased levels of serum alpha-fetoprotein were 13.7% and 4.2%, respectively. The results of culture in
all women were positive and 801 women (96%) had normal outcomes and 33 fetal abnormal karyotypes were diagnosed.

Frequency of abnormal karyotypes were 16 with trisomy 21 (1.9%), 3 with trisomy 18 (0.4%), 5 translocation (0.6), 1 triploid (0.1%), 7 inversion (0.8%) and 1 with trisomy 13 (0.1%). In study, abnormalities were noted in 4.3% of women. Statistical analysis showed that the sensitivity of ultrasound to detect abnormalities was 21.2%, which was inappropriate for detecting abnormalities, but the specificity was 96.4% and was suitable. Trisomy 21 was noted in 8 women aged > 35 years and 8 women aged < 35 years (Table 1). No screening test was performed for 59 patients.

### Table 1: Distribution of demographic characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td></td>
</tr>
<tr>
<td>18 – 35</td>
<td>469 (56.2)</td>
</tr>
<tr>
<td>&gt; 35</td>
<td>365 (43.8)</td>
</tr>
<tr>
<td>Level of education</td>
<td></td>
</tr>
<tr>
<td>Less than diploma</td>
<td>542 (65)</td>
</tr>
<tr>
<td>Academic</td>
<td>292 (35)</td>
</tr>
<tr>
<td>Occupation</td>
<td></td>
</tr>
<tr>
<td>Housewife</td>
<td>681 (81.7)</td>
</tr>
<tr>
<td>Employee</td>
<td>153 (18.3)</td>
</tr>
<tr>
<td>Blood group</td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>213 (25.5)</td>
</tr>
<tr>
<td>B</td>
<td>170 (20.4)</td>
</tr>
<tr>
<td>O</td>
<td>417 (50)</td>
</tr>
<tr>
<td>AB</td>
<td>34 (4.1)</td>
</tr>
<tr>
<td>RH</td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>736 (88.5)</td>
</tr>
<tr>
<td>Negative</td>
<td>96 (11.5)</td>
</tr>
<tr>
<td>History of successful pregnancy</td>
<td>467 (56)</td>
</tr>
<tr>
<td>History of stillbirth</td>
<td>55 (6.6)</td>
</tr>
<tr>
<td>History of miscarriage</td>
<td>193 (23.1)</td>
</tr>
<tr>
<td>Parity</td>
<td>0.74 ± 0.76</td>
</tr>
<tr>
<td>History of abnormal child</td>
<td>20 (2.4)</td>
</tr>
<tr>
<td>History of vaginal bleeding in 1st trimester</td>
<td>77 (9.2)</td>
</tr>
</tbody>
</table>

Three hundred and twenty-seven double tests were performed, which showed 16 anomalies based on amniocentesis and 4.8% coordination rate was noted. Also, 386 triple tests were noted and 13 anomalies were mentioned based on amniocentesis and 3.36% coordination rate was obtained. In addition, 62 quad tests were performed and only 1 anomaly after amniocentesis was noted and 1.65% coordination rate was noted. Totally, 83.2% of women had abnormal screening results (Table 2).

Eight women under 35 years and 8 women over 35 years had trisomy 21. Among the causes for amniocentesis, markers of trisomy 21 (70.1%) and high maternal age (50.5%) were the highest prevalent reasons for amniocentesis (Table 3).

### Table 2: The frequency of suspicious cases in screening test for amniocentesis

<table>
<thead>
<tr>
<th>Markers of screening tests</th>
<th>Suspicious cases n (%)</th>
<th>Confirmed cases n (%)</th>
<th>Cases causing fetal loss n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trisomy21</td>
<td>585 (70.1)</td>
<td>16 (61.6)</td>
<td>13 (65)</td>
</tr>
<tr>
<td>Trisomy18</td>
<td>24 (2.9)</td>
<td>3 (11.5)</td>
<td>3 (15)</td>
</tr>
<tr>
<td>NTD</td>
<td>45 (5.4)</td>
<td>4 (15.4)</td>
<td>2 (10)</td>
</tr>
<tr>
<td>Increased N</td>
<td>41 (4.8)</td>
<td>3 (11.5)</td>
<td>2 (10)</td>
</tr>
</tbody>
</table>

NTD: neural tube defect; NT: nuchal translucency

Among the 834 women surveyed, 11 (1.3%) short-term outcomes after amniocentesis were mentioned in nine patients and two women had two simultaneous symptoms including abdominal pain and bleeding. These symptoms included four types of complications. Abdominal pain and vaginal bleeding, each with 0.5% frequency (4 patients), were the most common short-term complications of amniocentesis. Four (0.5%) women had a history of vaginal bleeding after amniocentesis in the first trimester of pregnancy.

### Table 3: Frequency of reasons for amniocentesis in the second trimester of pregnancy in healthy adults

<table>
<thead>
<tr>
<th>Diagnostic markers in amniocentesis</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>High maternal age</td>
<td>412 (50.5)</td>
</tr>
<tr>
<td>Trisomy21</td>
<td>585 (70.1)</td>
</tr>
<tr>
<td>Trisomy18</td>
<td>24 (2.9)</td>
</tr>
<tr>
<td>NTD</td>
<td>45 (5.4)</td>
</tr>
<tr>
<td>NT increased</td>
<td>41 (4.8)</td>
</tr>
<tr>
<td>History of multiple abortions</td>
<td>17 (2)</td>
</tr>
<tr>
<td>History of Downi syndrome in previous child</td>
<td>5 (0.6)</td>
</tr>
<tr>
<td>History of abnormality in previous child</td>
<td>20 (2.4)</td>
</tr>
<tr>
<td>History of familial abnormality</td>
<td>39 (4.7)</td>
</tr>
<tr>
<td>Parental translocation</td>
<td>3 (0.4)</td>
</tr>
<tr>
<td>Existence of abnormality in ultrasound</td>
<td>36 (4.3)</td>
</tr>
<tr>
<td>Parental willing</td>
<td>11 (1.3)</td>
</tr>
</tbody>
</table>

NTD: neural tube defect; NT: nuchal translucency

One woman (0.01%) had amniotic fluid leakage within 48 hours after amniocentesis, which became normal 1 week after ultrasound and delivered successfully. Also, two cases (0.2%) of abortion after amniocentesis were mentioned. No chorioamnionitis and PROM was noted.

Pregnancy outcomes in women undergoing amniocentesis showed that among the 834 pregnant women, 812 cases of pregnant women delivered and of the 22 patients (2.6%) who were forced to terminate pregnancy, 20 legal abortions and two cases of spontaneous abortions were noted. Two cases of spontaneous abortions had a history of vaginal bleeding and threatened abortion in the first trimester before amniocentesis.
Assessing the relation between fetal loss and variables, results showed a significant relation between the history of abnormal child, hemorrhage during the first trimester and different karyotypes with the fetal loss (Table 4).

### Table 4: The relation between fetal loss and variables

<table>
<thead>
<tr>
<th>Variables</th>
<th>Fetal Loss</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 35 years</td>
<td>13 (2.7)</td>
<td>0.86</td>
</tr>
<tr>
<td>&gt; 35 years</td>
<td>9 (2.5)</td>
<td></td>
</tr>
<tr>
<td>History of abortion</td>
<td>4 (2.1)</td>
<td>0.58</td>
</tr>
<tr>
<td>History of stillbirth</td>
<td>1 (1.8)</td>
<td>0.57</td>
</tr>
<tr>
<td>History of abnormal child</td>
<td>3 (15)</td>
<td>0.014</td>
</tr>
<tr>
<td>Blood group</td>
<td></td>
<td>0.76</td>
</tr>
<tr>
<td>A</td>
<td>5 (2.3)</td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>5 (2.9)</td>
<td></td>
</tr>
<tr>
<td>O</td>
<td>12 (2.9)</td>
<td></td>
</tr>
<tr>
<td>AB</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>RH</td>
<td></td>
<td>0.26</td>
</tr>
<tr>
<td>Negative RH</td>
<td>1 (1)</td>
<td></td>
</tr>
<tr>
<td>Positive RH</td>
<td>21 (2.8)</td>
<td></td>
</tr>
<tr>
<td>Alfa fetoprotein</td>
<td></td>
<td>0.61</td>
</tr>
<tr>
<td>Decreased Alfa fetoprotein</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Increased Alfa fetoprotein</td>
<td>3 (2.6)</td>
<td></td>
</tr>
<tr>
<td>Karyotype</td>
<td></td>
<td>0.001</td>
</tr>
<tr>
<td>Trisomy21</td>
<td>13 (81.3)</td>
<td></td>
</tr>
<tr>
<td>Trisomy18</td>
<td>3 (100)</td>
<td></td>
</tr>
<tr>
<td>Translocation</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Triploid</td>
<td>1 (100)</td>
<td></td>
</tr>
<tr>
<td>Inversion</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Trisomy13</td>
<td>1 (100)</td>
<td></td>
</tr>
<tr>
<td>History of vaginal bleeding in 1st trimester</td>
<td>12 (15.6)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Considering amniocentesis complications which were associated with fetal loss, it was observed that there was a significant association between the history of vaginal bleeding in the first trimester of pregnancy and fetal loss. Although there was no statistically significant relationship in examining the complications of amniocentesis and fetal loss (Table 5), there was a significant relationship between vaginal bleeding after amniocentesis and vaginal bleeding in the first trimester of pregnancy. Of the 830 people with no vaginal bleeding after amniocentesis, 91.1% (756 women) had vaginal bleeding and just 1 woman had a history of bleeding in the first trimester and significant relation was noted (p = 0.003).

In multivariate regression logistic analysis by Backward LR method for detecting predictors of fetal loss, results showed that the history of child abnormality and the history of vaginal hemorrhage were predictors of fetal loss (p = 0.014, p = 0.0001) and they respectively made 4.7 fold (Odds Ratio (OR) = 4.78, 95% confidence interval (CI): 1.11 – 20.56) and 12.6 fold (OR = 12.6, 95% CI: 5.21 – 30.83) increase in the chance of fetal loss.

### DISCUSSION

The main concern for pregnant women undergoing amniocentesis is the risk of abortion or fetal loss. Overall, 0.5% fetal loss occurred commonly and by using techniques such as ultrasound, the mortality rate may be decreased.[4,6,13]

In this study, 834 samples were studied and all cultures were positive but previous studies mentioned 0.1 - 0.8% failure rate[14,15].

Most clinical indications for amniocentesis in the study were due to abnormal findings on screening (83.2%). However, in the study by Minim et al, the most common indications for amniocentesis were the history of Down syndrome (29.8%) and high maternal age (18.9%)[16]. Monterio et al[17] indicated amniocentesis due to high maternal age (94.6%) and positive prenatal screening reports (30.9%). But Anuwutnavin et al[6] mentioned high age as the leading cause of amniocentesis. These inconsistent results might be noted as a result of different methods of sampling[18], because women with high risk pregnancies were enrolled in this study.

Recently, using biochemical markers which are associated with nocal translucency and ultrasound markers (checking the nasal bone, venous and tricuspid regurgitation) are progressively replacing variables such as maternal age for screening[19]. However, Rihani et al reported maternal age, history of chromosomal abnormalities in children, abnormal ultrasound, single-gene disorders, and the history of parental chromosomal abnormalities as the indications for amniocentesis in high risk fetuses by the first and second trimester biochemical screenings[3], which was similar to the present study.

In the study by Kariminejad et al[3], which assessed 4244 Quid test, 158 abnormal fetuses with the concordance rate of 3.9% were noted. Also, from 2790 triple tests, 2100 ultrasound and 1324 first trimester screening tests, 84, 20 and 87 abnormal fetuses with the concordance rate of 3%, 9.8% and 6.6% were noted, respectively. Totally, 524 abnormal fetuses from 10,458
amniocentesis needed pregnancy termination and the remaining women continued their pregnancy\(^{[31]}\).

In this study, 54 participants had no screening tests. Three hundred and twenty-seven double screening tests were done and 16 anomalies based on amniocentesis were mentioned with the concordance rate of 4.8\%. Also, 386 triple tests were performed and 13 anomalies based on amniocentesis with the concordance rate of 3.6\% were noted. Quad screening tests were also performed in 62 cases and 1 anomaly with the concordance rate of 1.6\% was noted. The concordance rate in this study was slightly lower than previous investigations, which might be due to the lower sample size in this study.

The abnormal karyotype in amniocentesis was 1 - 6.7\%\(^{[20]}\). In this study, 33 patients (4\%) had chromosomal anomalies, of which 16 cases were trisomy 21, 7 inversions and 5 translocations. Jafarieh \(et\ al\) reported 5.3\% definite abnormality by amniocentesis\(^{[21]}\), which might have occurred as a result of the higher rate of high-risk pregnant women referred to Tehran. However, in another study by the Canadian Early and Mid-trimester Amniocentesis Trial (CEMAT), they reported 1.9\% chromosomal abnormalities in accordance with second trimester amniocentesis. Higher maternal age was noted as the only indication for amniocentesis\(^{[22,24]}\). Karimi Nejad and his colleagues also found that 3.8\% of cases had abnormal amniotic fluid, which was similar to our study. They mentioned that the most frequent chromosomal abnormalities referred to Down syndrome and inversion was the second most frequent abnormality\(^{[3]}\).

Reyhanifar \(et\ al\) found that 11.82\% of women had abnormal sonographic evidence\(^{[4]}\), while in our study, abnormalities were noted in 4.3\% of women. Statistical analysis showed that the sensitivity of ultrasound to detect abnormalities was 21.2\%, but the specificity was 96.4\%. Fetal loss was the most important concern for mothers after amniocentesis, therefore, thorough information regarding this procedure might be necessary. In this study, 22 (2.6\%) fetal losses which included 20 clinical abortions and 2 spontaneous abortions were reported. However, Jafarieh \(et\ al\) mentioned 5 clinical indications for abortion and 7 IUFD\(^{[21]}\). Kornacki \(et\ al\)\(^{[25]}\) mentioned 0.3 fetal loss after amniocentesis. This result was inconsistent with ours, which may be a result of different sample size and different legal abortion rules in diverse countries.

In another study, Enzensberger reported 0.4\% fetal loss after amniocentesis\(^{[10]}\). Eddleman \(et\ al\) also mentioned 1\% fetal loss. They mentioned no significant difference between amniocentesis and controls regarding fetal loss\(^{[8]}\). In another study, pregnancy loss within 4 weeks after the amniocentesis was 7 in 3307 cases (0.2\%, 95\% CI between 0.1 - 0.4\%)\[^{[6]}\]. These different results may be noted as a result of different levels of sonographer expertise and the high resolution of new ultrasound devices. Also, this result supports the safety of this diagnostic tool. The history of abnormal birth and vaginal hemorrhage were the predictors for fetal loss and had 4.7 fold and 12.6 fold risk, respectively. In a study by Corrado \(et\ al\)\(^{[26]}\) which assessed 2990 participants, 30 fetal losses were noted. They mentioned that the procedure-dependent variables such as transplacental sampling, multiple needle insertion and gestational age, and the history of 2 abortions could not be the pre-directing factors for fetal loss. However, the history of vaginal bleeding could significantly induce 1.4 fold increase in fetal loss.

Schulpen \(et\ al\), who assessed twin pregnancies, mentioned that the only risk factor for fetal loss was optional amniocentesis, which can increase the risk of fetal loss\(^{[27]}\) by 2.9 fold. Enzensberger observed that vaginal bleeding in the first trimester was a risk factor for the occurrence of fetal loss\(^{[10]}\), Tabor \(et\ al\)\(^{[7]}\), who assessed fetal loss in centers with <500 procedures, showed higher rate of fetal loss compared to centers with >1500 procedures. In the current study, 834 patients were assessed, as this is a referral center and patients are referred to this center from neighboring provinces.

In a study conducted in Thailand, potential risk factors for fetal loss were maternal age under 18 years\[^{[6]}\]. Theodora \(et\ al\), who assessed 6752 patients who underwent amniocentesis during seven years, reported 1.9\% fetal loss. Factors associated with an increased risk of amniocentesis were age (2 fold risk), vaginal bleeding (2.2 fold risk), serious bleeding during pregnancy (3.5 fold risk), history of pregnancy termination in second trimester (4 fold risk), history of more than 3 spontaneous abortions (3 fold risk), first trimester abortion (2.1 fold risk), fibroma (3 fold risk) and meconium-stained amniotic fluid (6.1 fold risk)\[^{[28]}\]. In a study by Muniium \(et\ al\)\(^{[16]}\) which assessed 228 pregnant women over ten years, the highest frequent cause of amniocentesis was the history of Down syndrome. Therefore, most of them had normal karyotype (86.6\%) and Down syndrome was seen in 14\% of women. Delivery outcome was normal in 77.3\%, 0.9\% intrauterine death, 11.7\% full-term pregnancy and 1 abortion (0.4\%) were noted.

Wilson \(et\ al\)^{[29]} suggested that the incidence of fetal loss after amniocentesis was exclusive and depended on individual characteristics and various variables. Previous study reported that fetal loss was 1.7\% in amniocentesis group compared to 0.7\% in the control group\[^{[29]}\]. The lack of control group in this study was a limitation of our study.
Other common complications reported during this procedure were the risk of bleeding, abdominal cramps and amniotic fluid leakage. The risk of fluid leakage following the procedure has been reported as 1%[30]. In this study, 1 case of amniotic fluid leakage during the first 48 hours after amniocentesis was reported. However, after a week, it was controlled with ultrasonography and successful delivery has been noted. Also, pain and vaginal hemorrhage were noted in 0.5% of women and were the most common symptoms after amniocentesis. Two cases of spontaneous abortion in the first trimester of pregnancy occurred in women with a history of hemorrhage in the first trimester. Results showed that the history of vaginal hemorrhage in the first trimester might increase the rate of fetal loss and this significant relation recommended that abnormal fetuses might cause higher rate of hemorrhage and this hypothesis should be evaluated more.

Johnson[24] previously suggested that the complications of amniocentesis related to early phase. Previous investigation mentioned that complications including fluid leakage and vaginal hemorrhage commonly occurred due to early amniocentesis[35]. Also, Jafarieh and colleagues[21] mentioned 3 leakages of amniotic fluid and 5 cases of bleeding after amniocentesis out of 201 women in the second trimester. Seeds et al[31] stated that amniocentesis with ultrasonography guidance could minimize complications of the procedure. Therefore, in this study, all amniocentesis were performed under ultrasonography guidance.

CONCLUSION
In this study, the incidence of spontaneous abortion after amniocentesis was 0.2%. The fetal loss considering the 20 medical abortions because of fetal abnormalities and 2 cases of spontaneous abortion, was 2.6%. The only factors relating with the incidence of fetal loss were the history of malformation in previous pregnancies and vaginal bleeding in the first trimester. Although amniocentesis is a safe procedure in the second trimester, in high-risk women, physicians should inform them regarding the probable complications when counseling patients considering performing one.

The limitation of the present study was the lack of a control group comparing the risks associated with the implementation of the procedure.

ACKNOWLEDGMENTS
Conflict of Interest: Authors declare that they have no conflicts of interest

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REFERENCES


Original Article

The Association of Vitamin D Deficiency with Hypothyroidism

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ABSTRACT

Objective: To identify whether or not there was a correlation between low serum 25(OH)D and hypothyroidism

Design: Retrospective study

Setting: King Abdulaziz University Hospital, from June 2014 to June 2016

Subjects: One thousand and forty-two patients suffering from hypothyroidism were enrolled in this retrospective study and serum 25(OH)D levels were measured in all patients. We divided them into two groups; the first included 373 patients with post radioactive Iodine (RAI) ablation hypothyroidism and the second group included 669 patients with Hashimoto’s hypothyroidism.

Main outcome measures: Vitamin D states in hypothyroid patients

Results: In the first group, 335 patients (90%) were afflicted with vitamin D deficiency and 636 patients (95%) from the second group were afflicted with vitamin D deficiency. Furthermore, it was also found that levels of serum 25(OH)D were lower in the Hashimoto’s group at 13.7 ng/mL in comparison with the post-RAI group at 15.6 ng/mL. There was no significant correlation between the serum thyroid-stimulating hormone (TSH) and the 25(OH)D parameter in patients with post-RAI hypothyroidism as per the Pearson scale reading (r = -0.004, p = 0.94). Similarly, the patients afflicted with Hashimoto’s disease had no significant correlation between their serum 25(OH)D and TSH levels since the Pearson scale read r = -0.04, p = 0.3.

Conclusion: Low serum 25(OH)D levels was found to be common amongst the patients affected with hypothyroidism.

INTRODUCTION

One of the most common illnesses in the Kingdom of Saudi Arabia is thyroid disease, which could be linked to vast numbers of people suffering from a vitamin D deficiency[1,2]. This deficiency is a consequence of many different traditional and cultural traits alongside religious teachings which are followed by the vast majority of the Saudi population. Firstly, traditional factors include the men wearing white clothing, also known as the thobe, to protect themselves from the sun. As for women, religious teachings instruct them to cover up, exposing only their faces and hands, and there are some who even cover up their faces, further reducing the chance for sun exposure. However, perhaps the main cause of the deficiency is the lack of physical activities outdoors, again further reducing their exposure to the sun’s rays[3,4].

Hashimoto’s thyroiditis (HT) is a disorder which arises due to either genetic factors or environmental factors. HT is differentiated from other disorders by its reactivity to the self-thyroid antigens[5]. Hashimoto’s disease is also an autoimmune thyroid disease; furthermore, it has been shown that Vitamin D deficiency has been associated with autoimmune diseases, including autoimmune thyroid disease, systemic lupus erythematosus, multiple sclerosis and type 1 diabetes[6,7]. Therefore, a link could be established between Hashimoto’s disorder and vitamin D deficiency.

Similarly, post radioactive Iodine (RAI) ablative hypothyroidism tended to be more prevalent in patients with Graves disease, which is also an autoimmune disorder, or thyroid cancer treated by RAI[8]. The objective of this retrospective study was to evaluate the association of low serum 25(OH)D and hypothyroidism due to either Hashimoto’s disease or post RAI treatment.

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MATERIALS AND METHODS

To begin with, data was collected from the master database of the Department of Clinical Biochemistry at King Abdulaziz University (KAU) Hospital during the period of two years from June 2014 to June 2016. The data included age, sex, nationality, thyroid function test (TFT), thyroid antibodies, RAI treatment, serum 25(OH)D, calcium, phosphorous, hemoglobin and sodium. All the clinical parameters were measured at the same time or close to the date of serum 25(OH)D measurement.

A total of 1042 patients were enrolled in this retrospective study. They were divided into two groups, the first group which consisted of 373 patients with post-RAI hypothyroidism and the second group comprising of 669 suffered solely from Hashimoto’s disease.

Patients with high titres of serum antithyroid peroxidase (antiTPO) and high antithyroglobulin (antiTG) were diagnosed with Hashimoto’s disorder. As for the post-RAI hypothyroidism, it was diagnosed after receiving RAI treatment for thyroid cancer or Graves disease.

Serum 25(OH)D levels were measured using a semi-automated, solid-phase extraction followed by reverse-phase high-performance liquid chromatography assay. As for the levels of thyroid stimulating hormone (TSH), they were determined using the enzyme-linked immunosorbent assay (ELISA) method. Furthermore, immunocitometry kits were used to measure the antiTPO antibodies of all patients in the same laboratory.

All 1042 patients had TSH values greater than the normal limit ranging from 0.27 to 4.2 IU/mL, and serum levels 25(OH)D < 30 ng/mL.

The exclusion criteria for this study were patients who received vitamin D or calcium supplements and medications that could have interfered with the levels of serum 25(OH)D. The study was approved by the Clinical Research Ethics Committee at KAU.

Statistical Methodology

Firstly, the categorical data was summarized using frequency and percentages, whilst the continuous data was summarized using mean and standard deviation. The independent test was then performed to find out the difference in average of continuous variable in the two groups, whereas the chi-square test of association was used for the categorical variables.

Patients with an odds ratio of 95% confidence interval (CI) were calculated to have a greater risk of vitamin D deficiency alongside hypothyroidism between the two groups.

As for Pearson’s correlation r, it was calculated to find out the strength of the relationship between TSH and other laboratory parameters. If the p-value was less than 0.05, all statistical tests were defined as statistically significant.

Furthermore, a box-plot was drawn to compare the descriptive statistics of vitamin D$_3$ (25(OH)D) among the two groups. For simplification and better understanding, log transformation was done for vitamin D values. A bar graph was drawn to highlight the difference in frequency between the groups. All statistical analysis was carried out using Statistical Packages for Social Sciences (SPSS) version 20.1.

RESULTS

Characteristics of HT versus post-RAI hypothyroidism

The baseline characteristics of the 1042 hypothyroid patients are presented in Table 1. Of the 1042 patients, 669 were diagnosed with Hashimoto’s hypothyroidism, 508 (75.9%) of those patients were females and the median age of the group was 45 years. Furthermore, 357 of the patients (53.5%) were expatriates. The second group consisted of 373 patients with post-RAI hypothyroidism, 283 (75.6%) of them were female with a median age of 42 years. In this group, the majority were also expatriates due to only 196 (47%) of them being Saudi. Statistically speaking, the age difference between the two groups is p > 0.011, which is significant.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hypothyroidism</th>
<th>P - Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Post-radioactive iodine</td>
<td>Hashimotos</td>
</tr>
<tr>
<td>Age a</td>
<td>42 (15)</td>
<td>45 (18)</td>
</tr>
<tr>
<td>Sex b</td>
<td>Male</td>
<td>90 (56)</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>283 (75.6)</td>
</tr>
<tr>
<td>Nationality</td>
<td>Saudi</td>
<td>196 (47)</td>
</tr>
<tr>
<td></td>
<td>Non-Saudi</td>
<td>177 (33)</td>
</tr>
</tbody>
</table>

*: Mean (SD) , b: Frequency (percentage) , * statistically significant with p-value < 0.05

Laboratory abnormalities: HT versus post-RAI hypothyroidism

The mean value of TSH for HT and post-RAI hypothyroidism was 79.2 IU/mL and 77.16 IU/mL respectively; due to the difference being very small, there is no statistically significant difference. However, there was a difference between both groups regarding their FT4 and FT3 figures with the post-RAI group, with a significant p-value < 0.0001. As for the antiTPO and antiTG patients with HT disorder, they incurred high titres with antiTPO at 496 ± 83 and antiTG at 510 ± 129.

The prevalence of vitamin D deficiency was 335 (90%) and 636 (95%) in groups 1 and 2 respectively. Furthermore, the vitamin D levels were lower in the
Hashimoto’s group (13.7) in comparison to the post-RAI group (15.6). However, there was no statistical significance since the p-value was 0.144.

Similarly, there was no significant difference in the sodium, calcium and PO_{4} levels between the two groups. However, the hemoglobin and serum iron were significantly lower in Hashimoto’s group in comparison to the post-RAI group (p-values 0.004 and 0.005, respectively) (Table 2 (A,B), Fig 1).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hypothyroidism [Mean (SD)]</th>
<th>P - Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TSH</td>
<td>79.21 (20.3)</td>
<td>0.143</td>
</tr>
<tr>
<td>25(OH)D</td>
<td>15.62 (20.4)</td>
<td>0.144</td>
</tr>
<tr>
<td>HB</td>
<td>11.01 (06.3)</td>
<td>0.001*</td>
</tr>
<tr>
<td>Iron</td>
<td>1.01 (03.7)</td>
<td>0.005*</td>
</tr>
<tr>
<td>Na</td>
<td>111.3 (52.7)</td>
<td>0.051</td>
</tr>
<tr>
<td>Ca</td>
<td>1.6 (0.9)</td>
<td>0.39</td>
</tr>
<tr>
<td>PO_{4}</td>
<td>0.78 (5.2)</td>
<td>0.39</td>
</tr>
</tbody>
</table>

* statistically significant with p-value < 0.05

TSH: thyroid-stimulating hormone; 25(OH)D: 25-hydroxy-vitamin D; HB: haemoglobin; Na: sodium; Ca: calcium; PO_{4}: phosphate

To begin with, the Chi-square test of association was used to figure out the categorical variables (Table 3). Patients with an odds ratio with 95% CI were associated to having a greater risk of vitamin D deficiency. However, the odds ratio for normal level of 25(OH)D in the two groups at 95% CI ranged from 0.2 to 0.78, with a significant p-value of 0.002.

The relation between serum 25 (OH)D and the TSH parameters in patients with post-RAI hypothyroidism was not statistically significant due to the Pearson r being at -0.004, and the p-value at 0.94. Correspondingly, patients with HT disorder did not have a strong correlation between serum 25(OH)D and TSH due to the statistics of Pearson r being at -0.04 and the p-value at 0.3. Similarly, there was no significant relationship observed between TSH and the haemoglobin, sodium and calcium parameters. However, in the Hashimoto’s group, there was a significant correlation between the TSH and PO_{4} values with the Pearson r value at -0.085.

DISCUSSION

Vitamin D deficiency is a global health problem with an estimate of over one billion people worldwide suffering from the deficiency\[9\]. Here in Saudi Arabia, the deficiency is one of the most common disorders faced by both males and females. It has even been reported by the Ardawi Group, that in Saudi Arabia,
In many recent studies, the relationship between the serum 25(OH)D levels and the autoimmune thyroid disorder has been thoroughly investigated[12,13]; and our aim was to investigate whether or not an association of low serum 25(OH)D (Vitamin D), and hypothyroidism, either due to Hashimoto’s disease or post-RAI ablation treatment, existed.

The data provided from the patients at KAU supported the association between the low serum 25(OH)D and hypothyroidism. The logistic regression model for the categorical data confirmed that in both groups 1 and 2, there was a relationship between the two disorders due to a significant p-value at <0.002. However, in all our patients, no significant correlation was observed between TSH and 25(OH)D, haemoglobin, sodium and calcium parameters.

Such a relationship between low levels of vitamin D and HT or post-RAI hypothyroidism was also established in many other researches. Recently, there were many studies which established a correlation between low levels of vitamin D and Graves’ disease[14,15], as well as HT[16,17]. However, fewer studies provided an association between low levels of 25(OH)D and thyroid cancer[18].

Overall, our data supports the thesis statement and provides evidence for an association between low serum 25(OH)D and hypothyroidism, either due to Hashimoto’s disease or post RAI ablation treatment of thyroid cancer or Graves’ disease, in the western region of the Kingdom of Saudi Arabia. However, such an association may not be due to a link between the two disorders but rather a consequence of overt hypothyroidism which causes malabsorption of 25(OH)D. Another factor which may trigger both the disorders simultaneously could be due to the lack of sun exposure in the country, causing a vitamin D deficiency in the majority of the citizens, even those who do not suffer from a thyroid disorder[19,20].

The study acknowledges several limitations; firstly and most importantly, this was a retrospective and cross-sectional study. Secondly, due to the fact that it is a retrospective study, we were not able to distinguish and adjust the analysis accordingly to the actual cause of the vitamin D deficiency, whether it is due to nutrition, or even a lack of sun exposure. Nonetheless, the study has much strength which includes a large sample of patients whose serum 25(OH)D was measured at a given time frame and in one institution, which removes a selection bias and increases the generalization of present results.
CONCLUSION
Regardless of any environmental factors, vitamin D deficiency is overwhelmingly common amongst patients with hypothyroidism at King Abdulaziz University Hospital. Moreover, although FT3 and FT4 established a strong relationship with serum 25(OH)D, there was no significant correlation between TSH and the serum 25(OH)D parameter.

Irrespective of the cause of hypothyroidism, we recommend hospitals to measure the vitamin D levels that the patients have due to the exceptionally strong link between the two, as seen in this study.

ACKNOWLEDGMENTS
I acknowledge all the hard work, time and effort which Miss Khawlah Al Nujaifi has poured into this study. In addition, the work and time which Mrs. Ching and Mrs. Jasamin have dedicated to this study in collecting the data is much appreciated. I would also like to take a moment to thank the Deanship of Scientific Research, King Abdulaziz University, Jeddah, Kingdom of Saudi Arabia for supporting and funding this project. I would finally like to thank Mrs. Shamna Safar for her statistical analysis, which contributed a great deal to this study.

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No disclosure: The article was not presented at any conference.

REFERENCES
The Possible Protective Role of Vitamin D against Allergic Rhinitis in Saudi Adults

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ABSTRACT

Objective: Several novel roles for Vitamin D have emerged. Besides its role in bone mineralization, it has a protective role against cancer, diabetes mellitus, multiple sclerosis, and immunological disorders. Our aim is to determine the possible role of vitamin D against allergic rhinitis in Saudi adults.

Design: A cross-sectional study. Patients were asked to answer a questionnaire and blood samples were collected to analyze vitamin D level, 25(OH) D, blood count, and renal profile.

Setting: Department of Otorhinolaryngology, King Abdulaziz University Hospital, King Saud University, Saudi Arabia

Subjects: A total of 976 patients from 1 January to 30 September, 2014

Intervention: Data on age, gender and blood samples of patients were obtained. Continuous variables were described as means ± standard deviation (SDs). Categorical variables were described as frequency and percentage. Chi-square test and logistic regression analysis were performed to determine the odds for allergic rhinitis.

Main Outcome Measures: Vitamin D level

Results: The mean vitamin D level was 43.3 ± 3.17 ng/ml. Vitamin D deficiency (vitamin D < 10 ng/ml) was present in 51 (5.2%) participants, and vitamin D insufficiency (vitamin D: 10.1 - 29.9 ng/ml) was present in 634 (65%) while 291 (29.8%) patients were normal. Allergic rhinitis was present in 221 (22.7%) patients and they had significantly lower levels of vitamin D than those without rhinitis (21.57 ± 2.84 vs. 46.66 ± 3.076, p = 0.001).

Conclusion: There is a potential association between Vitamin D level and allergic rhinitis in Saudi adults. Further studies are needed to evaluate the effect of Vitamin D supplementation on prevention or progress of allergic rhinitis.

INTRODUCTION

Interest in vitamin D is expanding worldwide due to its immense protective role against cardiovascular diseases (CVD)[1], diabetes mellitus (DM)[2], cancer[3], immunological disorders[4], allergic conditions[5], and multiple sclerosis[6], in addition to its role in bone mineralization and the prevention of bone fractures[7]. Several recent studies have shown the association of vitamin D deficiency with bronchial asthma and atopic dermatitis[8-10]. However, the association of vitamin D and allergic rhinitis is less defined. There are no studies on the correlation of vitamin D deficiency and allergic rhinitis in this region. Allergic rhinitis is a frequent and troublesome condition that reduces quality of life, increases sleep disturbance, and decreases working capacity of a patient[11]. The prevalence of allergic diseases, including allergic rhinitis, is increasing due to the increase in environmental allergens caused by urbanization and food allergens[12]. Further, recent studies have proposed an association between vitamin D deficiency and allergic disorders. Vitamin D influences allergy-mediating immune cells, such as T-cells, and immune functions of cells that form a barrier against allergens, for example epithelial cells. Similarly, vitamin D affects several aspects of innate immunity. Vitamin D affects allergy-mediating cells, such as mast cells, and increased levels of vitamin D can increase IL -10, which suppresses inflammation[13-16].

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Vitamin D deficiency is frequent in KSA, despite the availability of plenty of sunshine throughout the year, due to local traditions of covering the entire body with clothes and very limited outdoor activities in the sun, especially for females [17]. Comprehensive studies regarding the link between vitamin D and allergic rhinitis are lacking from this region. Since vitamin D deficiency is a modifiable risk factor and can be easily corrected, vitamin D supplementation may have a great public health benefit. The present study aims to correlate vitamin D levels and allergic rhinitis in Saudi adults.

**SUBJECTS AND METHODS**

The present study was a cross-sectional study conducted from 1 January to 30 September, 2014 after Institutional Research Board approval at King Saud University (E-14-978). A total of 976 patients consented to participation. The usefulness and purpose of the study was explained to the participants. A questionnaire regarding their socio-demographic details, dietary habits, degree of sun exposure (including both total time per day and frequency of such exposure per week), and symptoms of rhinitis (e.g., runny nose, nasal blockade, post-nasal drip, nasal obstruction, and smell impairment) was also explained. The presence of other co-morbidities, such as DM, hypertension (HTN), and bronchial asthma were recorded. Blood samples were collected by trained phlebotomists to analyze the levels of vitamin D, blood calcium, total blood count, liver profile, and renal profile.

**RESULTS**

A total of 1023 patients were included in the current study. However, after data cleaning and management, 47 patients were excluded either because of missing or inconvenient data or for not fulfilling the inclusion criteria. Thus, the final study sample was 976 patients (566 male (58%) and 410 female (42%)). The socio-demographic characteristics of the study population is given in Table 1. The mean age of patients was 33.95 ± 8.1 years while the mean BMI was 23.96 ± 5.9 kg/m². Among the recruited sample, 192 (19.7%) patients were diabetic, and 258 (26.5%) were hypertensive. The mean creatinine, calcium and albumin levels were 70.4 ± 16.9 mm/l, 2.3 ± 2.2 mmol/l, and 41.9 ± 5.1 g/liter, respectively.

Table 1: The socio-demographic characteristics of the study population

<table>
<thead>
<tr>
<th>Variables</th>
<th>Category</th>
<th>Number (n, %)</th>
<th>Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
<td>33.95 ± 8.1</td>
</tr>
<tr>
<td>Gender</td>
<td>Male</td>
<td>566 (58%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>410 (42%)</td>
<td></td>
</tr>
<tr>
<td>Body mass index</td>
<td></td>
<td></td>
<td>23.96 ± 5.9</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Present</td>
<td>258 (26.5%)</td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>Present</td>
<td>192 (19.7%)</td>
<td></td>
</tr>
<tr>
<td>Bronchial asthma</td>
<td>Present</td>
<td>18 (1.8%)</td>
<td></td>
</tr>
<tr>
<td>Vitamin D level - all patients</td>
<td></td>
<td></td>
<td>43.3 ± 31.7</td>
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<tr>
<td>Vitamin D level - lower quartile</td>
<td></td>
<td></td>
<td>15.8 ± 5.8</td>
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<tr>
<td>Vitamin D level - upper quartile</td>
<td></td>
<td></td>
<td>21.57 ± 28.4</td>
</tr>
<tr>
<td>Vitamin D level in allergic rhinitis group</td>
<td></td>
<td>46.66 ± 30.76</td>
<td></td>
</tr>
<tr>
<td>Vitamin D level in control group</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prevalence of allergic rhinitis</td>
<td>Present</td>
<td>221 (22.7%)</td>
<td></td>
</tr>
</tbody>
</table>

Table 2: Vitamin D levels in the study population.

<table>
<thead>
<tr>
<th>Vitamin D Grading</th>
<th>Vitamin D level (ng/ml)</th>
<th>n(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin D deficiency</td>
<td>&lt; 10</td>
<td>51 (5.2)</td>
</tr>
<tr>
<td>Vitamin D insufficiency</td>
<td>10.1 - 29.9</td>
<td>634 (65)</td>
</tr>
<tr>
<td>Vitamin D normal</td>
<td>&gt; 30</td>
<td>291 (29.8)</td>
</tr>
</tbody>
</table>

An inverse relationship was found between vitamin D status and allergic rhinitis. The patients with allergic rhinitis had significantly lower levels of vitamin D than the patients without rhinitis. The mean vitamin D level was 21.57 ± 2.84 ng/ml in patients with allergic rhinitis vs. 46.66 ± 3.076 ng/ml in normal controls without allergic rhinitis (p = 0.001).

Table 3 shows the correlates of allergic rhinitis. Conduct of multivariate analysis (binary logistic regression) kept allergic rhinitis as a dependent variable.
body. VDRs are activated by 1,25(OH)2 D3 and are found on and in most cell types and tissues of the body. Vitamin D receptor (VDR) and α-1-hydroxylase have been found to improve these allergic conditions, indicating that studies are underway to evaluate whether vitamin D supplementation can improve the outcomes of allergic rhinitis.

Michelle B. Lierl indicated that studies are underway to evaluate whether vitamin D supplementation can improve these allergic conditions. Vitamin D receptors are located on lymphocytes and affect expression of over 200 genes, up regulating nearly two-thirds and down regulating one-third of those genes. Therefore, VDRs found in different alleles have different effects. A mutated VDR in hereditary vitamin D-resistant rickets prevents induction of bronchial hyperreactivity and inflammation. VDR Apal a allele is associated with better childhood asthma control and improvement in ability for daily activities. Overall, these findings made us study vitamin D’s role on asthma and allergic disease development. In a 2014 study, vitamin D supplementation clinically improved the natural course of allergic rhinitis.

The present study revealed a high prevalence of allergic rhinitis in the study population (22.7%). Compared to other studies, the prevalence of allergic rhinitis in the present study was almost the same but was slightly more prevalent in females than in males. The present study revealed a definite and significant correlation of the study variables to allergic rhinitis.

Table 3: Correlation of the study variables to allergic rhinitis

<table>
<thead>
<tr>
<th>Variables</th>
<th>Odd Ratio</th>
<th>95% Confidence Interval (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin D deficiency</td>
<td>3</td>
<td>1.9 - 4.7</td>
</tr>
<tr>
<td>Females</td>
<td>1.6</td>
<td>1.1 - 2.3</td>
</tr>
<tr>
<td>Age &gt; 40 years</td>
<td>1.5</td>
<td>1.0 - 2.3</td>
</tr>
<tr>
<td>Body mass index &gt; 30</td>
<td>1.3</td>
<td>1.09 - 1.7</td>
</tr>
</tbody>
</table>

DISCUSSION

Due to the recent tremendous increase in environmental and food allergens, proper and effective allergy prevention has become a mandatory public health priority. Allergic rhinitis, asthma, and other allergic disorders are major healthcare problems. Worldwide, allergic rhinitis is often underdiagnosed, though it often leads to asthma and greatly reduces quality of life. Sleep disturbances lead to reduced work performance. Vitamin D deficiency is also a global issue. Recent studies have shown that vitamin D deficiency is a potential contributor to allergic diseases. Vitamin D receptors are located on lymphocytes. In 2014, Michelle B. Lierl indicated that studies are underway to evaluate whether vitamin D supplementation can improve these allergic conditions. Vitamin D directly acts on activated helper T, B and regulatory T cells. Vitamin D receptor (VDR) and α-1-hydroxylase have been found on and in most cell types and tissues of the body. VDRs are activated by 1,25(OH)2 D3 and affect expression of over 200 genes, up regulating nearly two-thirds and down regulating one-third of those genes. Therefore, VDRs found in different alleles have different effects. A mutated VDR in hereditary vitamin D-resistant rickets prevents induction of bronchial hyperreactivity and inflammation. VDR Apal a allele is associated with better childhood asthma control and improvement in ability for daily activities. Overall, these findings made us study vitamin D’s role on allergic rhinitis.

LIMITATIONS

The diagnosis of allergic rhinitis on the study population depends on typical history and nasal examination. No laboratory test for allergy was taken.

CONCLUSION

The present study revealed a correlation between vitamin D levels and allergic rhinitis in Saudi adults. The study showed a possible protective role of vitamin D against allergic rhinitis in Saudi adults. This finding has therapeutic value. Vitamin D is a widely available, safe, and affordable product. Vitamin D supplementation can be an attractive intervention to protect high-risk patients from allergic rhinitis. However, several trials are needed before its implementation, and frequent screening of vitamin D status is needed in high-risk patients.

ACKNOWLEDGMENT

I would like to thank my co-doctors from King Abdullah University Hospital who provided insight and expertise that greatly assisted the research.

I express my deepest thanks to Dr. Mohammed Saddiqi and Dr. Falah Syouri for assistance in diagnosing the study population and to Mr. Ahmed Mousa for the statistical analysis of the data. Without their help, this research could not have been completed.
them, this work may not have been completed. I am also grateful to Ms. Norjanah Dimatunday for her help in checking and editing the required format of this article.

Again, I humbly extend my thanks to all concerned persons who cooperated with me in this article.

REFERENCES

Comparison of the Postoperative Analgesic Effects of Morphine, Paracetamol and Ketorolac in Patient-Controlled Analgesia (PCA) in Patients undergoing Open Cholecystectomy

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ABSTRACT

Objectives: Effective post-operative pain management in abdominal surgeries which are painful procedures, plays an important role in reducing post-operative complications and increasing patient’s satisfaction. There are many techniques for pain control, one of which is patient-controlled analgesia (PCA). The aim of this study was to compare the analgesic effects of morphine, paracetamol and ketorolac in patients undergoing open cholecystectomy, using PCA method.

Design: Randomized controlled trial

Setting: Department of anesthesiology, Shahid Rajaee Hospital, Qazvin, Iran

Subjects: Three hundred and thirty ASA (American Society of Anesthesiology) I-II patients (three equal groups of n = 110) who were scheduled for elective open cholecystectomy.

Intervention: The control group received morphine with maximum dose of 0.02 mg/kg/h, the paracetamol group received paracetamol with maximum dose of 1 mg/kg/h, and the ketorolac group received ketorolac with maximum daily dose of 60 mg using IV-PCA method.

Main outcome measure: Post-operative pain

Results: There were no significant differences in demographic data between the three groups. There was a statistically significant difference with regard to the mean pain score at all times between morphine and paracetamol, morphine and ketorolac, and paracetamol and ketorolac groups (p < 0.001). The mean level of pain in ketorolac group was less than that in the other two groups (p < 0.001) at all times.

Conclusion: According to the results of this study, ketorolac is more effective than morphine and paracetamol in post-operative pain control.

KEYWORDS: analgesia, cholecystectomy, ketorolac, morphine, paracetamol

INTRODUCTION

Post-operative pain is the most common surgical complication, and is experienced by more than 70% of patients after surgery[1]. It is essential to control post-operative pain. It is often difficult to achieve an acceptable analgesia following a surgery with minimal side effects[2]. Various studies have described several undesirable effects of pain with maximum physiological effects on the body systems which include adrenal sympathetic activity, reduced blood flow to coronary arteries, deep vein thrombosis, inadequate depth of breathing, atelectasis, increased heart rate and blood pressure. Post-operative pain management leads to reduced mortality, length of hospital stay and costs, as well as early ambulation. Accordingly, management and control of pain is always regarded as a professional challenge[3-5]. There are several post-operative analgesic techniques, including local injection of anesthetics, nerve blocks, administration of systemic opioids, non-steroidal anti-inflammatory drugs (NSAIDs), intrathecal methods, epidural and patient-controlled analgesia (PCA)[6-8]. Intravenous PCA is a highly effective pain-reducing method with minimal side effects. Today, IV-PCA with

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morphine is recognized as an essential component of post-operative analgesia. In this method, morphine is the drug of choice. Some studies have shown that infusion dose of opioids causes respiratory depression, drowsiness and sedation, nausea and vomiting, pruritus, urinary retention, ileus and constipation and because of the respiratory events it is vital to monitor the patient\textsuperscript{10-12}. These undesirable side effects urged investigators to search for some other analgesic drugs. Intravenous acetaminophen (paracetamol) is one of the new strategies used for post-operative pain management. It is used for managing mild to moderate pain\textsuperscript{13-14}. NSAIDs are another class of analgesics used in some studies\textsuperscript{15}. Ketorolac and other NSAIDs have a powerful anti-inflammatory, analgesic, and antipyretic effect by inhibiting cyclooxygenase I and cyclooxygenase II and effectively control mild to moderate post-operative pain\textsuperscript{16,17}. Since ketorolac can be administrated intravenously, and serious complications such as respiratory and cardiovascular suppression was not seen, it has been used for post-operative pain control, alone or by mixing it with opioids through the PCA method\textsuperscript{18,19}. In recent years, several studies have compared the analgesic efficacy of patient-controlled morphine with paracetamol, but no such comparision has been performed with ketorolac. Considering the importance of post-operative pain control, IV-PCA as a beneficial method, and morphine's complications described above, we compared the analgesic efficacy and side effects of morphine, paracetamol and ketorolac administered by PCA method for post-operative pain management after open cholecystectomy in this study.

SUBJECTS AND METHODS
This randomized controlled clinical trial was registered in Iranian Registry of Clinical Trials (IRCT) with number 2014031717048N1. Written informed consent was obtained from all patients and they were informed about the visual analog scale (VAS) and PCA during the pre-operative visits. The study was performed on 330 patients in Shahid Rajaee Hospital of Qazvin, Iran from August 2013 until September 2015.

Inclusion criteria were patients aged between 20 and 50 years, ASA (American Society of Anesthesiology) class I-II and elective open cholecystectomy with Kokher incision. Exclusion criteria were inability to be trained to use the PCA pump, psychiatric illnesses, bronchial asthma, renal or hepatic disease, BMI ≥ 30, addiction, allergic reactions to opioids or paracetamol or other NSAIDs, cardiovascular disease, history of peptic ulcer and gastrointestinal bleeding, and routine analgesic consumption.

The technique of general anesthesia was similar in three groups. After standard monitoring including electrocardiography, pulse oximetry and non-invasive blood pressure monitoring, all patients were pre-medicated with midazolam (0.02 mg/kg) and fentanyl (2 µg/kg). Anesthesia was induced with propofol (2 mg/kg) and atracurium (0.5 mg/kg) and maintained with propofol (100 µg/kg/min) and remifentanil (0.4 µg/kg/min) and atracurium (0.15 mg/kg) was injected every 30 minutes. At the end of the surgery, the effects of the muscle relaxant were reversed using atropine (0.02 mg/kg) and neostigmine (0.04 mg/kg). After transfer to post-anesthesia care unit and achieving full consciousness, patients were randomly divided into three groups of 110 patients each to receive morphine (control group) and paracetamol or ketorolac (intervention groups). Assignment of patients into three groups was implemented using blocked randomization. One group received morphine sulphate (Daroupakhsh, Iran) with maximum dose of 0.02 mg/kg/h, another group received paracetamol (Unipharma, Greece) with maximum dose of 1 mg/kg/h, and the last group received ketorolac (Sinadauro, Iran) with maximum daily dose of 60 mg using IV-PCA method. The level of pain was assessed by VAS (0 = no pain, 10 = the most intense pain). Simultaneously with pain intensity, the presence and severity of nausea, patient's satisfaction (VAS), heart rate (HR) and blood pressure (BP) changes, subsequent itching and respiratory problems after using morphine, paracetamol, and ketorolac were recorded by a third person (trained colleague) every 2 hours for 8 hours post-operatively. Changes in HR and BP ≤20% baseline were considered as low, 20 - 40% moderate and > 40% were considered as high. Data were analyzed using SPSS 17 software. Demographic data were analyzed by one way ANOVA, and for comparison of group differences, we used the Kruskal-Wallis test. P-value < 0.05 was considered statistically significant.

RESULTS
We followed the CONSORT (Consolidated Standards of Reporting Trials) guidance for reporting results (Fig 1).

<table>
<thead>
<tr>
<th>Drug</th>
<th>Age</th>
<th>Gender (Female/Male)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine (n = 110)</td>
<td>37.15 ± 5.42</td>
<td>58/52</td>
</tr>
<tr>
<td>Paracetamol (n = 110)</td>
<td>39.27 ± 7.57</td>
<td>58/52</td>
</tr>
<tr>
<td>Ketorolac (n = 110)</td>
<td>37.21 ± 8.99</td>
<td>48/62</td>
</tr>
<tr>
<td>P-value</td>
<td>0.112</td>
<td>0.162</td>
</tr>
</tbody>
</table>

Table 1: Demographic characteristics in the three groups (mean ± standard deviation)
In this study, data obtained from 330 patients (110 in each group), aged 20 to 50 years, undergoing elective open cholecystectomy were analyzed. There were no significant differences in demographic data between the groups (Table 1).

As can be seen from Table 2, according to VAS, there was a statistically significant difference regarding the mean pain score at all hours between morphine and paracetamol, morphine and ketorolac, and paracetamol and ketorolac groups (p < 0.001). Post-operative pain scores decreased significantly with time in all three groups. At all times, the mean level of pain in ketorolac group was less than that in the other two groups.

According to Table 3, there were significant differences in changes in level of nausea at all hours between morphine and paracetamol and morphine and ketorolac groups (p < 0.001). In addition, there were significant differences between paracetamol and ketorolac groups only after 2 and 4 hours (p < 0.001).

As shown in Table 4, there were significant differences in patient’s satisfaction at all hours between morphine and paracetamol, morphine and ketorolac, and paracetamol and ketorolac groups (p < 0.001). Mean satisfaction in all three groups increased with time, and at all 4 data collection times, mean satisfaction was greater in ketorolac group.
According to Table 5, there were significant differences in changes in HR at all times between morphine and paracetamol and morphine and ketorolac groups (p < 0.001). Moreover, there were significant differences between paracetamol and ketorolac groups only after 2 and 8 hours (p < 0.001).

It can be seen from Table 6 that there were significant differences in changes in BP at all times between morphine and paracetamol and morphine and ketorolac groups (p < 0.001). In addition, there were significant differences between the paracetamol and ketorolac groups only after 6 and 8 hours (p < 0.001).

High changes in BP and HR were seen only in one patient in morphine group after 2 hours and not seen in other groups and times.

In this study, patients were also examined for presence of itching after 2, 4, 6, and 8 hours, and only one patient in morphine group complained of itching after 2 hours (2.9%). Furthermore, the three groups were assessed in terms of arterial oxygen desaturation using pulse-oximetry, and no arterial oxygen desaturation below 90% was reported.

**DISCUSSION**

Effective post-operative pain management is a major concern for anesthesiologists. Use of opioids for post-operative pain control has several side effects such as respiratory depression, nausea and vomiting, pruritus and urinary retention. Therefore, the use of non-opioids such as NSAIDs has become more popular to avoid these side effects. NSAIDs and acetaminophen (paracetamol) are commonly used in the management of mild to moderate pain alone or in combination with opioids.

In the current study, comparison of analgesic effects of morphine, paracetamol and ketorolac infusion after elective cholecystectomy was performed and the efficacy of ketorolac was approved. There have been many studies conducted in recent years on post-operative analgesia using various drugs and methods. Various studies have compared ketorolac with opioids. The findings range from ketorolac being more effective than opioids to being equally effective or to being less effective than opioids. According to the study of Taghavi Gilani, intravenous paracetamol added to morphine PCA for post-operative pain management decreases morphine intake and leads to better consciousness level without further complications. In the study of Alimian where analgesic effects of paracetamol and morphine after elective laparotomy surgeries were compared, significant difference in pain score was found between the two groups in the first 8 hours.

In the other study, Yaghoubi showed that morphine had superior analgesic effect than paracetamol 2 and

| Table 4: Mean patient’s satisfaction in three groups according to VAS at different hours (mean ± standard deviation) |
|-----------------|-----------------|-----------------|-----------------|-----------------|
| Drug            | After 2 hours   | After 4 hours   | After 6 hours   | After 8 hours   |
| Morphine (n = 110) | 5 ± 1.07        | 4.96 ± 0.95     | 5.04 ± 0.99     | 5.10 ± 1.01     |
| Paracetamol (n = 110) | 5.77 ± 0.99     | 6.99 ± 0.59     | 7.35 ± 0.67     | 7.53 ± 0.71     |
| Ketorolac (n = 110)  | 7.26 ± 0.89     | 8.13 ± 0.77     | 8.59 ± 0.63     | 8.72 ± 0.58     |
| P-value               | < 0.001         | < 0.001         | < 0.001         | < 0.001         |

| Table 5: Changes in heart rate in the three groups |
|-----------------|-----------------|-----------------|-----------------|-----------------|
| Drug            | After 2 hours   | After 4 hours   | After 6 hours   | After 8 hours   |
| Morphine (n = 110) | 14 (12.7)       | 76 (69.1)       | 99 (90)         | 110 (100)       |
| Paracetamol (n = 110) | 77 (70)        | 110 (100)       | 110 (100)       | 110 (100)       |
| Ketorolac (n = 110)  | 104 (94.5)      | 109 (99.1)      | 110 (100)       | 110 (100)       |

| Table 6: Changes in BP in the three groups |
|-----------------|-----------------|-----------------|-----------------|-----------------|
| Drug            | After 2 hours   | After 4 hours   | After 6 hours   | After 8 hours   |
| Morphine (n = 110) | 17 (15.5)       | 93 (84.5)       | 99 (90)         | 110 (100)       |
| Paracetamol (n = 110) | 107 (97.3)     | 110 (100)       | 110 (100)       | 110 (100)       |
| Ketorolac (n = 110)  | 110 (100)       | 110 (100)       | 110 (100)       | 110 (100)       |
4 hours after laparotomy, but after 6 and 8 hours they had similar effects[26]. In another study, morphine was a more efficacious analgesic than ketorolac for postoperative pain[23]. In the research conducted by Unlugenc, the analgesic effect and side effects of IV patient-controlled morphine, pethidine, and tramadol for post-operative pain management were compared and all the three drugs resulted in equivalent pain scores and side effects[27]. The reason for these discrepant results could have been related to the sample size, the moment of evaluation, the duration of follow-up, genetic variations and different responses to drugs and non equianalgesic dose used for drugs. The results of the present study showed that PCA-induced analgesia in ketorolac group was superior than paracetamol and morphine groups. Every factor studied, including nausea, patient’s satisfaction and hemodynamic changes, favored ketorolac compared with other groups.

CONCLUSION
According to the results of this study, we can explain that ketorolac provides superior analgesia compared to morphine and paracetamol for post-operative pain management.

REFERENCES


Original Article

The Prevalence of Urinary Incontinence among Women with Chronic Physical Diseases and their Coping Behaviours: A Turkish Case Study

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¹Department of Midwifery, Faculty of Health Sciences, Cumhuriyet University, Sivas, Turkey
²Department of Internal Diseases Nursing, School of Susehri Health High, Cumhuriyet University, Sivas, Turkey
³Department of Internal Diseases Nursing, Faculty of Healthy Science, Biruni University, Istanbul, Turkey

ABSTRACT

Objective: The study was conducted with the aim of identifying the prevalence of urinary incontinence (UI) among women with chronic physical diseases and the coping behaviours of women suffering from UI in Turkey.

Design: A cross-sectional and comparative study

Setting: The study was conducted at the general internal medicine, endocrinology, cardiology, neurology, and pulmonology clinics of the Cumhuriyet University Research and Implement Hospital, Turkey.

Subjects: Two hundred and fifty-seven female inpatients

Main Outcome Measure: The relevant data were collected through the use of a patient diagnosis form, the International Incontinence Consultation Questionnaire – Short Form, and the coping behaviours identification form.

Results: The rates of the women who experienced UI at least once a week was 78.9%. Only 54.6% of women with UI applied at a healthcare institution for UI-related complaints. The most common coping behaviours observed among the women with UI include working around the condition by using a pad or rag (77.3%), keeping feet warm (62.6%), and changing underwear (59.6%).

Conclusion: Turkish women with chronic physical diseases were identified to suffer more frequently from urinary incontinence than women in other cultures. As a finding similar to other cultures, Turkish women were observed to employ such personal behaviours as using pads or rags, keeping feet warm, and changing underwear to cope with UI. Health professionals should check for and treat UI in addition to chronic disease management.

INTRODUCTION

Urinary incontinence (UI) is defined by the International Continence Society (ICS) as involuntary leakage of urine, which is a social and hygienic problem that is objectively demonstrated[1]. Urinary incontinence is classified into three groups, namely stress (SUI), urge (UUI), and mixed (MUI)[2,3]. Even though UI is observed at a rate 2 - 3 times higher among women than among men[4,5], most women do not express this problem. Specifically in the Muslim culture encompassing such countries as Turkey, religious restrictions and shyness causes UI to be discussed or addressed to a lesser extent[6]. The prevalence of UI among women is specified to be 16.1% - 68.8% in Europe[7], 41.7% in Australia[8], 30.9% in China[9], and 17% in France[10]. Studies conducted in Turkey report the prevalence of UI among women to be in the range of 16.4% - 68.8%[11-14].

The occurrence of UI is reported to be due to the influence of a number of factors. These risk factors include age, menopause, parity, obesity, vaginal birth, newborn weighing over four kg, history of hysterectomy, body mass index (BMI), chronic diseases[15,16], history of chronic constipation, genetic predisposition, use of such drugs as diuretics, caffeine consumption, smoking, and physical exercise[15,17]. All of these risk factors cause pelvic support defects and pelvic floor dysfunction, thereby setting the stage for UI[3].
Women who are not able to receive healthcare services for various reasons have developed simple and economic coping terms to manage UI\[^{18}\]. Most women have recourse to such behaviours as going to the restroom before leaving home, using pads, or carrying extra clothing with them\[^{15}\]. In addition, women are forced to use certain restrictive practices in their life styles including limiting water consumption, refraining from going to places without restrooms, refraining from physical activity, and limiting social activities and relations\[^{19}\]. Therefore, understanding the coping behaviours employed by women suffering from UI is of great importance in terms of providing effective care to patients\[^{16}\].

Considering its prevalence and impact, UI may deteriorate the quality of life further for women suffering from chronic physical diseases\[^{20,21}\]. The literature encompasses studies pertaining to the co-prevalence of UI with a number of chronic physical diseases\[^{6,20-24}\], and to remedy-seeking behaviours\[^{15,16,18,25-28}\]. However, the limited number of studies, differences in subject population, and wide range of evaluation methods used in Turkey have led to a situation where the prevalence of UI among women suffering from chronic diseases is not known for certain. Furthermore, there is only a limited number of studies in the literature examining the coping behaviours employed by Turkish women in the presence of UI in comparison with women in other cultures\[^{15,16,28}\]. Thus, the present study was conducted with the aim of establishing the prevalence of UI and relevant risk factors among women suffering from chronic diseases and identifying their behaviours to cope with UI.

### SUBJECTS AND METHODS

#### Sample
The universe of this cross-sectional and comparative research study included 342 female in-patients admitted to the general internal medicine, endocrinology, cardiology, neurology, and pulmonology clinics of a state hospital for any chronic disease between 16\(^{th}\) February and 30\(^{th}\) April, 2015. The study sample composed of 257 female patients without any restrictions to verbal communication, with a sufficient cognitive level, without genetic predisposition to UI, and without any urinary system anomalies or diseases or a history of medicinal use, who had been diagnosed with a chronic physical disease at least in the last six months and who had consented to taking part in the study.

#### Materials
The relevant data were collected through the use of a patient diagnosis form, the International Incontinence Consultation Questionnaire – Short Form, and the coping behaviours identification form.

The patient diagnosis form consists of 22 questions concerning socio-demographic characteristics (age, sex, etc.), prevalent disease (name and term of the disease, etc.), and conditions that may lead to UI (number and form of births, menopausal status, etc.).

The International Consultation on Incontinence Questionnaire Short Form (ICIQ-SF) is a scale utilised with the aim of establishing the quantity, frequency and type of urinary incontinence well and demonstrating the extent to which urinary incontinence affects the quality of life of affected individuals. ICIQ-SF is quite a comprehensible and practical question form whose reliability and validity in Turkish has been established by Cetinel et al\[^{29}\]. ICIQ-SF includes 6 questions, three of which (3\(^{rd}\), 4\(^{th}\) and 5\(^{th}\) questions) are added to identify the score (minimum 3 and maximum 21). The 1\(^{st}\) and 2\(^{nd}\) questions in the ICIQ-SF question form pertain to age and sex and the 6\(^{th}\) question to the times when urinary incontinence is observed. The Cronbach-alpha reliability coefficient of the scale was determined to be 0.94 in this study.

The coping behaviours identification form is a 15-question form prepared by the authors in line with their literature review\[^{15,16,27,28}\]. This form was applied only to female patients with UI who were asked to mark the behaviour(s) employed by women to cope with urinary incontinence. Content validity was used for ensuring the validity of the form by obtaining the opinions of two urologists and three nurse academicians. The validity and comprehensibility of the form was tested in a pilot study with a sample group of 20 women. During the pilot study, content validity of the form was investigated, and similar questions were excluded. In addition, the form was administered to the women three weeks later, and the test-retest reliability of the measure was checked. The Cronbach alpha value of the form was found to be 0.93 (moderate = 0.88 - 0.94). All ambiguities were corrected before the administration of the form to the final sample. The evaluation of their results indicated no problems in terms of the clarity and the implementation of the form.

#### Procedures
The relevant data were collected by the authors through face-to-face interviews held in a separate room without any other persons present in an environment that lends itself to a private interview with the patient in order to protect patient confidentiality. The authors provided the patients with information on the aim and importance of the study. The completion of study forms took approximately 20 - 25 minutes.
Ethical dimension
Written permission was obtained from the ethics board of Cumhuriyet University (Decision No.: 2014-11/08) before the collection of data. In addition, information concerning the contents of the study and the voluntary nature of participation was imparted to every woman that would take part in the study and in turn, their written consent was obtained. The study was conducted in accordance with the ethical standards of the Helsinki Declaration.

Statistical analysis
The data were interpreted in the SPSS 23.0 software package. The breakdown of the demographic and disease-related characteristics of women was specified through the use of the distribution for average, standard deviation, and percentage. The comparison of descriptive and disease-related characteristics of women with or without UI was undertaken through the utilisation of the student t-test, chi-square test, and, for those with a frequency level below 5, Fisher’s exact test. The percentage distribution was employed for the identification of coping behaviours used by women with UI. Significance was adopted as p < 0.05 in statistical evaluation.

RESULTS
The average age among women with chronic physical diseases was 51.79 ± 11.7 years and 58.4% of them were married, 31.5% literate, and 75.5% homemakers. Fifty six percent of the women were obese and 24.5% still smoking. Thirty percent of the women were under treatment for gastrointestinal diseases, 26.8% for diabetes, and 24.9% for cardiovascular diseases and the average disease duration was 7.4 ± 5.37 years. The percentage of women who perceived their general health status to be poor was 47.1% and 7.8% were only able to perform their daily activities

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>General</th>
<th>Urinary incontinence</th>
<th>X²/p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Yes (n = 203)</td>
<td>No (n = 54)</td>
</tr>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
<td></td>
</tr>
<tr>
<td>Age (year) (X±SS)</td>
<td>51.79 ± 11.7</td>
<td>54.13 ± 11.11</td>
<td>43.9 ± 9.53</td>
</tr>
<tr>
<td></td>
<td>(min:28,max:70)</td>
<td>(min:28,max:70)</td>
<td>(min:28,max:62)</td>
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<tr>
<td>Marital status</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Married</td>
<td>150 (58.4)</td>
<td>127 (62.6)</td>
<td>23 (42.6)</td>
</tr>
<tr>
<td>Single</td>
<td>107 (41.6)</td>
<td>76 (37.4)</td>
<td>31 (57.4)</td>
</tr>
<tr>
<td>Educational status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Literacy</td>
<td>81 (31.5)</td>
<td>81 (39.9)</td>
<td>-</td>
</tr>
<tr>
<td>Primary education</td>
<td>71 (27.6)</td>
<td>58 (28.6)</td>
<td>13 (24.1)</td>
</tr>
<tr>
<td>Secondary education</td>
<td>66 (25.7)</td>
<td>40 (19.7)</td>
<td>26 (48.1)</td>
</tr>
<tr>
<td>Higher education</td>
<td>39 (15.2)</td>
<td>24 (11.8)</td>
<td>15 (27.3)</td>
</tr>
<tr>
<td>Profession</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Homemaker</td>
<td>194 (75.5)</td>
<td>169 (83.3)</td>
<td>25 (46.3)</td>
</tr>
<tr>
<td>Official</td>
<td>52 (20.2)</td>
<td>23 (11.3)</td>
<td>29 (53.7)</td>
</tr>
<tr>
<td>Self-employment</td>
<td>11 (4.3)</td>
<td>11 (5.5)</td>
<td>-</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Underweight (&lt; 18.5)</td>
<td>8 (3.1)</td>
<td>5 (2.5)</td>
<td>3 (5.6)</td>
</tr>
<tr>
<td>Normal weight (18.5 - 24.9)</td>
<td>25 (9.7)</td>
<td>8 (3.9)</td>
<td>17 (31.5)</td>
</tr>
<tr>
<td>Overweight (25 - 29.9)</td>
<td>80 (31.1)</td>
<td>60 (29.6)</td>
<td>20 (37)</td>
</tr>
<tr>
<td>Obese (&gt; 30)</td>
<td>144 (56)</td>
<td>130 (64)</td>
<td>14 (25.9)</td>
</tr>
<tr>
<td>Smoking status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current smoker</td>
<td>63 (24.5)</td>
<td>44 (21.7)</td>
<td>19 (35.2)</td>
</tr>
<tr>
<td>Never smoked</td>
<td>165 (64.2)</td>
<td>143 (70.4)</td>
<td>22 (40.7)</td>
</tr>
<tr>
<td>Ex-smoker</td>
<td>29 (11.3)</td>
<td>16 (7.9)</td>
<td>13 (24.1)</td>
</tr>
<tr>
<td>Type of chronic disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>64 (24.9)</td>
<td>59 (29.1)</td>
<td>5 (9.3)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>69 (26.8)</td>
<td>52 (25.6)</td>
<td>17 (31.5)</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>77 (30)</td>
<td>51 (25.1)</td>
<td>26 (48.1)</td>
</tr>
<tr>
<td>Respiratory</td>
<td>47 (18.3)</td>
<td>41 (20.2)</td>
<td>6 (11.1)</td>
</tr>
<tr>
<td>Duration of disease (year) (X±SS)</td>
<td>7.4 ± 5.37</td>
<td>7.69 ± 5.11</td>
<td>6.27 ± 5.18</td>
</tr>
<tr>
<td>Perception of general health status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Good</td>
<td>30 (11.7)</td>
<td>16 (7.9)</td>
<td>14 (25.9)</td>
</tr>
<tr>
<td>Moderate</td>
<td>106 (41.2)</td>
<td>83 (40.9)</td>
<td>23 (42.6)</td>
</tr>
<tr>
<td>Bad</td>
<td>121 (47.1)</td>
<td>104 (51.2)</td>
<td>17 (31.5)</td>
</tr>
<tr>
<td>Ability to perform daily activities</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Can by oneself</td>
<td>237 (92.2)</td>
<td>183 (90.1)</td>
<td>54 (100)</td>
</tr>
<tr>
<td>Need for help</td>
<td>20 (7.8)</td>
<td>20 (9.9)</td>
<td>-</td>
</tr>
</tbody>
</table>
The rates of the women who experienced UI at least once a week was 78.9%. Statistically significant differences were identified between women with or without UI in terms of age, marital status, educational status, profession, BMI, smoking, type of chronic disease, perception of general health status, and ability to perform daily activities (p < 0.05). In this context, the average age of women with UI is higher and most of them are married, obese and homemakers with an educational level of literacy. UI is observed more commonly among smoking women with the chronic diseases of diabetes or of cardiovascular or respiratory diseases. Additionally, the general health levels perceived by women with UI are poorer and the rates of their need for help to perform daily activities are higher than those for women without UI (Table 1).

Among women suffering from chronic diseases, 60.6% were determined to have SUI, 64.5% to have been experiencing UI for the past 1 - 5 years, 67.1% to experience involuntary leakage of urine at least once a day, and 51.2% to experience involuntary leakage of urine in small quantities (Table 3).

Considering the average scores obtained by women in the scale (10.85 ± 4.48), it is observed that UI

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>General</th>
<th>Urinary incontinence</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes (n = 203) n (%)</td>
<td>No (n = 54) n (%)</td>
<td>X2/p</td>
<td></td>
</tr>
<tr>
<td>Status in administration of diuretic therapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not administered</td>
<td>227 (88.3)</td>
<td>173 (85.2)</td>
<td>9.035 / 0.003*</td>
<td></td>
</tr>
<tr>
<td>Administered</td>
<td>30 (11.7)</td>
<td>30 (14.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of pregnancies</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>17 (6.6)</td>
<td>3 (1.5)</td>
<td>80.123 / 0.000*</td>
<td></td>
</tr>
<tr>
<td>1 - 2</td>
<td>122 (47.5)</td>
<td>82 (40.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 - 4</td>
<td>79 (30.7)</td>
<td>79 (38.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 or more</td>
<td>39 (15.2)</td>
<td>39 (19.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of births</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>24 (9.3)</td>
<td>10 (4.9)</td>
<td>52.252 / 0.000*</td>
<td></td>
</tr>
<tr>
<td>1 - 2 deliveries</td>
<td>135 (52.5)</td>
<td>95 (46.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 - 4 deliveries</td>
<td>67 (26.1)</td>
<td>67 (33.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 or more deliveries</td>
<td>31 (12.1)</td>
<td>31 (15.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Form of delivery</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vaginal delivery</td>
<td>195 (83.6)</td>
<td>168 (87.1)</td>
<td>64.212 / 0.000*</td>
<td></td>
</tr>
<tr>
<td>C-section</td>
<td>38 (16.4)</td>
<td>25 (12.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Menopausal status</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Menopausal</td>
<td>132 (51.4)</td>
<td>119 (58.6)</td>
<td>20.377 / 0.000*</td>
<td></td>
</tr>
<tr>
<td>Not menopausal</td>
<td>125 (48.6)</td>
<td>84 (41.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>History of hysterectomy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>31 (12.1)</td>
<td>26 (12.8)</td>
<td>5.221 / 0.073</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>226 (87.9)</td>
<td>177 (87.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>History of urinary tract infection in the last one year</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>61 (23.7)</td>
<td>50 (24.6)</td>
<td>5.221 / 0.073</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>118 (45.9)</td>
<td>86 (42.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not available</td>
<td>78 (30.4)</td>
<td>67 (33)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*p < 0.05, **p < 0.01

Table 3: Type, duration, frequency, and quantity of UI among women (n = 203)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of UI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stress</td>
<td>123</td>
<td>60.6</td>
</tr>
<tr>
<td>Urge</td>
<td>54</td>
<td>26.6</td>
</tr>
<tr>
<td>Mixed</td>
<td>26</td>
<td>12.8</td>
</tr>
<tr>
<td>Duration of UI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Less than one year</td>
<td>29</td>
<td>14.3</td>
</tr>
<tr>
<td>1 - 5 years</td>
<td>131</td>
<td>64.5</td>
</tr>
<tr>
<td>More than 6 years</td>
<td>43</td>
<td>21.2</td>
</tr>
<tr>
<td>Frequency of UI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Once a week or less frequent</td>
<td>40</td>
<td>19.7</td>
</tr>
<tr>
<td>Twice or three times a week</td>
<td>27</td>
<td>13.3</td>
</tr>
<tr>
<td>Once a day</td>
<td>74</td>
<td>36.5</td>
</tr>
<tr>
<td>A few times a day</td>
<td>59</td>
<td>29.1</td>
</tr>
<tr>
<td>At all times</td>
<td>3</td>
<td>1.5</td>
</tr>
<tr>
<td>UI Quantity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>In a small quantity</td>
<td>104</td>
<td>51.2</td>
</tr>
<tr>
<td>In a medium quantity</td>
<td>77</td>
<td>37.9</td>
</tr>
<tr>
<td>In a large quantity</td>
<td>22</td>
<td>10.8</td>
</tr>
</tbody>
</table>
affects the daily lives of women with chronic diseases at a medium level in terms of frequency, quantity, and effect (Table 4).

Only 54.6% of women with UI had applied to a healthcare institution with a complaint of UI. The reasons specified by patients for not having applied to a healthcare institution for UI included ignorance of symptoms (62.1%), perceiving the condition as a source of shame (34.7%), perceiving urinary incontinence as normal in advanced age (23.4%), and refraining from medical examination (17.8%).

Table 5 indicates that the most common behaviours employed by women to cope with UI are circumventing the condition by using pads or rags (77.3%), keeping feet warm (62.6%), and changing underwear (59.6%).

### DISCUSSION

The prevalence of urinary incontinence can be higher among individuals with chronic physical diseases[^16]. However, it is at times difficult to determine the prevalence of UI among women suffering from chronic physical diseases due to societal values, norms, lack of knowledge, or healthcare professionals not examining patients for this condition[^80]. The present study found that approximately three-fourth of Turkish women suffer from UI. In a study conducted with 6903 individuals with a range of chronic physical diseases, 47% of patients were determined to experience UI[^31]. Other studies on a limited number of patient groups in the literature identified the prevalence of UI to be in the range of 27 - 74%[^6,16,20,21,32-35]. When compared to studies undertaken without taking into account the disease factor[^4,10,11,14,17,36,37], women with chronic physical diseases are observed to suffer from UI more commonly. Therefore, it is important for all female in-patients to be examined for UI along with their complaints relating to physical diseases.

Most prominent risk factors in terms of the development of UI include old age, socioeconomic characteristics, obesity, smoking, certain chronic diseases, administration of diuretics, and obstetric characteristics[^80]. These risk factors can further increase the prevalence of UI among women with chronic physical diseases. In the present study, women suffering from UI were identified to demonstrate higher figures in terms of average age and rates of being married, literate, and a homemaker, incidence of obesity, smoking, rates of cardiovascular and respiratory diseases, and rate of diuretic use, number of pregnancies and deliveries, rate of vaginal delivery, and positive menopausal status. Studies undertaken with women suffering from chronic physical diseases determined that the prevalence of UI increases along with advanced age[^6,16,32,33,39], presence of obesity[^6,16,34,39,40], smoking[^39], diabetes[^6,11,16,39,41,42], chronic respiratory diseases including chronic obstructive pulmonary disease (COPD) and asthma[^20,34,43,44], cardiac diseases[^45], use of diuretics such as furosemide or hydrochlorothiazide[^38,42,46], higher number of deliveries, vaginal birth, positive menopausal status, and history of hysterectomy[^39] and urinary tract infections[^16]. However, certain studies failed to establish any association between UI

### Table 4: Breakdown of average scores of women in UI scale (n = 203)

<table>
<thead>
<tr>
<th>International Consultation on Incontinence Questionnaire</th>
<th>Mean ± SS</th>
<th>Minimum and maximum scores available</th>
<th>Minimum and maximum scores obtained</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency</td>
<td>2.79 ± 1.11</td>
<td>1 - 5</td>
<td>1 - 5</td>
</tr>
<tr>
<td>Quantity</td>
<td>3.18 ± 1.12</td>
<td>2 - 6</td>
<td>2 - 6</td>
</tr>
<tr>
<td>Effect</td>
<td>4.88 ± 2.25</td>
<td>0 - 10</td>
<td>1 - 10</td>
</tr>
<tr>
<td>General</td>
<td>10.85 ± 4.48</td>
<td>3 - 21</td>
<td>3 - 21</td>
</tr>
</tbody>
</table>

[^80]: n increased due to subjects who marked more than one option

[^n]: n increased due to subjects who marked more than one option

[^16]: n increased due to subjects who marked more than one option

[^4]: n increased due to subjects who marked more than one option

[^6]: n increased due to subjects who marked more than one option

[^10]: n increased due to subjects who marked more than one option

[^11]: n increased due to subjects who marked more than one option

[^14]: n increased due to subjects who marked more than one option

[^20]: n increased due to subjects who marked more than one option

[^34]: n increased due to subjects who marked more than one option

[^36]: n increased due to subjects who marked more than one option

[^37]: n increased due to subjects who marked more than one option

[^38]: n increased due to subjects who marked more than one option

[^39]: n increased due to subjects who marked more than one option

[^40]: n increased due to subjects who marked more than one option

[^42]: n increased due to subjects who marked more than one option

[^43]: n increased due to subjects who marked more than one option

[^44]: n increased due to subjects who marked more than one option

[^45]: n increased due to subjects who marked more than one option

[^46]: n increased due to subjects who marked more than one option
and age\textsuperscript{20,24}, marital and educational status, BMI\textsuperscript{20}, or smoking\textsuperscript{22,24} among women. Given the studies undertaken in this field, it is possible to state that women should be evaluated for these risk factors that cause UI among women and be provided with counselling services as a matter of importance.

In the present study, the incidence of different types of UI was established in parallel with the relevant literature and more than half of the women included therein were identified to be suffering from SUI. Other studies conducted with women suffering from chronic physical diseases strikingly identified higher incidences for SUI\textsuperscript{6,21,24,39,41}. The finding of the present study is of significance in that practices for alleviating the complaint of chronic coughing must be implemented for women.

Urinary incontinence affects the physical and psychological health and family and social lives of women in all aspects\textsuperscript{5,20,21,47}. The present study found that UI affected the daily lives of women with chronic diseases at a medium level in terms of frequency, quantity, and effects. One study established a severe level of UI among one-fourth of diabetic women\textsuperscript{16}, while another study found the same level among approximately half of the participating diabetic women\textsuperscript{23}. As women suffering from chronic physical diseases already have a chronic disease which they have to cope with and manage, the presence of UI adds further difficulties to their daily lives.

Women suffering from the problem of urinary incontinence do not take recourse to a physician upon the emergence of their complaints and postpone the treatment of the condition. In this respect, UI is observed to be an ignored health problem. In the present study, even though 64.5% of women had been experiencing the problem of UI for 1 - 5 years, only half of them had had recourse to a healthcare institution on grounds of the complaint of UI. A study undertaken on patients with bronchiectasis identified the rate of seeking treatment as 27%\textsuperscript{35} and the same rate was found to be 21.7% in another study concerning diabetic women\textsuperscript{16}. In studies pertaining to healthy women, the rate of applying to a physician for UI was in the range of 12.9 - 28%\textsuperscript{17,36}. Our study finding, although not sufficient when compared to the findings of other relevant studies, is quite pleasing. This is an important finding that indicates that women are in search for treatment.

As one moves from the Western to the Eastern provinces of Turkey, an incremental decline is observed in the socioeconomic level, cultural structure, and educational cluster. Therefore, women with UI living in these regions do not consider the presence of UI as a disease\textsuperscript{37}. However, women do not take the problem of UI seriously due to their sense of privacy, feeling of shame in exposing this problem, perception of the condition as a normal result of deliveries or advanced age, and avoidance of examination\textsuperscript{12,13}. In the present study, women were determined to refrain from having recourse to a physician mostly due to the fact that they don't take the condition seriously or perceive the condition to be shameful. According to studies conducted with individuals suffering from chronic physical diseases, the most important reasons why women do not want to receive treatment were the fact that they consider the condition as a part of aging (58.5%), they do not know what type of assistance they need (39.2%), they believe that they can manage this situation themselves (35.4%)\textsuperscript{16}, they feel shame in approaching a physician (33.3%), they do not know that the condition is treatable (28.4%), and they perceive the presence of UI as a normal condition arising from aging or deliveries (23.5%)\textsuperscript{17}. In a qualitative study, women were identified to believe that UI was a natural indication of aging and to consider it possible for them to apply to medical assistance only if coping with symptoms became more difficult\textsuperscript{67}. This study finding shows that women do not consider the problem of UI as a life-threatening problem and this is regarded by society as an ignored medical condition. This situation further augments the importance of screening programmes for the diagnosis of UI.

UI among women is managed through conservative treatment methods including dietary recommendations, weight loss, management of intestinal problems, and pelvic floor exercises\textsuperscript{17}. In addition, women take various measures in their daily lives to cope with UI. However, ethnic, cultural and social situations can have an impact on the coping styles used by women. The most common behaviours employed by women to cope with UI are circumventing the condition by using pads or rags, keeping feet warm, and changing underwear. Similar studies undertaken in different cultures also indicate that women suffering from UI most frequently employ the coping approaches of using pads or rags, etc., consuming fluids in lower quantities\textsuperscript{15,18,28}, staying in areas with access to restrooms\textsuperscript{15,18}, keeping themselves away from social activities, changing underwear frequently, refraining from coughing, sneezing, laughing, and sexual activity\textsuperscript{15}, keeping feet warm, and taking care not to lift heavy objects\textsuperscript{28}, etc. The present study and other relevant studies indicate that women make changes in their daily lives and apply restrictions to cope with UI.

**Limitations of the Study**

The study is under sampling and timing limitations...
as it was conducted with the in-patients of a single hospital with due concordance with admission criteria determined for the study in a limited period of time. In addition, the self-declarations of the patients with respect to UI and their coping behaviours are limited with the ICIQ-SF and Coping Behaviours Identification Form. Future studies need to evaluate the presence of UI among women with a range of chronic physical diseases in a wider sample and implement interventions to prevent UI.

CONCLUSION
Urinary incontinence is an important health problem with a high incidence among Turkish women suffering from chronic physical diseases, which is nonetheless ignored by patients and not questioned sufficiently by healthcare professionals. Women have recourse to cheap and easily applied interventions and restrictions in their daily lives in order to cope with the problem of UI.

Health professionals can contribute to ease women’s lives by helping to cope with the disease and by making women consider UI as a health problem. To accomplish this, health professionals should evaluate the risk factors that can lead to UI (such as number of births, menopause, etc.) no matter how old they are. Health professionals should check UI along with other physical illnesses, give a holistic healthcare service and take active part in counselling services for the protection and treatment of UI, in addition to chronic disease management. In addition, further researches should be done to put forth the efficacy of any attempt by women to cope with UI.

REFERENCES


Original Article

Assessment of Pre-operative Anxiety for Caesarean Section: General versus Spinal Anaesthesia

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ABSTRACT

Objective: To observe the effect of anxiety level of pregnant patients, for whom caesarean delivery was planned, on the choice of anesthesia method (general versus spinal anesthesia)

Design: Prospective observational study

Setting: Bozok University, Medical Faculty, Department of Anesthesiology, Yozgat, Turkey

Subjects: One hundred and fifty pregnant women

Intervention: Information about spinal anaesthesia and general anaesthesia was given to all patients scheduled for elective caserean section during pre-operative examinations at the anaesthesia clinic. Primarily, spinal was suggested to all patients in the absence of any contraindications. Patients were then divided into 3 groups with 50 patients each: patients who preferred spinal anesthesia (SA), patients who preferred general anesthesia (GA) and a control group of patients undergoing normal spontaneous vaginal delivery. The Beck Anxiety Inventory (BAI) was applied to all patients of the 3 groups in the pre-operative anesthesia clinic visit.

Main outcome measure: Preoperative evaluation of BAI scores

Results: BAI scores were significantly higher in the GA group than SA (mean ± SD = 13.94 ± 7.81) and control group (mean ± SD = 8.59 ± 3.79).

Conclusion: We detected that pregnant women with higher anxiety levels preferred general anesthesia and patients with lower anxiety levels preferred SA.

INTRODUCTION

Pre-operative anxiety affects surgery, anesthesia and post-operative recovery negatively and is seen in 60 - 80% of patients scheduled for surgery[1,2]. It causes physiopathological responses such as hypertension and dysrhythmia and can increase the anesthetic requirement and the risk of “awareness” during the operation[3,4]. It is associated with increased analgesic use and a prolonged hospital stay in the post-operative period[5]. Due to the importance of the health of both infant and mother, an elective cesarean operation increases the anxiety level more than any other surgery type. We believe that due to these negative consequences, pre-operative anxiety levels play a role in choosing the type of anesthesia.

The serious fear of spontaneous vaginal delivery is reported to be the most common reason for pregnant women’s claim for elective cesarean delivery[6]. Fear may create prejudgement against regional anesthesia in a pregnant patient while planning the anesthesia method.

In this study, it was aimed to observe the effect of anxiety level on the preference of anesthesia method in pregnant patients who were planned to have cesarean delivery.

SUBJECTS AND METHODS

Approval for the study was granted by the local Ethics Committee and informed consent was obtained from all the patients. Information about spinal anaesthesia and general anaesthesia, including a video presentation, was given to all patients scheduled for elective caserean section during pre-operative examinations at the anaesthesia polyclinic. Spinal anaesthesia, which is the most frequently used regional anaesthesia method for caesarean delivery,
was first suggested to the patients. Patients who did not accept spinal anesthesia and preferred general anesthesia were planned to have general anesthesia. Patients were then allocated to one of three groups. In the spinal anesthesia (SA) group (n = 50), spinal anesthesia was planned and in the general anesthesia (GA) group (n = 50), general anesthesia was planned and the patients who planned to have spontaneous vaginal delivery were placed in the control group (n = 50). Patients were excluded from the study if they had any visual or hearing problems, psychiatric illnesses or were unable to read and understand Turkish.

The Beck Anxiety Inventory (BAI) was applied to all patients in the SA group, the GA group and the control group (Table 1). Age, educational status and previous anesthesia experience of the patients were also recorded.

The BAI is a self-reported scale that determines the frequency of anxiety symptoms experienced by individuals. It consists of 21 items with Likert-type responses, scoring 0 to 3 points. The level of the total points obtained from the scale indicates the severity of the anxiety experienced by the individual[7].

Statistical analysis was performed using SPSS 17 (SPSS Inc. Chicago, IL, US) statistics software. The conformity to normal distribution of the variables was examined by visual and analytical methods (Kolmogorov-Smirnov/Shapiro-Wilk). The BAI scale was determined not to show normal distribution and parameters between groups were compared using the Mann-Whitney U test. A value of p < 0.05 was accepted as statistically significant.

RESULTS

No difference was determined between the groups in terms of age, weight and height (p = 0.26), nor in educational level and previous anesthesia experience. The educational level of the patients were: 48% (72) of patients graduated from primary school, 28% (43) from high school and 24% (35) from university. The level of anxiety in those with primary school level educational level and previous anesthesia experience of the patients were also recorded.

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At the pre-operative evaluation, the BAI scores of the SA group (mean ± SD = 13.94 ± 7.81) and control groups (mean ± SD = 8.59 ± 3.79). The BAI scores of the SA group were quite high compared to those of the control group (Table 1).

There was a statistically significant difference in favor of the GA group compared to the SA group in the post-hoc group comparison (Z = -3.77, p < 0.001). There was a statistically significant difference in favor of the GA group compared to the control group (Z = -7.27, p < 0.001). There was a statistically significant difference in favor of the SA group compared to the control group (Z = -4.34, p < 0.001) (Table 2).

<table>
<thead>
<tr>
<th>Statistic</th>
<th>Posthoc Comparison</th>
</tr>
</thead>
<tbody>
<tr>
<td>GA-SA</td>
<td>GA-Control</td>
</tr>
<tr>
<td>Z = -3.77</td>
<td>Z = -7.27</td>
</tr>
<tr>
<td>p &lt; 0.001</td>
<td>p &lt; 0.001</td>
</tr>
</tbody>
</table>

Table 2: Statistical comparison of groups

DISCUSSION

Concerns related to anesthesia and surgery cause anxiety in the pre-operative period. Pre-operative anxiety reduces patient satisfaction and extends the duration of hospital stay[8]. Maternal stress in pregnant rats has been reported to cause changes that may be harmful to the fetus in terms of blood pressure and heart rate[9]. Avoiding increments in the maternal anxiety level will be helpful not only for mothers but also for the fetus[10]. There have been previous studies about high maternal anxiety levels before caesarean delivery[11,12]. In caesarean section, both mother and the baby’s health is considered and this increases the anxiety more than any other surgery type. In the current study, the anxiety level of the SA and GA groups was found to be higher than that of the control group. This result shows that caesarean delivery increases anxiety more than vaginal delivery. Our literature knowledge demonstrates there have been no studies to evaluate how pre-operative anxiety levels may affect the type of anesthesia. Although several studies have focused on social, economic, cultural and psychological factors, there have not been many studies about the effect of increased anxiety level on anesthesia preference in literature[13].

In previous studies, it has been reported that spinal anesthesia shortens the duration of hospital stay compared with general anesthesia in elective caesarean delivery[12]. In our institution, spinal anesthesia is recommended as the first-choice anesthesia method for caesarean operations. Although the positive aspects of spinal anesthesia in terms of both mother
and baby’s health were explained verbally and visually to the patients, some refused spinal anesthesia. It was thought that these patients had high level of anxiety in their daily life independent of pregnancy and the BAI was applied to these patients in the polyclinic. In this study of patients who planned for caesarean delivery, the BAI scores of the general anesthesia group were higher than those of the spinal anesthesia group. It was considered that the anxiety level of patients with high anxiety BAI scores will increase with the thought of being awake during surgery, so they refuse spinal anesthesia for this reason. In literature, there have been studies of patients who planned to have caesarean delivery with spinal anesthesia and therefore had high anxiety levels\textsuperscript{[14]}. When the suggestion of spinal anesthesia causes an increased anxiety level, it is better to apply general anaesthesia to the patient if they wish so and if there are no contraindications.

The most important factor in reducing pre-operative anxiety level is informing the patients in a simple and clear way about the procedure. In this study, a variety of videos and visual sources prepared with pictures were used while suggesting spinal anesthesia for the patients, but these did not change the choice of the group who preferred general anesthesia. In a previous study, it has been reported that a method of visual information with pictures describing spinal anesthesia reduced anxiety levels in patients who opted for spinal anesthesia\textsuperscript{[15]}. In the current study, although patients preferring both spinal and general anesthesia were informed visually, the GA group with the higher anxiety level did not change their decision.

CONCLUSION

The results of this study show that pregnant patients with a high anxiety level preferred general anesthesia and pregnant patients with a low anxiety level preferred spinal anesthesia. This situation re-emphasizes the importance of one of the absolute contraindications of spinal anesthesia, which is “rejection by the patient”\textsuperscript{[17]}. According to this result, it can be considered that efforts to change the choice of pregnant patients who prefer general anesthesia due to a high level of anxiety about spinal anesthesia will increase the anxiety level.

ACKNOWLEDGMENT

Source(s) of support: None

REFERENCES

Objectives: A higher conversion rate from laparoscopic to open cholecystectomy in the setting of acute cholecystitis was reported, with an increased risk for morbidity and longer hospital stay. In critically ill patients with gallbladder stones and cholecystitis, percutaneous gallbladder drainage serves as a temporizing procedure, palliating the gallbladder-related sepsis. Compared with surgery in critically ill patients, percutaneous drainage has a relatively low complication rate and is rapidly effective. We report our institution’s experience in using percutaneous cholecystostomy tube (PCT) insertion as a temporizing measure prior to laparoscopic cholecystectomy.

Design: A retrospective study on prospectively collected data
Settings: Tertiary care center in Riyadh, Saudi Arabia
Subjects: Patients who underwent PCT insertion for acute cholecystitis

Intervention: PCT insertion
Main outcome measure(s): Clinical picture of the patient, hospital stay and sepsis indicators

Results: A total of 25 patients underwent a PCT insertion for acute cholecystitis. Clinical improvement of the patients’ symptoms (right upper quadrant pain and fever) and normalization of white blood cells following the insertion of the PCT was achieved in 66 hours ≈ 2.75 days (range : 1 - 7 days). The mean hospitalization time was 15.44 days and the median was 15 (3 – 42) days. All 24 patients subsequently underwent laparoscopic cholecystectomy without conversion nor common bile duct injury in our series.

Conclusion: PCT insertion followed by laparoscopic cholecystectomy is an effective and safe treatment in patients with acute cholecystitis and concomitant comorbidities.

INTRODUCTION

Eleven to 20% of patients with symptomatic gallstones present with acute cholecystitis[1,2]. Although the laparoscopic approach was initially contraindicated, owing to experience, the application of laparoscopic surgery has extended to the treatment of patients with acute cholecystitis. Notably, laparoscopic cholecystectomy has similar operation times, shorter hospital stay and smaller complication rates compared to that of the open technique[3,4].

The conversion rate of laparoscopic cholecystectomy for acute cholecystitis has been reported to range from 11% to 28%[4,5], which is significantly higher than the rate reported for elective laparoscopic cholecystectomy (less than 5%)[3]. With conversion, not only is the advantage of this minimally invasive procedure lost, but the cost and complication rates are also increased[1].

In critically ill patients with gallbladder stones and cholecystitis, percutaneous gallbladder drainage serves as a temporizing procedure, palliating the gallbladder-related sepsis while the underlying critical conditions are treated. Subsequently, surgery can be performed semi-electively. Compared with surgery in critically ill patients, percutaneous drainage has a relatively low complication rate and is rapidly effective[6].
SUBJECTS AND METHODS

The study was approved by the institution’s ethical committee. From the interventional radiology database at our institution, we identified 25 patients who underwent percutaneous decompression of the gallbladder for treatment of acute cholecystitis between February 1987 and May 2008.

Table 1: Demographics of the patients (n = 25)

<table>
<thead>
<tr>
<th>Patient Demographics and Characteristics</th>
<th>Number of Patients</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>17</td>
<td>68</td>
</tr>
<tr>
<td>Female</td>
<td>8</td>
<td>32</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 60</td>
<td>16</td>
<td>64</td>
</tr>
<tr>
<td>&gt; 60</td>
<td>9</td>
<td>36</td>
</tr>
<tr>
<td>Mean of age</td>
<td>52.56</td>
<td>52.56</td>
</tr>
<tr>
<td>Standard deviation</td>
<td>17.38</td>
<td>17.38</td>
</tr>
<tr>
<td>Associated factors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Advanced cardiovascular diseases</td>
<td>5</td>
<td>20</td>
</tr>
<tr>
<td>Advanced respiratory diseases</td>
<td>2</td>
<td>8</td>
</tr>
<tr>
<td>Empyema of gall bladder</td>
<td>5</td>
<td>20</td>
</tr>
<tr>
<td>Unresponsive to broad spectrum antibiotics</td>
<td>4</td>
<td>16</td>
</tr>
<tr>
<td>Unclear anatomy intra-operatively</td>
<td>3</td>
<td>12</td>
</tr>
<tr>
<td>Hemodynamic instability</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Uncontrolled diabetes mellitus</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Advanced malignancy</td>
<td>2</td>
<td>8</td>
</tr>
<tr>
<td>Surgeons preference</td>
<td>2</td>
<td>8</td>
</tr>
</tbody>
</table>

Patients’ demographics were reviewed, as well as their symptoms, signs and co-morbid conditions (Tables 1, 2). Blood works, mainly complete blood counts and liver function tests (LFTs) (Table 2) were collected, in addition to all diagnostic radiological studies.

The main outcome was time to improvement after tube insertion, i.e. normal white blood cell (WBC) count, absence of fever, and absence of pain (Table 3).

We also looked at the length of hospital stay, percutaneous cholecystostomy tube (PCT) placement, early and late complications, removal indications (Fig. 1), and any further biliary procedures (Fig. 2).

Table 2: Symptoms, signs and ultrasound findings of the studied patients

<table>
<thead>
<tr>
<th>Symptoms, Signs, and Ultrasound Findings</th>
<th>Number of Patients</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptoms</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right upper quadrant abdominal pain</td>
<td>25</td>
<td>100</td>
</tr>
<tr>
<td>Fever</td>
<td>8</td>
<td>32</td>
</tr>
<tr>
<td>Nausea</td>
<td>12</td>
<td>48</td>
</tr>
<tr>
<td>Vomiting</td>
<td>16</td>
<td>64</td>
</tr>
<tr>
<td>Anorexia</td>
<td>2</td>
<td>8</td>
</tr>
<tr>
<td>Jaundice</td>
<td>4</td>
<td>16</td>
</tr>
<tr>
<td>Pruritus</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Dark urine</td>
<td>4</td>
<td>16</td>
</tr>
<tr>
<td>Pale stool</td>
<td>3</td>
<td>12</td>
</tr>
<tr>
<td>Signs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fever &gt; 38 ºC</td>
<td>3</td>
<td>12</td>
</tr>
<tr>
<td>Palpable masses</td>
<td>3</td>
<td>12</td>
</tr>
<tr>
<td>Tender right upper quadrant area</td>
<td>23</td>
<td>92</td>
</tr>
<tr>
<td>Leukocytosis</td>
<td>18</td>
<td>72</td>
</tr>
<tr>
<td>Ultrasound findings</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gall stones</td>
<td>18</td>
<td>72</td>
</tr>
<tr>
<td>Sludge</td>
<td>6</td>
<td>24</td>
</tr>
<tr>
<td>Wall thickening</td>
<td>13</td>
<td>52</td>
</tr>
<tr>
<td>Pericholecystic fluid</td>
<td>11</td>
<td>44</td>
</tr>
<tr>
<td>Murphy’s sign</td>
<td>4</td>
<td>16</td>
</tr>
<tr>
<td>Gas (gangrenous gall bladder)</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Distended gall bladder</td>
<td>7</td>
<td>28</td>
</tr>
</tbody>
</table>

Fig 1: Times of removal of PCT

- Elective laparoscopic cholecystectomy
- Urgent laparoscopic cholecystectomy
- Continue to drain due to cystic duct stone till laparoscopic cholecystectomy
- Operation not done due to the morbidity, drain removed after 15 days
- Died due to cardiac arrest
- Signed DAMA and lost

Fig 2: Final outcomes in patients with and without response to PCT
Percutaneous Cholecystostomy Tube (PCT) placement

PCT insertion was performed in critically ill patients with strong clinical and imaging evidence of acute cholecystitis who were deemed unfit to undergo immediate surgery (Table 1). Acute cholecystitis was diagnosed based on both the clinical and radiological picture. All of our patients were kept in fasting and broad-spectrum IV antibiotics were administered as part of their initial management.

Percutaneous cholecystostomy technique

PCT insertion was performed under sterile conditions using intravenous sedation and local anesthesia with 1% lidocaine hydrochloride. The procedure was performed using ultrasound (US) guidance in 20 patients. Adequate visualization of the gallbladder using US was not possible in 2 patients, who then underwent PCT insertion under computerized tomography (CT) scan guidance. Additionally, 3 patients underwent cholecystostomy tube placement intra-operatively. An 8-F pigtail catheter was placed into the gallbladder using a single step technique via a transhepatic or transperitoneal approach.

PCT was considered technically successful when the pigtail catheter was visualized sonographically in the gallbladder lumen and the gallbladder contents could be aspirated freely through the PCT. All patients had their vital signs monitored and were observed for symptoms of local pain or shoulder discomfort up to four hours after the procedure.

RESULTS

Demographics and pre-operative status

There were 17 males and 8 females. Mean patient age was 52.56 years (range 20 - 80 years) (Table 1). The diagnosis of acute cholecystitis was made in all patients on the basis of clinical and radiological findings (Table 2). The most common symptoms were right upper quadrant pain in 25 patients (100%), vomiting in 16 patients (64%), nausea in 12 patients (48%), and fever in 8 patients (32%) (Table 2). While the most common sign was right upper quadrant tenderness in 23 patients (92%), 3 patients (12%) also presented with fever (temperature > 38°C), and a palpable mass in 3 patients (12%). Eighteen patients (72%) had leukocytosis (Table 2). None of the patients developed gallstone pancreatitis.

Associated factors were advanced cardiovascular diseases (5, 20%), advanced respiratory diseases (2, 8%), empyema of the gall bladder (5, 20%), unresponsiveness to broad spectrum antibiotics (4, 16%), unclear anatomy intraoperatively (3, 12%), hemodynamic instability (1, 4%), uncontrolled diabetes mellitus (1, 4%), advanced malignancy (2, 8%), and surgeons preference (2, 8%) (Table 1).

Our radiological studies consisted of abdominal US as the initial confirmatory test for acute cholecystitis, which almost all our patients underwent (24 of the 25). The US diagnostic criteria used were the signs of acute inflammation of the gall bladder; this included presence of gall stones, sludge, wall thickening, pericholecystic fluid, sonographic Murphy’s sign, and gas in the gallbladder wall (Table 2). US was diagnostic of acute cholecystitis in 24 patients (96%), and one patient (4%) had his diagnostic US at another institution. Abdominal CT scan was performed in seven patients (28%). Hepatobiliary (HIDA) scan was not done for any of our patients.

Post-operative outcomes

The procedure was successful at the time of insertion of the catheter in all patients. Clinical improvement of the patients’ symptoms (right upper quadrant pain and fever) and normalization of WBC following the insertion of the PCT was achieved in 66 hours (∼ 2.75 days on average). All patients showed clinical improvement within a week of tube placement, although notably, the majority (84%) improved within 4 days (Table 3).

<table>
<thead>
<tr>
<th>Time till improvement (days)</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 - 4</td>
<td>21 (84%)</td>
</tr>
<tr>
<td>7</td>
<td>3 (12%)</td>
</tr>
</tbody>
</table>

The mean hospitalization time was 15.44 days, ranging from 3 - 42 days. The majority of patients (88%) spent 3 weeks or less in the hospital.

While the mean draining duration was 19.67 days, around two thirds of the PCTs drained for a month or less (16 patients, 64%). Five PCTs continued to drain for 56 days (20%), whereas a minority continued to drain until an urgent laparoscopic cholecystectomy was performed (2 patients, 8%).

Patients were observed daily for early or late complications, including bile peritonitis, bleeding, vagal hypotension and bradycardia, vagal bradycardia alone, respiratory distress and catheter dislodgment. There were no immediate complications. Two patients did have a minor leak, however they did not need any further biliary intervention.

Twenty patients (80%) later underwent elective laparoscopic cholecystectomy with no conversion and no common bile duct (CBD) injury, two patients...
(8%) had urgent cholecystectomies, one patient (4%) had the PCT removed and is being followed up while receiving chemotherapy, one patient (4%) died due to a cardiac arrest unrelated to PCT, and one patient (4%) was lost to follow up (Fig. 2). We didn’t encounter any CBD injury nor did we need to convert to an open procedure in any of the operated cases.

Cholecystocholangiography was performed prior to the removal of the catheter to visualize the bile tree and gallbladder in 12 patients (48%), 10 patients (40%) had a normal flow and two patients (8%) had a stone at the cystic duct, while the other 13 patients (52%) did not undergo cholecystocholangiography.

PCT was removed in 12 patients (48%) after resolution of symptoms and signs, and a nil output from the PCT was observed. Seven patients (28%) had PCT removed when the output was nil and the cholecystocholangiography was within normal flow. Three patients (12%) had PCT removed with a normal result of cholecystocholangiography regardless of the output. Two patients (8%) had the PCT removed intraoperatively. Finally, one patient (4%) was lost to follow up with the tube.

No complications were faced in the 24 patients (96%) after removal of the PCT, however as aforementioned, one patient (4%) was lost to follow up before removal of the PCT.

All 24 patients subsequently underwent laparoscopic cholecystectomy without conversion or CBD injury in our series.

**DISCUSSION**

PCT is an effective, safe, temporizing treatment in patients with acute cholecystitis who have a concomitant co-morbidity that prevents them from undergoing immediate cholecystectomies[7-9]. There is a wide range of reasons for not performing cholecystectomy and thus inserting a PCT instead, but the most common are cardiopulmonary disorders[10]. In rare cases, potentially difficult emergency surgery can be avoided with PCT insertion[11]. Following PCT insertion, most patients will have resolution of their symptoms[9]. Therefore, cholecystectomy can be performed at a later stage as an elective procedure when the patient’s condition has improved[12].

Drains can be safely removed when drainage has stopped without the need for cholangiography. If drainage continues, then cholangiography needs to be performed. A normal study means PCT can be safely removed[13]. Laparoscopic cholecystectomy remains the definitive treatment when the patient’s condition permits[14].

**CONCLUSION**

Percutaneous cholecystostomy tube insertion, followed by laparoscopic cholecystectomy, is an effective and safe treatment in patients with acute cholecystitis and concomitant comorbidities. The drains can be safely removed after a nil output reading, or with normal result of a cholangiogram, regardless of the output. This is to be followed by a laparoscopic cholecystectomy in a later elective setting. We have not experienced any conversion procedures nor biliary injuries. However, larger studies are needed to generalize this statement.

**AKNOWLEDGMENT**

We would like to thank Dr. Faisal Al-alem, MBBS, SBGS from the Department of Surgery, College of Medicine, King Saud University, Riyadh, Saudi Arabia for his assistance in the publication process of this article.

**Author contributions:** Al-Saif FA generated the idea and provided the patient cohort; AlSubaie HS did the literature review and wrote the manuscript; Mattar RE reviewed and edited the manuscript; Qazi SA and AlFuhaid TR provided interventional radiology expertise; Zubaidi A supervised the process.

**REFERENCES**


Evaluation of Serum Levels of Progranulin and Bone Morphogenetic Protein-4 in Female Patients with Knee Osteoarthritis

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ABSTRACT

Objective: To investigate serum bone morphogenetic protein-4 (BMP-4) and progranulin (PGRN) levels in patients with osteoarthritis (OA) and to present a new evidence of pathogenesis of OA disease

Design: Prospective study

Setting: Dicle University Medical Faculty Hospital

Subjects: Thirty-eight female knee osteoarthritis patients and thirty-eight healthy female volunteers were enrolled from January 2016 to April 2016.

Intervention: Family histories, clinical histories and examinations, and radiological examinations were obtained from the hospital data system. Blood samples were obtained from the antecubital vein of all participants after overnight fasting.

Main outcome measures: Serum PGRN and BMP-4 concentrations were measured using enzyme-linked immunosorbent assay. Body mass index, erythrocyte sedimentation rate, white blood cells and neutrophil lymphocyte ratio were also assessed.

Results: Mean BMP-4 levels were significantly lower in OA women compared to controls (p < 0.001). Mean PGRN levels were found to be significantly lower in OA women compared to controls (p < 0.001). There was a significant positive correlation between BMP-4 and PGRN in patients with OA.

Conclusions: BMP-4 and PGRN levels may play a role in the pathogenesis of knee OA and could be a useful biomarker of knee OA, as well as a potential therapeutic target for the management of knee OA.

INTRODUCTION

Osteoarthritis (OA) is a chronic, slowly progressive disease of the joints and is the most common form of arthritis worldwide⁴¹. It is one of the most common causes of pain and disability in middle-aged and older people. The incidence of OA is increasing because of the aging population and the obesity epidemic⁴³. It is characterized by articular cartilage degeneration, subchondral sclerosis, osteophyte formation, and inflammation of the synovial membrane. However, the etiology and pathogenesis underlying this disease are poorly understood⁴³.

Progranulin (PGRN), a secreted glycoprotein expressed in many cell types, has been linked to a wide variety of biological processes, including inflammation, infection, wound healing, angiogenesis, cell proliferation, neurodegeneration and tumorigenesis⁴⁴⁻⁴⁷. PGRN is also secreted in adipose tissue and contributes to the regulation of appetite and satiety, fat distribution, insulin secretion and sensitivity, energy expenditure and inflammation as adipokines⁴⁸. It has a regulatory role in musculoskeletal diseases, autoimmune disorders, cardiac diseases, neurodegenerative diseases, metabolic disease and obesity pathogenesis⁴⁶⁻⁴⁸,⁹,¹⁰. Recently, studies revealed that it has a chondro-protective role in the cartilage degenerative cascade, stimulates chondrocyte proliferation and is considered an essential regulator of cartilage metabolism⁴⁶,⁴¹,¹².
Bone morphogenetic protein-4 (BMP-4), a member of transforming growth factor-β superfamily of proteins, is involved in bone and cartilage metabolism, muscle development, and induction of adipogenesis\cite{8,12}. BMP-4 regulates adipogenic precursor cell commitment and differentiation and is associated with obesity and inflammation as adipokines\cite{8}. Studies showed that BMP-4 is expressed in normal synovial tissue, induces chondrogenesis and may be important in cartilage repair\cite{14,15}.

The aim of this study was to compare BMP-4, PGRN and other inflammatory parameters such as erythrocyte sedimentation rate (ESR), white blood cell (WBC) count, and Nod-like receptor (NLR) levels between knee OA patient group and the control group and to present new evidence of pathogenesis of OA disease.

**SUBJECTS AND METHODS**

**Study population**

This pilot, prospective, case control study was conducted at Dicle University, Medical Faculty Hospital, Diyarbakir, Turkey between January 2016 and April 2016. Thirty-eight female knee OA patients diagnosed according to the American College of Rheumatology were included in the study. To evaluate radiographic severity of knee OA, the Kellgren and Lawrence (KL) classification were used as follows: grade 1 - suspicious narrowed joint gap; grade 2 - definite cleared osteophytes and narrowed joint space; grade 3 - moderate multiple osteophytes, definite narrowing of joints space, some sclerosis, and possible deformity of bone contour; grade 4 - large osteophytes, marked narrowing of joint space, severe sclerosis, and definite deformity of bone contour.

Thirty-eight female grade 2 and grade 3 knee osteoarthritis patients aged between 39 - 59 years were included in the study. We included only female patients to homogenize the sample, as there are differences between women and men that could affect the adipokine profile\cite{16}. Thirty-eight healthy female volunteers, with normal radiological examinations and clinical histories and examinations, who visited the hospital for routine physical examinations were enrolled as controls. Controls were matched in terms of age and body mass index (BMI) with the patients. The BMI is defined as the body mass (weight) divided by the square of the body height, and is universally expressed in units of kg/m². Clinical information such as age, course of disease, joint X-ray grades and biochemical analyses (whole blood count, ESR) were obtained from the hospital data system.

Participants were excluded on the base of having rheumatoid arthritis, post-traumatic arthritis, previous joint infection, crystal deposition arthritis, enteropathic arthritis, hemophilic arthropathy, previous knee injury, infectious- or endocrine-related arthropathy, clinically unstable medical illness, the use of any medication (such as non-steroidal anti-inflammatory analgesic, corticosteroids, etc.) within 4 weeks prior to initiation of the study, pregnant and lactating women and those who had severe cardiovascular disease, cerebrovascular disease, acute or chronic infectious diseases, systemic inflammatory, endocrine or autoimmune disorders, liver or renal insufficiency, immune system disease, and malignant diseases.

The study was approved by the Research Ethics Committee of Dicle University Medical School and was performed in accordance with the ethical standards stated in the 1964 Declaration of Helsinki. Written informed consent was obtained from all patients and healthy volunteers prior to their participation in this study.

Standard tubes with a constant amount of ethylenediaminetetraacetic acid (EDTA) were used for the whole blood count. All blood samples were studied within one hour of sampling. The whole blood count analyses, based on the technique of laser flow cytometry scattergrams, were performed in the central laboratory of our institution using the same analyzer (Medonic CA-620, Sweden) which is routinely checked every day. Whole blood count parameters of participants were recorded from the same computerized database. ESR was determined using an automated Westergren method (Sedimat 15, LP Italiana, Italy).

**Measurement of PGRN and BMP-4**

Blood samples were obtained from the antecubital vein of all participants after overnight fasting. After clotting, blood samples were centrifuged at 2000 × g for 15 min, serum was separated, and aliquots stored at −80 °C until examination. Serum PGRN and BMP-4 concentrations were determined using a commercially available enzyme-linked immuosorbent assay kit (ELISA) (SunRedbio; Shangai, China) according to the manufacturer’s instructions. The samples were processed as recommended by the kit and run in random for the ELISA. The colour intensities were measured by a plate reader (DAR 800 microplate reader, Chemtron Pte Ltd, Singapore) with a measuring filter of 450 nm. The results were expressed as nanograms per milliliter (ng/mL). The standard curve ranged from 10 ng/mL to 160 ng/mL of BMP-4 and the standard curve showed a direct relation between optical density and BMP-4 concentration. The standard curve of ELISA for PGRN ranged from 25 ng/mL to 400 ng/mL and the standard curve showed a direct relation between optical density and PGRN concentration. The sensitivity of the BMP-
4 and PGRN commercial kit were 0.927 ng/mL and 2.158 ng/mL, respectively. The intra-assay coefficients of variation of the assays were < 10%. Assay ranges were 1 - 300 ng/mL for BMP-4 and 2.5 - 720 ng/mL for PGRN.

Statistical analysis
All statistical analyses were performed using SPSS 22.0 software (Chicago, IL, USA). Data were tested for normal distribution using the Shapiro-Wilk test. Data are expressed as mean ± standard deviation. Student’s t-test for independent samples was used to analyze and in cases of normal distribution, Mann-Whitney’s U test was used to compare the groups. The correlations between the variable pairs were analyzed using Spearman’s correlation test. Differences between groups were significant when p < 0.05.

RESULTS
A total of 76 female patients (38 knee OA and 38 controls) were included in the study. Baseline clinical characteristics are shown in Table 1. There were no significant differences between patient group with OA and healthy controls in terms of age and BMI (p = 0.522, p = 0.452, respectively). WBC values were 7.25 ± 1.55 x10³/mm³ in patients with OA vs. 7.39 ± 1.44 x10³/mm³ in the control group. Mean NLR levels were 2.16 ± 0.49 in patients with OA vs. 2.19 ± 0.47 in the control group. No difference was found between the two groups in terms of WBC and NLR values (p = 0.763, p = 0.925, respectively). ESR values were significantly higher in patients group than controls group (p = 0.022) (Table 1).

Mean BMP-4 values were 29.66 ± 13.61 ng/mL in patients with OA vs. 72.81 ± 44.06 ng/mL in the control group. BMP-4 values were found to be significantly lower in OA group (p = 0.001). Mean PGRN values were 71.93 ± 33.83 ng/mL in patients with OA vs. 268.33 ± 180.45 ng/mL in the control group. PGRN values were found to be significantly lower in OA group (p = 0.001) (Table 2).

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Osteoarthritis patients (n = 38)</th>
<th>Control Group (n = 38)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMP-4 (ng/mL)</td>
<td>29.66 ± 13.61</td>
<td>72.81 ± 44.06</td>
<td>0.001*</td>
</tr>
<tr>
<td>PGRN (ng/mL)</td>
<td>71.93 ± 33.83</td>
<td>268.33 ± 180.45</td>
<td>0.001*</td>
</tr>
</tbody>
</table>

BMP-4: Bone morphogenetic protein 4; PGRN: Progranulin; *: statistically significant

Patients with OA had a positive correlation between serum BMP-4 levels and serum PGRN levels (Table 3). There was no correlation between serum BMP-4 levels and WBC, NLR and ESR levels (Table 3). There was also no correlation between serum PGRN levels and WBC, NLR and ESR levels (Table 4).

Table 3: Relationship between BMP-4 and PGRN, WBC, NLR and ESR in osteoarthritis patients

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>BMP-4 r-value</th>
<th>WBC p-value</th>
<th>NLR p-value</th>
<th>ESR p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PGRN</td>
<td>0.898</td>
<td>0.001*</td>
<td>0.154</td>
<td>0.106</td>
</tr>
</tbody>
</table>

ESR: Erythrocyte sedimentation rate; WBC: White blood cell; NLR: Neutrophil to lymphocyte ratio; BMP-4: Bone morphogenetic protein 4; PGRN: Progranulin; *: statistically significant

Table 4: Relationship between PGRN and BMP-4, WBC, NLR and ESR in osteoarthritis patients

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>PGRN r-value</th>
<th>WBC p-value</th>
<th>NLR p-value</th>
<th>ESR p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMP-4</td>
<td>0.898</td>
<td>0.001*</td>
<td>0.206</td>
<td>0.354</td>
</tr>
</tbody>
</table>

ESR: Erythrocyte sedimentation rate; WBC: White blood cell; NLR: Neutrophil to lymphocyte ratio; BMP-4: Bone morphogenetic protein 4; PGRN: Progranulin; *: statistically significant

DISCUSSION
OA is an age-related, chronic, progressive, degenerative joint disease, but its inductive factors and underlying mechanisms are still largely unknown. It can be the result of a complex interplay of metabolic, genetic, biomechanical and biochemical factors. To our knowledge, this is the first study to show serum BMP-4 and PGRN levels in OA patients and we demonstrated that PGRN and BMP-4 levels were significantly decreased in sera of knee OA patients.

Progranulin, a secreted multifunctional growth factor, is widely expressed in epithelial, neurons, chondrocyte and immune cells and regulates
cell proliferation, migration and survival\cite{17,18}. It plays a critical role in various diseases and conditions including wound repair, the regulation of inflammation, host defense, angiogenesis, early embryogenesis, bone regeneration, tumorigenesis and neurodegenerative diseases\cite{17,19-22}. PGRN is a key regulatory factor in the resolution of inflammation. PGRN blocks the production of neutrophil attracting chemokines and cleavage of PGRN is promoted by enzymes including elastase and proteinase 3, which is secreted by neutrophils\cite{9}. Kessenbrock et al showed that mice lacking both elastase and proteinase 3 were directly linked to the accumulation of anti-inflammatory activity of PGRN, and they concluded that proteinase 3 and elastase enhance neutrophil-dependent inflammation by eliminating the local anti-inflammatory activity of PGRN\cite{23}. PGRN functions as an endogenous modulator of innate immune responses and promotes the upregulation of Th2 cytokines such as IL-4, IL-10 and IL-15\cite{24}. It plays an important role in bone metabolism, especially inflammatory conditions, and is a critical mediator of the bone healing process modulating BMP-2 and TNF-α signaling\cite{20}.

PGRN is also expressed in human articular cartilage tissue and plays a crucial role in chondrocyte proliferation, differentiation and endochondral ossification during development\cite{26}. PGRN is upregulated in the synovium of both OA and rheumatoid arthritis (RA)\cite{27}. Studies revealed that cartilage oligomeric protein (COMP), a prominent non-collagenous component of cartilage, directly binds PGRN and enhances PGRN mediated chondrocyte proliferation\cite{11}. Guo et al showed that PGRN is a novel specific inhibitor of a disintegrin and metalloproteinase with thrombospondin motifs (ADAMTS) 7/12 mediated COMP degradation, and may play a significant role in preventing the destruction of joint cartilage in arthritis\cite{28}. They also showed that expression of PGRN is increased in cartilage of OA patients and suggested that PGRN may play a role in the inflammatory component of arthritis pathogenesis, and supports the concept that arthritic chondrocytes may exhibit increased anabolic activity, including the release of growth factors. Tang et al showed that PGRN is a ligand of tumor necrosis factor receptors (TNFR), an antagonist of TNF-α signaling and plays a critical role in the pathogenesis of inflammatory arthritis in mice models\cite{29}. They suggested new potential therapeutic interventions for various TNF-α mediated pathologies and conditions and showed that the administration of recombinant human PGRN or a recombinant PGRN derivative named Atstrin, had strong anti-inflammatory effects comparable to the administration of Etanercept. Therefore, PGRN is also a potential target for the treatment of inflammatory diseases and autoimmune diseases including OA and RA. Zhao et al found that deficiency of PGRN led to spontaneous OA-like phenotype in ‘aged’ mice\cite{26}. They suggested that PGRN protects the progression of OA through multiple pathways in which first, PGRN activates the ERK1/2 signalling pathway and elevates levels of anabolic biomarkers in a TNFR2-dependent manner. Second, PGRN interacts with TNF-α and prevents the activation of the NF-κ B pathway, which upregulate the levels of various matrix metalloproteinases (MMPs) and ADAMTS, thus inhibiting cartilage degradation in OA. They also suggested that PGRN inhibits β-catenin signalling, which is also known to play a critical role in the development of OA. These findings were consistent with our study. In our study, we showed decreased serum PGRN levels in OA patients. Our results indicate that PGRN is related to the pathogenesis of osteoarthritis.

BMPs are signaling molecules, which are a member of transforming growth factor-β superfamily of proteins and were identified for their ability to induce bone formation\cite{28}. BMP-4, a member of BMPs family, promotes bone formation by inducing endochondral ossification and promotes cartilage formation by inducing mesenchymal stem cells to become chondroprogenitors and chondrocyte maturation\cite{15}. BMP-4 enhances the production of articular cartilage matrix by stimulating the synthesis of collagen type II and aggrecan and prevents chondrogenic hypertrophy by suppressing the production of collagen type X\cite{25,30}. BMP-4 also accelerates chondrocyte maturation\cite{31}. Miljkovic et al suggested with these findings that BMP-4 can be a promising agent for promoting cartilage repair in the future and modulation of BMP signaling may also become an important therapeutic approach in chronic joint diseases including RA and OA\cite{13}. These findings were consistent with our study. To our knowledge, there is no study to show serum BMP-4 in OA patients and we showed decreased serum BMP-4 levels in OA patients. Our results indicate that serum BMP-4 levels can be of use to the osteoarthritis patients as a marker.

Given that PGRN acts as a strong anti-inflammatory mediator by antagonist of TNF-α signaling and BMP-4 contributes to inflammation, we further investigated the relationship between serum PGRN and BMP-4 levels and inflammatory markers including NLR and ESR in patients with osteoarthritis. We did not find any correlations between BMP-4 and PGRN levels and inflammatory markers. This may be because we could not use specific inflammatory markers. Furthermore, our results showed that ESR levels were higher in OA
patients than controls, but our ESR level results were in normal range.

BMP-4 and PGRN are members of adipokines. Adipokines are cytokines, predominantly produced in adipose tissue and are involved in many metabolism and disease pathogenesis. In previous studies, relationship between adipokines and osteoarthritis has been widely investigated[32]. Adipokines are produced in knee OA joints by infrapatellar fat pads, chondrocytes, synovium, osteoblasts and osteoclasts and secreted to circulation[33,34]. Adipokines could affect cartilage remodeling such as chondrocyte proliferation, proteoglycan synthesis, collagen synthesis and matrix mineralization in cartilage[32,33]. Adipokines also affect bone remodeling in OA[32]. Serum and synovial levels of adipokines have been shown in many studies and they suggested that adipokines may be used for monitoring disease progression including bone erosions and osteophyte formation and following the efficiency of therapeutic interventions as biomarkers[32,33]. For future clinical applications in OA disease, adipokine-targeted therapeutic strategies are considered to prevent cartilage and bone alteration as well as inflammation[32]. Our results support the hypothesis that adipokines are involved in the pathogenesis of osteoarthritis.

In our study, patient and control groups consisted of same gender (female), age and body mass index. They also had similar ethnicity, eating patterns and lifestyles. These factors may cause interferences to analyze BMP-4 and PGRN. BMI levels in patients group was normal range and there were no differences in BMI levels between the two groups. Previous studies have shown that serum BMP-4 and PGRN levels changed in obesity patients[8,35,36]. Obesity also contributes to OA pathogenesis[37]. Therefore, we included patients with normal BMI levels in our study.

We must acknowledge some limitations of this study. The sample size of our study was small. Statistical tests usually require a larger sample size to justify that the effect did not happen by chance alone. Moreover, in our study, patient and control groups consist of same gender (female). Thus, the subjects are not representative of the general population, but instead representative of the female gender. In future studies, the levels of BMP-4 and PGRN should be analyzed in the general population. Despite these limitations, these data do form a basis for future studies examining the relationship between OA patients and serum BMP-4 and serum PGRN levels.

CONCLUSIONS

This pilot study demonstrates that serum PGRN and serum BMP-4 levels decrease in female knee osteoarthritis patients group. Serum BMP-4 and PGRN levels could be useful biomarkers of knee OA. The level of PGRN and BMP-4 in patients with OA should be paid high attention and these markers could be a potential therapeutic target for the management of OA. Further studies using larger populations and more detailed investigation will be needed to confirm our observations and to validate the current findings.

ACKNOWLEDGMENT

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REFERENCES


Comparative Evaluation of Accuracy and Compatibility Level of Different Diagnostic Methods for Bacterial Vaginosis

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ABSTRACT

Objectives: Bacterial vaginosis belonging to women of reproductive age is a common clinical problem. It is associated with several adverse gynaecological and pregnancy outcomes. Successful management of vaginal infections lies in the diagnostic approach. This study was conducted to compare the accuracy and the compatibility level of different diagnostic methods of bacterial vaginosis.

Design: Prospective study

Setting: Department of Gynecology and Obstetrics, Ayatollah Musavi hospital, Zanjan, Iran

Subjects: One hundred women aged 18 - 49 years with symptomatic vaginal discharge

Intervention: Patients were evaluated for signs and symptoms of candidal, trichomonal, and bacterial infections through interviews. Then, the participants were physically examined. Subsequently, the specimens of vaginal secretions obtained from each subject were tested for the presence of vaginal infections through microbiological diagnosis.

Main outcome measures: Compatibility level of different diagnostic methods for bacterial vaginosis

Results: In this study, 60% of the patients were diagnosed by self-reported symptoms and 54% by clinical examination to have vaginal infection. In addition, lab diagnosis confirmed the presence of vaginal infection in 47% of these patients. The results found an agreement between patients’ history, clinical examination and lab diagnoses for candidal diagnosis in 46%, Gardnerella diagnosis in 50%, and Trichomonal diagnosis in 66% of the cases.

Conclusion: This study shows that there is a significant correlation between clinical and lab diagnoses of vaginal secretions. It is therefore inferred that clinical examination is the key to early diagnosis and appropriate treatment of vaginal infections.

INTRODUCTION

Bacterial vaginosis (BV) was first described by Gardner and Dukes[1]. BV is an extremely common gynaecological problem in women of reproductive age[2]. It develops when the vaginal normal flora is altered and characterized by replacement of vaginal lactobacilli with a mixed aerobic and predominantly anaerobic micro-organisms such as Gardnerella Vaginalis (GV), Trichomona Vaginalis (TV), Candida, Prevotella, and Bacterioides[2–5]. Vaginal bacterial communities differ dramatically between healthy patients and patients with BV, where Gardnerella Vaginalis is present in over 90% of BV cases[6]. GV has been suggested as the principal cause of bacterial vaginosis, although the isolation rate of this organism from patients of bacterial vaginosis is variable (6 – 94%) due to a broad diversity in the selection of the patients’ materials, methods, and criteria for establishing a diagnosis[5]. Another important pathogen causing vaginitis is TV, which is an anaerobic flagellated protozoa; it is the causative agent of trichomoniasis[7,8]. In women, symptoms of infection may include thick, yellow, purulent vaginal discharge,
pruritus, dyspareunia, and dysuria. BV is associated with gynaecological and pregnancy complications such as increased risk of HIV infection and other sexually transmitted infections, pelvic inflammatory disease, preterm delivery and postpartum endometritis. The diagnosis of BV remained problematic because of its complex polymicrobial nature. The different diagnostic methods of BV are clinical diagnosis and laboratory-based tests. A careful consideration of patient history and physical examination may help to separate and point to an etiology. The etiologic agent can also be distinguished by appropriate laboratory tests. The diagnosis is usually based on Amsel criteria, which requires the presence of at least three out of four criteria: first, an elevated vaginal pH greater than 4.5; second, increased vaginal discharge; third, the presence of clue cells (vaginal epithelial cells covered by bacteria) in the vaginal fluid; and finally, an amine (fishy) odour after the addition of 10% potassium hydrochloride to the vaginal fluid, positive ‘whiff test’. Laboratory-based tests include gram staining of vaginal smears, vaginal culture, PCR-based test, and gas-liquid chromatography. The traditional diagnostic method is laboratory diagnosis. However, this approach is expensive and not available at all health centres. In some cases, a probable diagnosis is made on the basis of the nature of the discharge, which is often inaccurate and incomplete. The World Health Organisation (WHO) developed and advocated the syndromic management approach (clinical diagnosis) which is based on the identification of a relatively constant combination of symptoms and signs (syndrome) and on the knowledge of the most common causative organisms of these syndromes.

Because of the high prevalence and already-mentioned serious complications associated with this common disorder, its accurate diagnosis and treatment is critical. The aim of the present study was to compare the compatibility between a diagnosis based on the self-reported symptoms, clinical diagnosis, and microbiological diagnosis in the etiology of BV.

SUBJECTS AND METHODS
After approval by the ethical committee of Zanjan University of Medical Sciences, this prospective study was conducted on 100 married women with vaginal discharge who attended the gynaecological outpatient department during the period between July 2013 and July 2014 at Ayatollah Mousavi Hospital, Zanjan, Iran. Written informed consent was obtained from all patients. The inclusion criteria were patients aged between 18 and 49 years with vaginal discharge. The exclusion criteria were menstruation, virgin, pregnant, and post-menopausal women, those with chronic diseases such as diabetes, kidney transplantation, immune system disorders, corticosteroid use, receiving antimicrobials or antifungals (topical/oral) in the previous week, and those with sexual intercourse during the past 48 hours.

The examination programme consisted of three parts: taking a history (interview), clinical gynaecological examination, and microbiological examination of vaginal and cervical sample. The interviews consisted of the following data: demographic characteristics, data on BMI, educational level, occupation, symptoms such as itching, burning, abdominal pain, dysuria, type of discharge (clear, thick, foamy, cheese), discharge colour (white, green and yellow), and the smell of the discharge, and duration of symptoms which indicated the presence or absence of vaginitis. The patients were given a first diagnosis based on self-reported symptoms.

The gynaecological examinations were performed by gynaecologists in gynaecological clinic, while the pelvic examinations were performed with speculum and bimanual. Observations included type of discharge, colour, smell, amount of discharge, and the appearance of the cervix recorded in the form of data collection. The speculum examinations showed the clinical characteristics of the vaginal wall redness, presence of vaginal secretion, and change in its quality. The patients were given a second diagnosis (clinical diagnosis) based on the clinician’s judgement. The microbiological examinations were performed by using vaginal samples for the detection of Candidial, Trichomonal and Gardnerella vaginitis. The endocervix was first cleaned with a sterile cotton swab to remove mucus and exudates; next, two vaginal Dacrone swabs were collected from the upper part of the posterior fornix and lateral vaginal walls by using sterile cotton-tipped swabs. One Dacrone swab was taken to prepare two smears for gram and papanicolaou staining for the detection of Gardnerella vaginalis and Trichomona vaginalis. The remaining Dacrone swab sample was used for Candida culture. Once the samples were obtained, they were transported to the laboratory in less than 15 minutes. After the samples were submitted to the microbiology laboratory, they were processed immediately for possible isolation and identification of pathogenic microorganisms in accordance with standard laboratory methods.

For the detection of GV, the patient was considered to have bacterial vaginosis if at least three or more of the four Amsel criteria were present. The pH of the discharge was measured with a Nitrazin Merck paper (Germany). The swab samples were used for amine test, direct microscopy, and culture. The wet film was examined microscopically for the presence of clue cells. To improve BV diagnosis, all samples...
were Gram-stained and analysed by using the Nugent score[27]. Briefly, the Gram-stained vaginal smears were examined under the oil immersion objective (1000x magnification). We created a Gram stain scoring system based on the evaluation of the following morphotypes: small Gram-variable rods (GV morphotypes), small gram-negative rods (Bacteroides spp. morphotypes), and curved Gram-variable rods (Mobiluncus spp. morphotypes). The vaginal Gram-stained smears were scored by using the Nugent method in which a Nugent score of 7 - 10 is classified as positive for bacterial vaginosis, 4 - 6 as intermediate, and 0 - 3 indicates normal vaginal microbiota.

The Nugent score is a Gram stain scoring system for vaginal swabs to diagnose bacterial vaginosis. It was first described in 1991 by R.P Nugent, after whom it is named. The Nugent score is calculated by assessing for the presence of large Gram-positive rods (Lactobacillus morphotypes; decrease in Lactobacillus scored as 0 - 4), small Gram-variable rods (Gardnerella vaginalis morphotypes; scored as 0 - 4), and curved Gram-variable rods (Mobiluncus spp. morphotypes; scored as 0 - 2); it can range from 0 - 10. A score of 7 - 10 is consistent with bacterial vaginosis without culture. The Nugent score is now rarely used by physicians due to the time it takes to read the slides and the requirement for a trained microscopist[28].

For detection of TV, a swab was gently agitated in the saline, and a wet mount on a clean slide was prepared and observed under a microscope for motile trichomonads to confirm flagellar movement, morphological features, and the number of TV. Also, papanicolaou staining was conducted on the smear from vaginal discharge posterior fornix to confirm the diagnosis of trichomonas. The prepared smear for detection of TV was also used for the detection of Candida hyphae. All the vaginal swabs that were smear positive for Candida were inoculated on Sabouraud’s Dextrose Agar (Germany) and the colonies were identified by the germ tube test.

All the findings were recorded, and comparisons were drawn between clinical and microbiological diagnostic approaches. The collected data was analysed by using SPSS 11.5. The descriptive results were expressed as mean and standard deviation. Categorical tables, Chi-square values, probability coefficients, sensitivities, specificities, positive predictive values, and negative predictive values of the three diagnostic approaches were derived and compared. Further, κ statistics (kappa) and interpretation of κ are also reported to measure the amount of agreement between the two variables. Conclusions were drawn from the tabulated results.

RESULTS

The age of the participants in this survey ranged from 18 - 49 years, with a mean of 33.05 ± 7.97 years. Vaginal infections were common in women between the age groups of 20 - 40 years and accounted for 73% of the cases. BMI ranged from 18.37 - 37.17 kg/m², with a mean of 26.78 ± 18.37 kg/m². As many as 23% of the patients were illiterate and 97% were housewives.

Table 1 depicts the symptoms and signs of vaginitis based on patients’ complaints and clinical examination. The most common symptom noted was abdominal pain, seen in 61% of the patients with vaginal discharge. The majority of the women (61%) had thick and white secretions, and complained of unpleasant smell of the discharge. Appearance of the cervix was normal in most cases (81%). 35% of cases had normal oestrogen discharge. Only 3% of these women were found to have cervical motion tenderness in bimanual examination. The majority (49%) of the cases with vaginal discharge had pH ranging from 5 - 6.

Table 2 shows the prevalence of GV, TV, and Candida based on the three diagnostic methods.

<table>
<thead>
<tr>
<th>Symptoms and signs of vaginitis</th>
<th>Variables</th>
<th>n(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptoms observed</td>
<td>Abdominal pain</td>
<td>61 (61)</td>
</tr>
<tr>
<td></td>
<td>Itching</td>
<td>59 (59)</td>
</tr>
<tr>
<td></td>
<td>Burning</td>
<td>47 (47)</td>
</tr>
<tr>
<td>Discharge color</td>
<td>White</td>
<td>50 (50)</td>
</tr>
<tr>
<td></td>
<td>Yellow</td>
<td>46 (46)</td>
</tr>
<tr>
<td></td>
<td>Green</td>
<td>4 (4)</td>
</tr>
<tr>
<td>Type of discharge</td>
<td>Thick</td>
<td>42 (42)</td>
</tr>
<tr>
<td></td>
<td>Clear</td>
<td>38 (38)</td>
</tr>
<tr>
<td></td>
<td>Cottage cheese</td>
<td>20 (20)</td>
</tr>
<tr>
<td></td>
<td>Unpleasant smell of discharge</td>
<td>61 (61)</td>
</tr>
<tr>
<td>Appearance of the cervix</td>
<td>Normal cervix</td>
<td>81 (81)</td>
</tr>
<tr>
<td></td>
<td>Ectropion</td>
<td>14 (14)</td>
</tr>
<tr>
<td></td>
<td>Cervicitis</td>
<td>5 (5)</td>
</tr>
<tr>
<td>Discharge pattern</td>
<td>Normal estrogen</td>
<td>35 (35)</td>
</tr>
<tr>
<td></td>
<td>Normal progesterone</td>
<td>25 (25)</td>
</tr>
<tr>
<td></td>
<td>Yellow and green</td>
<td>23 (23)</td>
</tr>
<tr>
<td></td>
<td>Cottage Cheese white</td>
<td>13 (13)</td>
</tr>
<tr>
<td></td>
<td>Curdy white</td>
<td>4 (14)</td>
</tr>
<tr>
<td>Vaginal discharge pH</td>
<td>4</td>
<td>21 (21)</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>49 (49)</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>27 (27)</td>
</tr>
<tr>
<td></td>
<td>7</td>
<td>3 (3)</td>
</tr>
<tr>
<td>Uterus and cervical tenderness</td>
<td>Cervical motion tenderness negative</td>
<td>97 (97)</td>
</tr>
<tr>
<td></td>
<td>Cervical motion tenderness positive</td>
<td>3 (3)</td>
</tr>
</tbody>
</table>
Based on self-reported symptoms, clinical examination, and lab diagnosis, 60%, 54%, and 47% of the patients, respectively, had vaginal infection. According to this table, the agreement between clinical and lab diagnosis for Candida was 46%, 50% for GV and 66% for TV.

<table>
<thead>
<tr>
<th>Type of vaginitis</th>
<th>Self-reported symptoms</th>
<th>Clinical diagnosis</th>
<th>Lab diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gardnella Vaginalis</td>
<td>10</td>
<td>7</td>
<td>14</td>
</tr>
<tr>
<td>Trichomona Vaginalis</td>
<td>14</td>
<td>9</td>
<td>10</td>
</tr>
<tr>
<td>Candida</td>
<td>14</td>
<td>13</td>
<td>7</td>
</tr>
<tr>
<td>Etiology not found</td>
<td>22</td>
<td>25</td>
<td>16</td>
</tr>
<tr>
<td>Physiological leucorrhea</td>
<td>40</td>
<td>46</td>
<td>53</td>
</tr>
<tr>
<td>Overall</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>

Table 2: Prevalence of Gardnella Vaginalis, Trichomona Vaginalis, and Candidal vaginitis based on three diagnostic approaches

The results of the comparison between the self-reported symptoms with the lab diagnosis showed that there is a significant correlation between these two diagnostic approaches for the diagnosis of Candida, GV, and TV (Kappa = 0.343, p-value < 0.001) (Table 4).

The final results showed that there is a significant homogeneity between clinical and lab diagnosis for the diagnosis of Candidal, GV, and TV (Kappa = 0.521, p-value < 0.001) (Table 5).

### DISCUSSION

Due to the high prevalence of BV in women of reproductive age and its serious complications, clear diagnosis and treatment is critical. The main goal of the present study was to compare the accuracy and compatibility of different diagnostic methods of BV.

Table 3 depicts the prevalence of Candida, TV, and BV based on self-reported symptoms and clinical examination. The results showed that there is a significant homogeneity between two diagnostic approaches for the diagnosis of vaginitis (Kappa = 0.571, p-value < 0.001).

<table>
<thead>
<tr>
<th>Diagnosis based on self-reported symptoms</th>
<th>Candida</th>
<th>Gardnella Vaginalis</th>
<th>Trichomona Vaginalis</th>
<th>Physiologic leucorrhea</th>
<th>Etiology not found</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>Candida</td>
<td>9</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>3</td>
<td>14</td>
</tr>
<tr>
<td>Gardnella Vaginalis</td>
<td>1</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>7</td>
<td>10</td>
</tr>
<tr>
<td>Trichomona Vaginalis</td>
<td>0</td>
<td>0</td>
<td>8</td>
<td>4</td>
<td>2</td>
<td>14</td>
</tr>
<tr>
<td>Physiological leucorrhea</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>37</td>
<td>1</td>
<td>40</td>
</tr>
<tr>
<td>Etiology not found</td>
<td>2</td>
<td>3</td>
<td>1</td>
<td>4</td>
<td>12</td>
<td>22</td>
</tr>
<tr>
<td>Overall</td>
<td>12</td>
<td>7</td>
<td>9</td>
<td>46</td>
<td>25</td>
<td>100</td>
</tr>
</tbody>
</table>

Kappa = 0.571, P value < 0.001, *Kappa statistic measures inter-rater reliability (sometimes called inter-observer agreement). Inter-rater reliability, or precision, happens when the data raters (or collectors) give the same score to the same data item. This statistic should only be calculated when: two raters each rate one trial on each sample, or one rater rates two trials on each sample. Kappa less than 0.3 is weak, between 0.3 to 0.7 is fair and more than 0.7 is excellent.**Measure of agreement = 68% [(9+2+8+37+12)/100], Measure of agreement is calculated as the number of the cases with the same diagnosis divided by total number.

In our study, maximum cases of vaginal discharge were observed between 20 - 40 years of age (73%). Similar peak age incidence (82.8% between 20 - 40 years) was noted in other studies.

A number of studies explored the association of vaginal discharge with vaginal infections.

Table 4: Prevalence of Gardnella Vaginalis, Trichomona Vaginalis, and Candidal vaginitis based on self-reported symptoms and lab diagnosis

<table>
<thead>
<tr>
<th>Diagnosis based on self-reported symptoms</th>
<th>Candida</th>
<th>Gardnella Vaginalis</th>
<th>Trichomona Vaginalis</th>
<th>Physiologic leucorrhea</th>
<th>Etiology not found</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>Candida</td>
<td>5</td>
<td>0</td>
<td>1</td>
<td>3</td>
<td>5</td>
<td>14</td>
</tr>
<tr>
<td>Gardnella Vaginalis</td>
<td>5</td>
<td>5</td>
<td>0</td>
<td>3</td>
<td>1</td>
<td>10</td>
</tr>
<tr>
<td>Trichomona Vaginalis</td>
<td>0</td>
<td>1</td>
<td>5</td>
<td>4</td>
<td>4</td>
<td>14</td>
</tr>
<tr>
<td>Physiological leucorrhea</td>
<td>2</td>
<td>2</td>
<td>0</td>
<td>35</td>
<td>3</td>
<td>40</td>
</tr>
<tr>
<td>Etiology not found</td>
<td>1</td>
<td>6</td>
<td>4</td>
<td>8</td>
<td>3</td>
<td>22</td>
</tr>
<tr>
<td>Overall</td>
<td>7</td>
<td>14</td>
<td>10</td>
<td>53</td>
<td>16</td>
<td>100</td>
</tr>
</tbody>
</table>

Kappa = 0.343, P-value < 0.001
Regarding the clinical manifestations of vaginal infections among symptomatic women, all these studies found a variable degree of association between complaint of vaginal discharge and vaginal infections. Although these symptoms are not reliable, they are described in textbooks as aids for the clinician to make a diagnosis of vaginal infection and to help choose the proper medication[31]. In this study, abdominal pain and pruritis were the most common symptoms in patients with vaginal discharge. Similar findings were noted by other authors[26,32]. The nature of vaginal discharge may be helpful as one of the criterion in differentiating the types of vaginal infections as noted by other authors[26]. Consistently thick secretion was seen in 42% of the participants, while 50% of the cases had white discharge. The majority of the cases with vaginal discharge had pH ranging from 5 to 6. Vaginal pH has been regarded as a sensitive, but not a specific, criterion for diagnosing vaginal infections. The appearance of the cervix was normal in 81% of the women, while 35% had normal oestrogen discharges and 97% had no cervical motion tenderness in bimanual examination. These findings will probably help the syndromic management of abnormal vaginal discharge[26,33,34].

In 80 - 90% of cases, enhanced vaginal secretion is associated with the microbiological cause, which can be identified, and most vaginal infections are a consequence of infection with synergistic bacteria (bacterial vaginosis and nonspecific vaginitis), fungi (vulvovaginal candidiasis), and protozoa (trichomoniasis). Approximately 50% of infections are caused by bacteria and 50% by fungi and parasite[35]. In the present study, the etiological diagnosis was reached in 84% of the patients. In the remaining 16% of patients, no diagnosis could be made with the microbiological diagnostic approach. This is in accordance with other studies that show that in 10 - 58% of patients complaining of vaginal discharge, no diagnosis could be reached by using any of the diagnostic approaches under consideration[26,27,36,37]. This group of patients may have normal physiological discharge or less frequent viral vaginitis, aerobic vaginitis or vaginal lactobacillosis that are not routinely detected[38]. Epidemiological studies have been limited by the use of variable diagnostic methods among heterogeneous populations. The results of our study showed that there is a significant association between patient complaints and clinical and microbiological examinations for the diagnoses of vaginitis, while the percentage agreements between clinical diagnosis and lab diagnosis to diagnose BV were 50%, 66% for TV and 46% for Candida. In the study of Tehrani et al, there was concordance between clinical diagnosis and diagnosis by patient complaints, which is similar to our results[34]. Similarly, Goudarzi stated that the patient complaints and clinical examination can be a quick and accurate diagnosis for the diagnoses of BV, which could help proper treatment[33]. There was a good agreement between the clinical and microbiological diagnostic approaches for the diagnosis of TV in the present study. In contrast, some studies suggest that diagnosis of trichomoniasis based on only clinical symptoms should not be done due to two reasons: first, clinical symptoms of trichomoniasis may be similar to those of other STDs; second, clinical symptoms such as strawberry cervix and spumy discharge are seen in 2% and 12% of TV-infected patients, respectively[39]. According to some studies, a diagnosis of trichomoniasis through clinical examinations has 88% false negative and 29% false positive results, which is not consistent with our study[40].

In the study of Rekha and Jyothi, when the visual and clinical diagnostic approaches were compared with the microbiological diagnosis, visual diagnosis was noted to have moderate sensitivity for BV and Candida, moderate specificity for TV, lower sensitivity for TV, and lower specificity for BV[26]. This implies that if the visual or clinical approaches were used to diagnose the infections, BV and Candida would be over-treated, while TV would be under-treated. Also, this study showed that the visual diagnosis was not suited for diagnosis of TV.

Table 5: Prevalence Candidial, Gardnella Vaginalis and Trichomona Vaginalis based on clinical and lab diagnosis

<table>
<thead>
<tr>
<th>Clinical Diagnosis</th>
<th>Lab Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Candida</td>
</tr>
<tr>
<td>Candida</td>
<td>6</td>
</tr>
<tr>
<td>Gardnella Vaginalis</td>
<td>0</td>
</tr>
<tr>
<td>Trichomona Vaginalis</td>
<td>0</td>
</tr>
<tr>
<td>Physiologic leucorrhrea</td>
<td>0</td>
</tr>
<tr>
<td>Etiology not found</td>
<td>1</td>
</tr>
<tr>
<td>Overall</td>
<td>7</td>
</tr>
</tbody>
</table>

Kappa = 0.521, p-value < 0.001
and Candida, but has a moderate reliability for BV. Our results showed that when clinical approaches are used to diagnose the infections, Candida would be over-treated, while GV and TV would be under-treated—this is somewhat consistent with the study of Rekha and Jyothi[26].

The diagnosis based only on the presence of signs or symptoms were insufficient to diagnose Candida in the absence of any laboratory confirmation. In this study, 14 samples were diagnosed by self-reported symptoms to have Candida infection and lab diagnosis confirmed the presence of Candida in seven of these patients. Our results are consistent with other studies detailing the over treatment that results from the use of syndromic diagnosis based on vaginal discharge to diagnose vaginal conditions[41,42]. Previous findings also demonstrate that a minority of women with vaginal discharge have vulvovaginal candidiasis[41,43,44]. Thus, the diagnosis of Candida based solely on signs or symptoms leads to over estimation of the prevalence of vulvovaginal candidiasis and its over treatment while leaving the actual cause of the vaginal symptoms untreated. This finding of misdiagnosis based on symptoms is relevant for women who self-diagnose vulvovaginal candidiasis.

In this study, the percentage agreement between the clinical and lab diagnostic for the diagnosis of GV and Candida was good. The study by Singh et al showed that history and clinical examination alone are not accurate in establishing the correct diagnosis for BV and Candida in women with symptomatic vaginal discharge. This study suggests, however, that bypassing the physical examination would result in misdiagnosis in both Candida and BV[45]. In addition, women with two or more infections would be inadequately diagnosed and treated; for example, women infected with Candida may have discharge caused by bacterial vaginosis and could thus be misdiagnosed with vulvovaginal candidiasis[41]. These findings emphasize the problems inherent in diagnosing vaginal conditions based on clinical examination alone[46-48]. Some authors show that by adding simple tests, as recommended by WHO (for example, addition of simple Gram staining of the vaginal smears), the sensitivity of clinical diagnosis for all the vaginal infections improved[34,49].

A meta-analysis evaluated the role of the clinical examination for a diagnosis of vaginal microorganisms. The results of that study showed that the cause of vaginal complaints could be easily diagnosed when typical findings appear in microscopy[50]. The cause of vaginitis in most patients might be determined by vaginal pH, a potassium hydroxide (KOH) test, and microscopic examination of fresh samples of the discharge[51].

There are some reasons for these discrepancies. First, epidemiological studies have been limited by the use of variable case definitions and diagnostic methods among heterogeneous populations. Second, the women in this cohort were selected from urban areas, which can limit the generalizability of these results. Third, because of the cross-sectional nature of our analysis, we could not immediately perform any follow-up of the female patients. Finally, some limitations are actually inherent to cross-sectional studies. Survey studies are valuable for estimating the burden of an event and for generating hypotheses, but they do not provide strong evidence for risk factors.

Owing to the time-constraint at the outpatient clinic and patient overload, physicians often use clinical laboratory tests to diagnose vaginitis. Since laboratory techniques require approximately two days, empirical treatment is sometimes started based on clinical findings depending on the severity of patient complaints. Early detection and treatment of vaginitis appear to have a role in reducing the complications associated with these infections. However, problems relating to a diagnosis continue to dominate the clinical practice, even though new tests have been introduced. Hence, it may be important to explore primary preventive strategies to target the risk factors or behaviours of bacterial vaginosis.

Although most of the literature reviewed showed poor correlation between self-reported symptoms, clinical diagnosis and microbiological diagnosis of BV and TV and Candida infection in term of false positives and false negatives, the authors concluded that their study proves the correlation is excellent and that in diagnosing infective vaginosis, one can depend on self-reported symptoms.

CONCLUSIONS

This study showed that there is a significant correlation between self reported symptom, clinical examination and lab diagnoses of vaginal secretions. It is, therefore, inferred that clinical examination is key to early diagnosis and appropriate treatment of vaginal infections. Further studies are needed to know the utility of various diagnostic approaches and the best approach that could be implemented for rapid and accurate diagnosis.

ACKNOWLEDGMENT

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Patterns and Predictors of Premenstrual Syndrome in Jordanian Women

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1Department of Family and Community Medicine, School of Medicine, University of Jordan, Jordan
2School of Medicine, University of Jordan, Jordan
3Emergency Medicine Resident, University of Jordan, Jordan

ABSTRACT

Objective: To determine the prevalence of premenstrual syndrome (PMS) in Jordanian women and to determine the socio-demographic, gynecological, and lifestyle predictors for the occurrence of PMS

Design: Cross-sectional study

Setting: Family medicine clinic at the Jordan University Hospital

Subjects: A convenient sample of 179 women who attended the clinic for different reasons, who fit the inclusion criteria and who agreed to participate in the study were included.

Intervention: The women completed a self-administered questionnaire, including an Arabic validated version of the Shortened Premenstrual Assessment Form (SPAF).

Main outcome measures: Women were classified as no PMS, mild, moderate or severe PMS according to their SPAF total score. Data were analyzed using SPSS (version of the 19). P-values were considered significant at p < 0.05.

Results: Of the 179 women, 88% were identified as suffering from PMS to some degree. Women aged 21 – 25 years and those with dysmenorrhea were more likely to suffer from severe symptoms with statistically significant p-value. Interestingly, women who engaged in regular effective exercise were more likely to suffer from severe PMS symptoms (p = 0.013). Also, women who consumed fast food regularly were more likely to suffer from PMS symptoms (p = 0.047).

Conclusion: PMS is a common problem that affects women in the reproductive age group. Health care providers should consider socio-demographic, gynecological and lifestyle factors associated with PMS.

INTRODUCTION

The menstrual cycle has attracted research interest since the 1930s and is an excellent model of ovarian steroid influence on emotion, behavior, and cognition[1]. Premenstrual syndrome (PMS) is a condition of recurrent physical and psychological symptoms occurring in a cyclic fashion during the luteal phase of the menstrual cycle[2]. Over 150 PMS symptoms have been identified[3], including physical, behavioral, and emotional. Although different definitions of PMS might focus on one or more of those domains[4], each is important and should not be underestimated.

Worldwide data suggests that 75 – 85% of women experience PMS to some extent during the late luteal phase of each menstrual cycle (7 – 14 days prior to menstruation)[5-7]. Data from university students and employers in Jordan demonstrate similar findings, with 80.2% of the studied population suffering from PMS[8]. Moreover, 20 – 40% of menstruating women experience PMS to a degree that warrants clinical treatment[2,9]. Diagnosing and effectively treating PMS is of vital importance for both the clinician and patient, considering the prevalence, chronicity, and potential distress.

Although the exact etiology of PMS is unknown[10,11], there are many new hypotheses, including deficiencies in some minerals, serotonin deficiency, and an exaggerated response to normal...
hormonal changes. Other hypotheses currently under investigation include increased endorphins, alterations in the gamma-aminobutyric acid system, and hypoprolactinemia\cite{12,13}. Regardless of the exact pathophysiology behind PMS, its importance as a chronic, distressing, and disabling problem affecting women of reproductive age should not be overlooked.

Depending on the defining body, there are many definitions of PMS\cite{3}. One well-recognized tool to assess PMS is the Shortened Premenstrual Assessment Form (SPAF), which classifies PMS symptoms into pain, affect, and water retention symptoms. Once PMS is recognized, it is crucial to determine the important risk factors, including sociodemographic factors, lifestyle, and gynecological factors. Some risk factors, such as younger age, higher body mass index, menstrual cycle regularity, and history of abuse have been studied\cite{14}.

As there are very limited data regarding the prevalence and associated risk factors of PMS in Jordanian women, the purpose of the current study was to determine the prevalence of premenstrual syndrome in Jordanian women and to determine the sociodemographic, gynecological, and lifestyle predictors for the occurrence of PMS. These data will help clinicians to better understand the problem and tailor management plans accordingly.

SUBJECTS AND METHODS

Design

This cross-sectional study was conducted at a family medicine walk-in clinic in a hospital in Amman, the capital of Jordan. The patients at this hospital are primarily medically insured through the Ministry of Health, universities, and many affiliated public institutions and companies, although there are also some private patients. The clinics serve patients of all age groups who attend the clinic complaining of acute, sub-acute, and chronic complaints, as well as those who attend for health checkups and preventive services.

Participants

A convenience sample of 179 women was recruited. Women attending the clinic for various reasons from February 2015 through November 2015 were asked to complete a self-administered questionnaire. Inclusion criteria were all women aged 15 – 45 years old who attended the clinic in the aforementioned period of time and who agreed to participate in the study. Women were excluded from the study if they were pregnant, had given birth in the last 6 months, or were on hormonal contraception; each of these factors might affect the occurrence and severity of PMS\cite{15}. A trained research assistant was responsible for obtaining consent from patients, explaining the purpose of the study, distributing the questionnaire, ensuring that all questions were answered, and helping fill out the questionnaires for patients with literacy problems or poor eyesight. Ethical approval was obtained from the appropriate ethical committees.

**Questionnaire**

The questionnaire consisted of two main parts. The first part asked about sociodemographic variables and gynecological history, including age, education level, average income, marital status, occupation, age at menarche, menstrual cycle regularity, and any history of chronic gynecological problems (mainly polycystic ovary syndrome, endometriosis, and/or pelvic inflammatory disease).

The second part of the questionnaire consisted of a modified SPAF. This form, developed by Allen, McBride, and Pirie\cite{2}, was used to determine the degree of premenstrual symptoms. The 10-item SPAF is used to assess the presence and/or change in intensity of symptoms that are typically expressed during the luteal phase of the menstrual cycle. The SPAF provides the same assessment as the original 95-item Premenstrual Assessment Form as demonstrated by its equally strong reliability (test-retest coefficient

<table>
<thead>
<tr>
<th>Sociodemographic variable</th>
<th>Frequency</th>
<th>Percent</th>
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<tr>
<td>Age Groups</td>
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<tr>
<td>15 - 20</td>
<td>20</td>
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<td>26 - 30</td>
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<td>20.8</td>
</tr>
<tr>
<td>31 - 35</td>
<td>33</td>
<td>18.5</td>
</tr>
<tr>
<td>36 - 40</td>
<td>20</td>
<td>11.2</td>
</tr>
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<td>41 - 45</td>
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<tr>
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<td>0.6</td>
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<td></td>
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<td></td>
</tr>
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</tr>
<tr>
<td>More than 1500</td>
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<td>9.6</td>
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<tr>
<td>Occupation</td>
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<td></td>
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<td>Student</td>
<td>51</td>
<td>28.7</td>
</tr>
<tr>
<td>Housewife</td>
<td>51</td>
<td>28.7</td>
</tr>
<tr>
<td>Full time job</td>
<td>71</td>
<td>39.9</td>
</tr>
<tr>
<td>Part time job</td>
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<td>1.1</td>
</tr>
<tr>
<td>Other</td>
<td>3</td>
<td>1.7</td>
</tr>
</tbody>
</table>

JOD : Jordanian dinar

Table 1: Sociodemographic characteristics of the sample
range of 0.6 – 0.7) and validity (internal consistency coefficient of 0.95)[16]. Owing to linguistic reasons, during translation for the current study, we divided the first item in the questionnaire into two questions; accordingly, patients were asked about breast pain and tenderness in one question and breast enlargement in another question. We also added two more items as per our literature review, including the appearance of acne on the face, upper chest or back, and headaches[15,17,18]. Our new version of SPAF was examined by three full professors and three assistant professors in the appropriate medical department; all suggested changes were discussed and resolved. The final Arabic version of our modified SPAF was examined for reliability in a pilot study of 40 patients who were not included in the present analysis. The analysis revealed the questionnaire to be reliable (Cronbach’s α of 0.747).

As the SPAF is scaled from 0 – 3 according to the severity of the symptoms (0, no symptoms; 1, mild symptoms; 2, moderate symptoms; and 3, severe symptoms), PMS diagnosis was given on the basis of a PMS score >14 with the symptoms preceding menses. PMS scores from 0 – 14 were rated as no PMS, 15 – 29 as mild PMS, 30 – 44 as moderate PMS, and > 45 as severe PMS.

### Statistical Analysis

Data were analyzed using SPSS (version 19). The χ² test was used to compare the frequencies of categorical variables; an independent T-test, analysis

### Table 2: Comparison of population demographics in women with mild, moderate and severe PMS (N = 179)

<table>
<thead>
<tr>
<th>Sociodemographic variable</th>
<th>No PMS n (%)</th>
<th>Mild PMS n (%)</th>
<th>Moderate PMS n (%)</th>
<th>Severe PMS n (%)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of women</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15 - 20</td>
<td>6 (20)</td>
<td>10 (12)</td>
<td>3 (4.8)</td>
<td>1 (33.3)</td>
<td>0.047*</td>
</tr>
<tr>
<td>21 - 25</td>
<td>6 (20)</td>
<td>20 (24.1)</td>
<td>27 (43.5)</td>
<td>2 (66.7)</td>
<td></td>
</tr>
<tr>
<td>26 - 30</td>
<td>8 (26.7)</td>
<td>14 (16.9)</td>
<td>15 (24.2)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>31 - 35</td>
<td>5 (16.7)</td>
<td>20 (24.1)</td>
<td>8 (12.9)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>35 - 40</td>
<td>1 (3.3)</td>
<td>11 (13.3)</td>
<td>8 (12.9)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>41 - 45</td>
<td>4 (13.3)</td>
<td>8 (9.6)</td>
<td>1 (1.6)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Marital status</td>
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<td></td>
<td></td>
<td>0.447</td>
</tr>
<tr>
<td>Single</td>
<td>17 (56.7)</td>
<td>37 (44)</td>
<td>34 (54.8)</td>
<td>3 (100)</td>
<td></td>
</tr>
<tr>
<td>Married</td>
<td>13 (43.3)</td>
<td>44 (52.4)</td>
<td>23 (37.1)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Widowed</td>
<td>0 (0)</td>
<td>1 (1.2)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Divorced</td>
<td>0 (0)</td>
<td>2 (2.4)</td>
<td>4 (6.5)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (1.6)</td>
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<tr>
<td>Level of Education</td>
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<tr>
<td>Illiterate</td>
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<td>1 (1.2)</td>
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<tr>
<td>Elementary</td>
<td>1 (3.3)</td>
<td>3 (3.6)</td>
<td>1 (1.6)</td>
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<td></td>
</tr>
<tr>
<td>High school</td>
<td>8 (26.7)</td>
<td>19 (22.6)</td>
<td>11 (17.7)</td>
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<tr>
<td>Bachelor's degree</td>
<td>20 (66.7)</td>
<td>50 (59.5)</td>
<td>44 (71)</td>
<td>3 (100)</td>
<td></td>
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<tr>
<td>Higher education</td>
<td>1 (3.3)</td>
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<td>5 (8.1)</td>
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<tr>
<td>Less than 800</td>
<td>17 (56.7)</td>
<td>50 (61)</td>
<td>34 (54.8)</td>
<td>2 (66.7)</td>
<td></td>
</tr>
<tr>
<td>800 - 1500</td>
<td>11 (36.7)</td>
<td>27 (32.9)</td>
<td>19 (30.6)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>More than 1500</td>
<td>2 (6.7)</td>
<td>5 (6.1)</td>
<td>9 (14.5)</td>
<td>1 (33.3)</td>
<td></td>
</tr>
<tr>
<td>Job</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.985</td>
</tr>
<tr>
<td>Student</td>
<td>11 (36.7)</td>
<td>20 (24.1)</td>
<td>18 (29)</td>
<td>2 (66.7)</td>
<td></td>
</tr>
<tr>
<td>Housewife</td>
<td>8 (26.7)</td>
<td>26 (31.3)</td>
<td>17 (27.4)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Full time job</td>
<td>10 (33.3)</td>
<td>35 (42.2)</td>
<td>25 (40.3)</td>
<td>1 (33.3)</td>
<td></td>
</tr>
<tr>
<td>Part time job</td>
<td>0 (0)</td>
<td>1 (1.2)</td>
<td>1 (1.6)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>1 (3.3)</td>
<td>1 (1.2)</td>
<td>1 (1.6)</td>
<td>0 (0)</td>
<td></td>
</tr>
</tbody>
</table>

* significant p ≤ 0.05; JOD : Jordanian dinar
of variance, and linear correlation were used to compare continuous data as appropriate. P-values were considered significant at \( p < 0.05 \).

**RESULTS**

Of the studied population, 88% suffered from some degree of PMS, 50% had mild PMS, and only 2% suffered from severe PMS (Figure 1). As plotted in Table 1, more than 50% of the studied population was 20 – 30 years old, 50.8% were single women, more than 65% had attained a bachelor’s degree, and ~40% worked full-time.

Regarding PMS and sociodemographic variables (Table 2), women aged 21 – 25 years were more likely to suffer from severe PMS \( (p = 0.047) \). However, education level, marital status, occupation, and income were not significantly associated with the occurrence or severity of PMS.

Table 3 demonstrates the association between lifestyle factors, smoking, medication and over-the-counter daily supplement use on prevalence of PMS. Interestingly, women who engaged in regular exercise of 150 minutes or more a week were more likely to suffer from severe PMS \( (p = 0.047) \). In addition, women who consumed fast food weekly were also more likely to suffer from severe PMS symptoms \( (p = 0.013) \). However, smoking, type of bread, use of a daily vitamin and mineral supplement, and the daily consumption of caffeinated drinks were not significantly associated with the occurrence or severity of PMS.

When comparing gynecological factors with PMS occurrence (Table 4), women who suffered from dysmenorrhea were more likely to suffer from severe PMS. However, parity and the presence of other gynecological diagnoses (such as polycystic ovarian syndrome and endometriosis) were not statistically significantly associated with PMS. Interestingly, women with severe PMS symptoms were more likely to seek medical consultation for their symptoms \( (p = 0.009) \).

**DISCUSSION**

Premenstrual syndrome remains a clinical entity of great significance in medical practice\[^5\]. The prevalence of PMS varies significantly, depending on the studied age group, race, and methodology to define PMS, ranging from 10% in Switzerland\[^{19}\] to 98.2% in one Iranian study\[^{20}\]. According to a meta-analysis, the pooled prevalence was estimated to be 48% (95% confidence interval (CI): 33 – 63%). One recent Jordanian study reported a prevalence of 80% in college students and workers\[^{8}\]. The current study found some degree of PMS in 88% of participants; this number lies on the higher border among reported populations. Compared to the previous study from Jordan, we believe that our sample was more representative of the normal Jordanian population, as it consisted of patients who were attending the clinic for different reasons and had variable educational and sociodemographic backgrounds.

### Table 3: Comparison of lifestyle in women with mild, moderate and severe PMS

<table>
<thead>
<tr>
<th>Life style and habitual factors</th>
<th>No PMS n (%)</th>
<th>Mild PMS n (%)</th>
<th>Moderate PMS n (%)</th>
<th>Severe PMS n (%)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoking</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>3 (10)</td>
<td>7 (8.2)</td>
<td>2 (4.8)</td>
<td>0 (0)</td>
<td>0.740</td>
</tr>
<tr>
<td>No</td>
<td>27 (90)</td>
<td>77 (91.7)</td>
<td>59 (95.2)</td>
<td>3 (100)</td>
<td></td>
</tr>
<tr>
<td>Daily over the counter supplements</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>8 (26.7)</td>
<td>21 (25)</td>
<td>22 (35.5)</td>
<td>0 (0)</td>
<td>0.357</td>
</tr>
<tr>
<td>No</td>
<td>22 (73.3)</td>
<td>63 (75)</td>
<td>40 (64.5)</td>
<td>3 (100)</td>
<td></td>
</tr>
<tr>
<td>Medications</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>2 (6.7)</td>
<td>5 (6)</td>
<td>6 (9.7)</td>
<td>0 (0)</td>
<td>0.801</td>
</tr>
<tr>
<td>No</td>
<td>28 (93.3)</td>
<td>79 (94)</td>
<td>56 (90.3)</td>
<td>3 (100)</td>
<td></td>
</tr>
<tr>
<td>Drinks</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>28 (93.3)</td>
<td>80 (95.2)</td>
<td>59 (95.2)</td>
<td>3 (100)</td>
<td>0.951</td>
</tr>
<tr>
<td>No</td>
<td>2 (6.7)</td>
<td>4 (4.8)</td>
<td>3 (4.8)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Exercise</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>16 (53.3)</td>
<td>42 (50)</td>
<td>43 (96.4)</td>
<td>3 (100)</td>
<td>0.047*</td>
</tr>
<tr>
<td>No</td>
<td>14 (46.7)</td>
<td>42 (50)</td>
<td>19 (30.6)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Type of bread</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>25 (83.3)</td>
<td>72 (86.7)</td>
<td>49 (79)</td>
<td>2 (66.7)</td>
<td>0.434</td>
</tr>
<tr>
<td>Whole</td>
<td>3 (10)</td>
<td>8 (9.6)</td>
<td>7 (11.3)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Both</td>
<td>2 (6.7)</td>
<td>3 (3.6)</td>
<td>6 (9.7)</td>
<td>1 (33.3)</td>
<td></td>
</tr>
<tr>
<td>Fast Food</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>16 (53.3)</td>
<td>51 (60.7)</td>
<td>50 (80.6)</td>
<td>3 (100)</td>
<td>0.013*</td>
</tr>
<tr>
<td>No</td>
<td>14 (46.7)</td>
<td>33 (39.3)</td>
<td>12 (19.4)</td>
<td>0 (0)</td>
<td></td>
</tr>
</tbody>
</table>

* significant \( p \leq 0.05 \)
Data regarding the effect of different sociodemographic variables on the occurrence of PMS are conflicting\(^8,\)\(^{20,21}\). Nonetheless, the current data are consistent with a number of other studies, confirming that younger women (aged 21 – 25 years in the current study) are more prone to PMS than older age groups\(^8,\)\(^{20,22}\). In one recent large survey, younger persons were found to be more prone to stress\(^{23}\); this might explain our results, as younger women might be more prone to express symptomatology related to PMS in the presence of stress. It is notable that many studies focused on PMS in adolescents and/or college students, thus limiting our ability to compare the present results to those of other studies\(^{22-26}\).

Although previous studies have reported that low income and lower educational level are predictive of PMS\(^6,\)\(^{27}\); in the current study, there was no association between PMS and income, marital status, education level, or occupation. Nonetheless, poverty and poor education are risk factors for suffering from chronic stressors and having fewer coping mechanisms to deal with different stressors\(^{28}\). Having fewer coping mechanisms might influence the severity of PMS symptoms.

The American College of Obstetricians and Gynecologists and the National Health Service (NHS) have provided recommendations about the role of exercise as a treatment for menstrual cycle-related disorders\(^{29}\), and recent data suggests that exercise reduces premenstrual symptoms in women running in excess of 50 km/month\(^{30}\). However, in the current study, women who exercised were more likely to have experienced PMS symptoms compared to those who did not exercise. Those findings do not imply that exercise is not beneficial in reducing PMS symptoms in women with mild PMS, as found by some studies\(^{29,30}\), as the current study does not look at the effect of initiating exercise in already sedentary women with PMS. Still, this supports the suggestion that prior to advising women that exercise is an effective treatment for PMS, high-quality randomized controlled trials are needed\(^{29}\).

Regarding diet, although “PMS diets” have been recommended, few of the recommendations were founded on scientific fact\(^{30,31}\). However, there is some evidence that sufficient calcium, magnesium, vitamin E and restricted caffeine and salt are beneficial for PMS patients with different symptoms\(^{31}\). Although we did not directly assess this in the present study, we found that women who regularly consumed fast food had a higher PMS score on the SPAF. Data is scarce concerning the role of fast food on the occurrence of PMS; most studies tend to discuss a healthy diet as a general rule\(^{31}\).

In summary, PMS is a common problem that affects women in their most productive years. Doctors, especially those who take care of women in this age group, should be more vigilant in enquiring about PMS and addressing the needs of women who suffer from this common problem. In addition, they should consider the effect of different sociodemographic,
gynecological, and lifestyle factors associated with the occurrence and severity of PMS.

CONCLUSION

PMS is a common condition in reproductive age females, especially in younger females, and those who suffer from dysmenorrhea. Doctors should take the initiative and ask women at risk about PMS symptoms, offering help and advice, and referring severe cases if needed. Further research is needed to explore common therapies and remedies used traditionally and their effect on such a severe, common condition.

ACKNOWLEDGMENT

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REFERENCES


Effect of Training on Stiffness of Distal Biceps Tendon: A Pilot Study

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INTRODUCTION

Biceps brachii muscle, more commonly known as biceps, is the muscle in the upper arm. It is of vital importance for biceps muscle to function optimally. The most imperative function of biceps muscle is supination of forearm and flexion of elbow[1]. Biceps brachii muscle has 3 tendons: short and long tendon in the proximal part of the muscle and one at the distal end. The former is commonly involved in pathological condition of shoulder pain[2]. Rupture of distal biceps tendon is rather an uncommon phenomenon that accounts for a mere 3% of all biceps-related tendon tears[3,4]. However, this may involve complete or partial tear. Complete tears are usually determined with excellent clinical outcomes by simply retracting the muscle belly and tendon[5]. However, in case of partial tear, the diagnosis is uncertain. Various methods are utilised to determine partial tears, ranging from magnetic resonance (MR) imaging[6] to ultrasound[7]. Results of conservative treatment of rupture of distal tendon of the biceps are far from excellent and surgical treatment is usually recommended.

Due to the extensive function of biceps muscle, the tendons associated with the biceps muscle are directly affected. Research suggests that exercise can cause muscle damage that can be inferred by imaging techniques like MR imaging, MR elastography and ultrasound elastography[8,9]. Mostly, the research is focused on muscle stiffness and scarce data is available for stiffness of tendon[10]. Although literature is available on the effect of changes in tendon stiffness before and after exercise for Achilles tendon[11], calcaneal tendon[12] and patella tendon[13], there is no data that suggests the effect of training on distal biceps tendon stiffness.

Furthermore, conventional methods to determine tendon stiffness include MR imaging or ultrasound.
MR imaging is expensive and time consuming while plain ultrasound does not provide quantification to the problem. A quicker, safer and inexpensive approach is imaging via ultrasound elastography.

Elastography is an enhanced form of ultrasound. It follows the principle of palpation to detect difference in tissue stiffness before and after a minor manual compression of the tissue. Elastography is a novel imaging modality that provides quantitative results by evaluating Young’s modulus or strain ratio among target and surrounding tissue[14].

It is known that exercise keeps the body in shape and regular exercise helps maintain a good fitness level[15].

However, the long term effects of weight training on the distal biceps tendon are not documented. This is a pilot study which determines the distal biceps tendon stiffness and thickness among trained and untrained individuals. Therefore, the results revealed here will serve as a guide to clinicians and as a reference to researchers.

SUBJECTS AND METHODS

Study design

This is a retrospective cohort study and subjects were divided according to trained and untrained individuals. Untrained individuals were selected as controls.

The current study was performed at the Department of Biomedical Technology, College of Applied Medical Science, King Saud University, Riyadh, KSA from January 2016 to April 2016.

This study was approved by the ethical review board vide letter no. CAMS 146-36/37 at King Saud University, Riyadh, KSA. All subjects were informed regarding the study aims, examination procedures and safety concerns. A signed consent was taken from each subject individually before the examination.

Selection criteria for participants

Individuals who had prior history of hormone therapy, tendon injury, hypothyroidism, having corticosteroids treatment, with any metabolic or inflammatory diseases and with shoulder pain were excluded from the study.

Twenty healthy male subjects of Middle Eastern descent volunteered for this cohort study. All subjects were studying at the same university where this research was undertaken. Subjects were screened with a questionnaire.

Subjects were divided according to their training activity. Individuals undergoing biceps training for 4 or more days in a week for at least a year were considered to be trained while untrained individuals never went for biceps training during the last 1 year.

All subjects were evaluated for their age, weight, height and body mass index (BMI). Moreover, their dominant hands were also recorded.

Examination

All ultrasound examinations were performed with Ultrasonix SonixTouch Q+, ultrasound unit (Analogic Corporation, 8 Centennial Drive, Peabody, MA, USA) having a linear transducer L14-5/38.

Examination was performed only on distal biceps tendon of dominant hands of each respective subject. Ultrasound examination was performed on each subject with their arm extended 180° lying on the table (as shown in Fig 1) while their forearm was maximally supinated.

Fig 1: Position of forearm to observe distal biceps tendon. The green marking shows the probable tendon length as observed through B-mode imaging. The region of interest for obtaining strain ratio was within the box as marked on arm.

A generous amount of gel was applied in order to increase coupling efficiency of ultrasound and to minimise error in stiffness. Normal gray scale image was initially used to identify the distal biceps tendon longitudinally as longitudinal scans have higher probability of reproducibility than transverse scans[16]. The transducer was placed over the proximal forearm longitudinally while the orientation marker was towards the patients shoulder to determine the location of tendon. The transducer was adjusted so that tendon fibers were visible. The distal biceps tendon appears as a hyperechoic fibrillar patterned structure. Once an optimal image was obtained, the transducer was used to manually generate pulsations. After a series of pulsations, the loop was frozen and measurements were taken by selecting best images from a pool of more than 100 images. Elastographic strain ratios were obtained for only the central part of tendon above the humeral caputellum and anterior fat pad. Three images per subject were selected and in each single image, 3 strain ratios were determined. To determine strain ratios at 3 different locations, one area within the tendon while another area in the surrounding muscle was selected as shown in Fig 2.

The BMI of each individual was calculated using formula stated in equation 1. However, the volunteers were not categorized according to BMI.

\[
BMI = \frac{\text{Weight}}{\text{Height}^2} \quad \text{Equation 1}
\]
June 2018

Where:

a. Weight is in kg
b. height is in meters

The demographic data for all the subjects is present in Table 1.

Table 1: Demographic data of subjects in untrained and trained study groups

<table>
<thead>
<tr>
<th>Demographic Data</th>
<th>Untrained</th>
<th>Trained</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male, (n)</td>
<td>10</td>
<td>10</td>
<td>-</td>
</tr>
<tr>
<td>Dominant hand (Left), (Right)</td>
<td>(0), (10)</td>
<td>(2), (8)</td>
<td>-</td>
</tr>
<tr>
<td>Age</td>
<td>22.50 ± 0.97</td>
<td>21.90 ± 1.10</td>
<td>0.21</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>71.58 ± 15.13</td>
<td>72.07 ± 13.53</td>
<td>0.94</td>
</tr>
<tr>
<td>Height</td>
<td>175.15 ± 3.95</td>
<td>172.75 ± 5.95</td>
<td>0.30</td>
</tr>
<tr>
<td>BMI</td>
<td>24.09 ± 3.96</td>
<td>24.09 ± 3.96</td>
<td>0.67</td>
</tr>
</tbody>
</table>

BMI: Body mass index

Statistics

All statistical analysis was performed on SPSS v21 (SPSS 21.0 for Windows, Chicago, IL, USA). Data is represented as mean ± standard deviation. Unpaired t-test was performed to determine the level of significance among groups at a p-value of less than 0.05. All parameters in ultrasound unit were kept constant, except depth and focus, as they both were changed according to each subject to obtain optimal image.

RESULTS

A total of 20 subjects volunteered for the study. All were healthy males in their early or mid-twenties. Two subjects were left hand dominant in the trained group while untrained group had none. Table 1 show significant difference for the untrained and trained group in their BMI (Fig 3A). Average BMI for untrained and trained subjects was calculated to be in the healthy range. Untrained and trained groups had a mix of all; underweight, healthy and overweight individuals.
There was no obese subject in either group. BMI for trained subjects on average was insignificantly higher when compared to untrained subjects.

Furthermore, elastographic strain ratios were recorded and the statistics reveal that strain ratios for distal biceps tendon for untrained and trained subjects were insignificant (p = 0.23), though, strain ratios for trained individuals were higher (Fig 3B).

Another factor that was measured was the thickness of the distal biceps tendon. The results demonstrated that thickness of distal biceps tendon among untrained and trained subjects significantly (p = 0.03) varied. Subjects who undergo regular training for their biceps demonstrated an increased thickness (Fig 4A and 4B). No correlation was observed among thickness and BMI values in either of the study groups.

**Fig. 4a**

![Graph of thickness of distal biceps tendon among trained and untrained participants.](image)

**Fig. 4b**

![Graph showing thickness of distal biceps tendon for each individual participant.](image)

DISCUSSION

The current study is a pilot study where the stiffness of distal biceps tendon was evaluated using strain elastography technique among individuals who train their biceps muscle regularly with those who have a sedentary lifestyle.

Results of the present study reveal stiffer distal biceps brachii tendon among the individuals who perform weight training of their biceps on a routine basis than those who have a sedentary lifestyle. Although there is no data available specifically on the effect of exercise over stiffness of distal biceps tendon, a recent study suggested that tendon stiffness is increased due to exercise[14]. In a separate research by S. Bohm and co-workers, they reported that tendon adapts to long-term exercise in a more efficient way than in a short-term period[17]. Moreover, it has also been reported that tendon stiffness is proportional to the time spent in training[18]. Biceps tendon injuries are usually seen with individuals lifting weights more than 68 kg[19]. Furthermore, the incidence occurs commonly within the groove and for a population who are in their 60s or 70s, the reason behind it being the weakening in tendon as a result of degenerative changes over time[20].

In the present study, an increased stiffness in tendon can also be associated to upturn in the type I collagen content in the tendon[21], as prolonged exercise plays an important role in synthesis of type I collagen[22]. The current study is based on an all-male population. However, it is essential to study tendon stiffness among women as well because the collagen in tendon develops differently among women than in men[23].

In the present study, it was observed that distal biceps tendon of trained individuals appeared clearer and demonstrated intense fibrillar pattern (Fig 5) than their untrained counterparts. Analogous results were presented by Vilarta and Vidal in their studies for Achilles tendon[24]. They reported stiffness of Achilles tendon among rats increased after exercise and the collagen fibers were better aligned.

Although ultrasound elastography studies on biceps muscle suggests that muscle hardness is associated with exercise, there is no data available if stiffness of distal biceps tendon is associated with exercise. Further studies are essential in order to establish a relationship between distal biceps tendon and exercise. The present research aimed to find the stiffness of distal biceps tendon among untrained and trained subjects using strain elastography.

This research provides first-hand information about the role of exercise on distal biceps tendon stiffness. The insignificant differences in strain ratios of distal biceps tendon may be due to the small number of participants. Moreover, the high standard deviation in strain ratios of trained subjects is likely due to the variation in exercise type that an individual performs to train their biceps. Findings here can be related to an earlier study where Arampatzis and co-workers found that stiffness in tendon increases due to exercise with a high strain magnitude only[25]. In the present study, the type of exercise that an individual performed was not recorded. Future studies must be directed towards the type of exercise and its effect on distal biceps tendon. Moreover, the sample size in future studies should be enhanced significantly.
and a measure of repeatability and reproducibility should also be taken into account. The current study classified individuals with respect to their activity in the past year. Previous physical activity must also be taken into account in future.

CONCLUSION

The pilot study reveals that distal biceps tendon stiffness increases due to training and the thickness of distal biceps tendon is also dependent upon exercise. However, none of them are dependent upon the BMI. Individuals who regularly exercise their biceps are less prone to sudden injury in their biceps as their tendons are stiffer than their counterparts. More specifically, sports personnel and scientists should be aware of the difference in physical attributes of trained and untrained individuals.

ACKNOWLEDGMENT

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REFERENCES


Original Article

Evaluation of Knowledge Levels and Lifestyle Practices of Patients with Chronic Hepatitis B in a Tertiary Hospital in Turkey

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ABSTRACT

Objective: This study aimed to evaluate the knowledge levels and lifestyle practices of patients diagnosed with chronic hepatitis B (CHB).

Design: Prospective study

Setting: Department of Infection Diseases and Clinical Microbiology, Evliya Celebi Training and Research Hospital, Kutahya, Turkey

Subjects: One hundred and ninety-five patients who were followed up with CHB in the outpatient clinic of infectious diseases between November 2015 and May 2016 were included.

Interventions: A questionnaire was applied to patients

Main outcome measures: Level of knowledge and lifestyle practices

Results: A total of 195 CHB patients were included in the study (51.3% were males). The mean age was 43.41 ± 13.1 years. The mean knowledge level of the patients about the hepatitis B virus (HBV) was 13.54 ± 2.87. The percentage of patients with a good knowledge level was 55.9%, whereas 44.1% had a poor knowledge level. Higher educational status was found to be correlated with higher knowledge level (p < 0.05). After being diagnosed with hepatitis B, 99.7% of our patients stated that they did not donate blood and 98.5% of them stated that they did not share their personal items such as razor blades or toothbrushes. The percentage of patients that continued to share their dishes and cups with other people after their diagnosis was 63.1% and 15.9% used an alternative treatment method for hepatitis B.

Conclusion: In conclusion, the current study found gaps and misperceptions in the knowledge levels of CHB patients, particularly concerning HBV transmission. Increasing the number of studies performed on this subject will help to understand how the patients regard their disease.

KEY WORDS: hepatitis B, knowledge, misperceptions, practices

INTRODUCTION

Hepatitis B virus (HBV) infection, an important cause of acute and chronic liver diseases, is regarded as a significant public health problem worldwide, especially in endemic areas. HBV is one of the leading causes of cirrhosis and hepatocellular carcinoma (HCC) worldwide. The World Health Organization (WHO) reports that more than 350 million individuals are affected by HBV infection around the world[1-4]. The prevalence of HBV infection in Turkey is approximately 4%[5]. Although our country has an intermediate-level endemicity for hepatitis B, there are only a few studies assessing the knowledge levels of the patients about HBV infection[6-7].

It is necessary for patients with hepatitis B to have information about symptoms, severity, follow-up, and treatment options of the disease to achieve appropriate self-care, adherence to follow-up, early detection of disease signs, and timely treatment[6]. It is also important for patients with chronic hepatitis B (CHB) to receive information about the disease to prevent transmission of HBV infection[6]. Such information can enable patient-centered care, helping patients and their families to better understand the illness and how
it affects their lives. Also, it may help the patient lead as normal a lifestyle as possible[9]. There are only a few studies assessing the knowledge levels of patients with CHB and their lifestyle practices[6,9,10]. Therefore, in this study, we aimed to evaluate the knowledge levels and lifestyle practices of patients diagnosed with CHB.

SUBJECTS AND METHODS
Study population
The patients who were followed up with CHB in the outpatient clinic of infectious diseases of a tertiary hospital between November 2015 and May 2016 were included in the study. The study was approved by the local Ethics Committee. Written informed consents of all patients who agreed to participate in the study were obtained after they were informed about the study protocol. A questionnaire evaluating demographic characteristics, level of knowledge, and lifestyle practices was administered to the patients.

Questionnaire
The questionnaire was developed based on information from various studies[6,9-14]. It contained a total of 40 questions as follows: 10 questions related to age, gender, geographic location, educational status, occupation, marital status, duration of hepatitis, history of antiviral use, and demographic data including screening and vaccination status of family members regarding HBV infection; 19 questions related to the knowledge level about HBV infection; 8 questions to evaluate lifestyle practices following diagnosis with CHB; 2 questions for comprehension and adequacy of the physician’s explanations about CHB; and 1 question related to receiving an alternative treatment for CHB.

The level of knowledge about HBV infection was assessed based on the answers to 19 questions. One point was given for each correct answer and no points were given for a wrong or “don’t know” response. The mean knowledge score was used for discrimination. A score higher than the mean score was considered to be a good knowledge level and a score lower than the mean to be a poor knowledge level[15].

Statistical analysis
The NCSS (Number Cruncher Statistical System) 2007 (Kaysville, Utah, USA) program was used for the statistical analysis. During the evaluation of the study data, regarding the comparisons of descriptive statistical methods (mean, standard deviation, median, frequency, ratio, minimum, and maximum) as well as quantitative data, Student’s t-test was used for the intergroup comparisons of parameters with normal distribution. One-way ANOVA test was used for the comparison of three or more groups with normal distribution and Tukey honest significance test (HSD) test was used to determine the group causing the difference. Kruskal Wallis test was used for the comparison of three or more groups without normal distribution and Mann Whitney U test was used to determine the group causing the difference. Pearson’s chi-square test, Fisher’s exact test, Fisher Freeman Halton test and Yates’ continuity correction tests (Yates’s ‘corrected’ chi-square test) were used for comparison of qualitative data. Significance was evaluated at the levels of p < 0.01 and p < 0.05.

RESULTS
Patient characteristics
A total of 195 CHB patients were included in the study; 51.3% (n = 100) of them were males. The mean age was 43.41 ± 13.1 years (min: 18, max: 77). The duration of diagnosis of CHB ranged between 6 months and 36 years, with a mean period of 7.51 ± 6.92 years. Demographic characteristics of the patients are shown in Table 1. While the families of 86.7% (n = 169)
of the patients were given a screening test, the families of 9.7% (n = 19) of the patients did not know whether their families were given a screening test. While the families of 74.9% (n = 146) of the patients were vaccinated, the families of 20.5% (n = 40) of the patients were not vaccinated, and 4.6% (n = 9) of the patients did not know whether their families were vaccinated or not. 64.1% of the patients with CHB were followed up without antiviral treatment, while 35.9% (n = 70) of them used antiviral treatment. One hundred and eighty patients (92.3%) stated that they could usually understand their physicians’ explanations about hepatitis B and 79.5% (n = 155) found the explanations to be sufficient.

Level of knowledge
The mean knowledge level of the patients about HBV was 13.54 ± 2.87 (min: 2, max: 19). Answers given by our CHB patients to knowledge questions are shown in Table 2. One hundred and ninety patients (95.4%) had a good knowledge level, but 4.6% (n = 86) of the patients had a poor knowledge level. Higher educational status was found to be correlated with higher knowledge level (p < 0.05). Correlation between knowledge levels and demographic characteristics of the patient are shown in Table 3.

Evaluation of lifestyle practices after Hepatitis B diagnosis
Lifestyle practices of our patients after being diagnosed with hepatitis B are shown in Table 4. The patients who continued to share their dishes and cups were determined to be more knowledgeable (p = 0.044; p < 0.05). The patients who did not donate blood after the diagnosis were determined to be more knowledgeable (p = 0.036; p < 0.05). Evaluation of the behaviors after diagnosis of the disease according to the knowledge levels are shown in Table 5.

Use of alternative treatment
Thirty-one patients (15.9%) used an alternative treatment method for hepatitis B. Only 14 of our patients stated what they used as alternative treatment. Ten of these patients stated that they used herbal teas and 4 of them used artichoke extract tablets. A total of 19 patients explained the reason for the use of alternative treatment: 10 patients due to belief in the benefit from alternative treatment, 3 patients with the advice of their relatives, 2 patients due to not wanting to use drugs for CHB, 2 patients due to relying on a person who suggested alternative treatment, and 2 patients due to believing that there is no effective treatment of the disease.

No statistically significant difference was determined between the knowledge levels, antiviral treatment, finding the physician’s explanations to be sufficient according to the state of using alternative treatment (p > 0.05).

DISCUSSION
There are only a few studies assessing the knowledge levels of patients with CHB and their lifestyle practices[6,9,10]. In a study performed in Turkey, 85.7% of patients knew that CHB could cause cirrhosis, 65.7% knew that CHB could cause HCC, and 58.1%
knew that CHB could cause death[7]. Similarly, most of our patients knew that CHB could cause severe complications such as cirrhosis, HCC, and death. However, approximately 23 - 32% of the patients expressed that they did not know whether the disease caused or could cause severe complications. This shows us that some of our patients still lack information about the most fundamental features of the disease.

We think that the insufficiencies on these fundamental issues are an important factor in decreasing adherence to treatment or follow-up.

In our study, only 31% of our patients correctly replied to the question of whether hepatitis B always causes symptoms in infected individuals. Some similar studies found a lack of understanding that the disease can be asymptomatic[14,16]. CHB can be asymptomatic, even including the conditions that cause severe complications such as cirrhosis and HCC. Raising awareness of the patients about this subject may help to start treatment earlier and halt progression of the disease.

In one study, 25.7% of the patients stated that the virus can be spread through sharing dishes[17]. A similar misconception is that the virus can be spread through sharing dishes of patients with CHB[8,16]. Similarly, in our study, approximately half of our patients stated that HBV could be spread through sharing dishes and cups or that they did not have information on this subject. These types of misperceptions cause anxiety in the patients about transmitting the virus, thus interfering with their social relations. They also cause patients to try to hide their disease for fear of social isolation[17].

As educational status increases, the knowledge level of the patients with CHB about the disease increases[8,10,18,19]. In the study performed by Mohammed et al, being in the age group of 30 - 39 years, tertiary education level, and being aware of the disease for a longer time were found to be associated with a higher knowledge score[8]. In our CHB patients, only a higher education level and antiviral use were

### Table 3: Correlation between average knowledge levels about Hepatitis B and characteristics of the patients

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Poor knowledge n (%)</th>
<th>Good knowledge n (%)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
<td>0.206</td>
</tr>
<tr>
<td>&lt; 30</td>
<td>11 (12.8)</td>
<td>19 (17.4)</td>
<td></td>
</tr>
<tr>
<td>30 - 39</td>
<td>16 (18.6)</td>
<td>22 (21.9)</td>
<td></td>
</tr>
<tr>
<td>40 - 49</td>
<td>28 (32.6)</td>
<td>25 (22.9)</td>
<td></td>
</tr>
<tr>
<td>50 - 59</td>
<td>17 (19.8)</td>
<td>30 (27.5)</td>
<td></td>
</tr>
<tr>
<td>≥ 60</td>
<td>14 (16.3)</td>
<td>10 (9.2)</td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td>0.236</td>
</tr>
<tr>
<td>Men</td>
<td>40 (46.5)</td>
<td>60 (55)</td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>46 (53.5)</td>
<td>49 (45)</td>
<td></td>
</tr>
<tr>
<td>Educational Status</td>
<td></td>
<td></td>
<td>0.02</td>
</tr>
<tr>
<td>Primary school</td>
<td>57 (66.3)</td>
<td>46 (42.2)</td>
<td></td>
</tr>
<tr>
<td>Secondary school</td>
<td>11 (12.7)</td>
<td>14 (12.8)</td>
<td></td>
</tr>
<tr>
<td>High school</td>
<td>6 (7)</td>
<td>25 (22.9)</td>
<td></td>
</tr>
<tr>
<td>University</td>
<td>12 (14)</td>
<td>24 (22)</td>
<td></td>
</tr>
<tr>
<td>Occupation</td>
<td></td>
<td></td>
<td>0.935</td>
</tr>
<tr>
<td>Housewife</td>
<td>39 (45.3)</td>
<td>46 (42.2)</td>
<td></td>
</tr>
<tr>
<td>Self-employed</td>
<td>12 (14)</td>
<td>20 (18.3)</td>
<td></td>
</tr>
<tr>
<td>Worker</td>
<td>15 (17.4)</td>
<td>20 (18.3)</td>
<td></td>
</tr>
<tr>
<td>Retired</td>
<td>6 (7)</td>
<td>9 (8.3)</td>
<td></td>
</tr>
<tr>
<td>Officer</td>
<td>8 (9.3)</td>
<td>10 (9.2)</td>
<td></td>
</tr>
<tr>
<td>Student</td>
<td>3 (3.5)</td>
<td>2 (1.8)</td>
<td></td>
</tr>
<tr>
<td>Unemployed</td>
<td>3 (3.5)</td>
<td>2 (1.8)</td>
<td></td>
</tr>
<tr>
<td>Diagnosis of hepatitis B (years)</td>
<td></td>
<td></td>
<td>0.109</td>
</tr>
<tr>
<td>0-5</td>
<td>44 (51.2)</td>
<td>51 (46.8)</td>
<td></td>
</tr>
<tr>
<td>6-10</td>
<td>27 (31.4)</td>
<td>24 (22)</td>
<td></td>
</tr>
<tr>
<td>11-15</td>
<td>6 (7)</td>
<td>21 (19.3)</td>
<td></td>
</tr>
<tr>
<td>16-20</td>
<td>5 (5.8)</td>
<td>8 (7.3)</td>
<td></td>
</tr>
<tr>
<td>≥ 21</td>
<td>4 (4.7)</td>
<td>5 (4.6)</td>
<td></td>
</tr>
<tr>
<td>Found physician’s explanations sufficient</td>
<td></td>
<td></td>
<td>0.036</td>
</tr>
<tr>
<td>No</td>
<td>24 (27.9)</td>
<td>16 (14.7)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>62 (72.1)</td>
<td>93 (85.3)</td>
<td></td>
</tr>
<tr>
<td>Screening for HBV by family members</td>
<td></td>
<td></td>
<td>0.129</td>
</tr>
<tr>
<td>No</td>
<td>12 (14.5)</td>
<td>7 (6.7)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>71 (85.5)</td>
<td>98 (93.3)</td>
<td></td>
</tr>
<tr>
<td>Vaccinating for HBV by family members</td>
<td></td>
<td></td>
<td>1.000</td>
</tr>
<tr>
<td>No</td>
<td>17 (21.3)</td>
<td>23 (21.7)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>63 (78.8)</td>
<td>83 (78.3)</td>
<td></td>
</tr>
<tr>
<td>Medical treatment for HBV</td>
<td></td>
<td></td>
<td>0.027</td>
</tr>
<tr>
<td>No</td>
<td>63 (73.3)</td>
<td>62 (56.9)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>23 (26.7)</td>
<td>47 (43.1)</td>
<td></td>
</tr>
<tr>
<td>Understand physician’s explanations</td>
<td></td>
<td></td>
<td>0.118</td>
</tr>
<tr>
<td>No</td>
<td>10 (11.6)</td>
<td>5 (4.6)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>76 (88.4)</td>
<td>104 (95.4)</td>
<td></td>
</tr>
</tbody>
</table>

### Table 4: Evaluation of lifestyle practices of the patients after Hepatitis B diagnosis

<table>
<thead>
<tr>
<th>Lifestyle practices</th>
<th>Answer</th>
<th>n</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>I stopped smoking</td>
<td>No</td>
<td>55</td>
<td>28.2</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>22</td>
<td>11.3</td>
</tr>
<tr>
<td>I stopped drinking alcohol/ I reduced alcohol intake</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>4</td>
<td>2.1</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>17</td>
<td>8.7</td>
</tr>
<tr>
<td>I do more physical activity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>58</td>
<td>29.7</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>52</td>
<td>26.7</td>
</tr>
<tr>
<td>I do not</td>
<td>85</td>
<td>43.6</td>
<td></td>
</tr>
<tr>
<td>I try to eat healthier foods</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>32</td>
<td>16.4</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>163</td>
<td>83.6</td>
</tr>
<tr>
<td>I continue to share my dishes and cups with other people</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>72</td>
<td>36.9</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>123</td>
<td>63.1</td>
</tr>
<tr>
<td>I encouraged my family members to have blood test for hepatitis B</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>17</td>
<td>8.7</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>178</td>
<td>91.3</td>
</tr>
<tr>
<td>I do not engage in blood donation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>4</td>
<td>2.1</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>191</td>
<td>97.9</td>
</tr>
<tr>
<td>I do not share my personal items such as razor blade, toothbrush</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>3</td>
<td>1.5</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>192</td>
<td>98.5</td>
</tr>
</tbody>
</table>

...
found to be associated with a higher knowledge score about the disease. Significantly higher knowledge levels of the patients using antiviral drugs might be because using these drugs may cause patients to regard their disease more seriously and to pay more attention to it.

Contrary to the study performed by Mohammed et al, in our study, no significant association was determined between period of awareness of the disease and knowledge level. In another study performed, which supports our data, no association was found between knowledge levels of the patients about HBV and time to referral to a hepatologist[20]. This suggests that evaluation of knowledge levels and correction of insufficient perceptions or misperceptions is more important for increasing the knowledge level rather than the period of awareness of the disease or follow-up.

When it is considered that in Asian populations the most common route of transmission for HBV is vertical transmission, the patient’s family becomes the primary target for screening programs. There is a small amount of information regarding barriers to communication with the families of HBV-infected individuals about HBV and screening of those families[21]. One study observed that as the knowledge level and educational status increased, the rate of patients having their families vaccinated for HBV increased[6]. Contrary to this, in our study, no significant association was determined between the knowledge level and educational status of the patients and vaccination of their families. Also, no significant association was determined between other sociodemographic characteristics and the status of vaccination of the families. Therefore, further clinical studies are needed to explore the underlying problems in order to increase the rate of vaccination.

The percentage of our patients that continued to share their dishes and cups after being diagnosed with the disease was 36%. In the study performed by Mohammed et al, this ratio was determined to be 49.4%. In this study, it was demonstrated that the practice of sharing dishes and cups decreased in the presence of Indian ethnicity, advanced age, and cirrhosis. The advanced age group was less educated, with a limited ability to access and understand health information. Accordingly, they took the unnecessary precaution of not sharing dishes and cups[9]. Similarly, in our study, it was determined that dishes and cups were less commonly shared by the advanced age group. Again, a good knowledge level about HBV was determined to be significantly higher in patients who shared their dishes and cups. Informing the patients about transmission routes of the virus could avoid unnecessary precautions to prevent transmission.

CONCLUSION

The current study found gaps and misperceptions in the knowledge level of CHB patients, especially about HBV transmission. Consequently, educational programs that address misperceptions related to HBV transmission in CHB patients are of vital importance. Increasing the number of studies performed on this subject will help to understand how patients regard their disease. Also, it might help these patients avoid taking unnecessary precautions to prevent transmission of HBV after diagnosis, thereby improving their quality of life.

<table>
<thead>
<tr>
<th>Lifestyle practices</th>
<th>Answer</th>
<th>Knowledge level about Hepatitis B disease</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Poor knowledge n (%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Good knowledge n (%)</td>
<td></td>
</tr>
<tr>
<td>I stopped smoking</td>
<td>No</td>
<td>21 (67.7)</td>
<td>0.741</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>10 (32.3)</td>
<td></td>
</tr>
<tr>
<td>I stopped drinking alcohol</td>
<td>No</td>
<td>3 (33.3)</td>
<td>0.272</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>6 (66.7)</td>
<td></td>
</tr>
<tr>
<td>I do more physical activity</td>
<td>No</td>
<td>25 (54.3)</td>
<td>0.924</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>21 (45.7)</td>
<td></td>
</tr>
<tr>
<td>I eat healthier foods</td>
<td>No</td>
<td>9 (10.5)</td>
<td>0.072</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>77 (89.5)</td>
<td></td>
</tr>
<tr>
<td>I continue to share dishes and cups with other people</td>
<td>No</td>
<td>39 (45.3)</td>
<td>0.044</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>47 (54.7)</td>
<td></td>
</tr>
<tr>
<td>Encouragement of family members to have blood test for hepatitis B</td>
<td>No</td>
<td>7 (8.1)</td>
<td>1.000</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>79 (91.9)</td>
<td></td>
</tr>
<tr>
<td>I do not engage in blood donation</td>
<td>No</td>
<td>4 (4.7)</td>
<td>0.036</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>82 (95.3)</td>
<td></td>
</tr>
<tr>
<td>I do not share personal items such as razor blade, toothbrush</td>
<td>No</td>
<td>2 (2.3)</td>
<td>0.584</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>84 (97.7)</td>
<td></td>
</tr>
</tbody>
</table>
REFERENCES

Laparoscopic Upper Pole Partial Nephrectomy with Ureterectomy in Duplicated Collecting System

Selahattin Caliskan, Mustafa Sungur
Department of Urology, Corum Training and Research Hospital, Hitit University, Corum, Turkey

Kuwait Medical Journal 2018; 50 (2): 232 - 235

ABSTRACT

Duplicated collecting system is a relatively common congenital abnormality of the genitourinary tract with an incidence of 0.8%. This abnormality is frequently associated with an obstructed and poorly functioning upper pole moiety. Most of the patients are asymptomatic and diagnosed incidentally. The diagnosis and optimal management of duplicated collecting systems are difficult due to high anatomical variability, the degree of obstruction and chronic damage. The clinical presentations are flank pain, hematuria and urolithiasis and may be complicated by urinary tract infections. Surgery is the main treatment for symptomatic patients.

KEY WORDS: duplex kidney, duplicated renal collecting system, upper pole nephrectomy

INTRODUCTION

Ureteral duplication is a rare congenital abnormality and is found in 0.9% of autopsy series[1]. A duplex urinary system means that a kidney has two pelvicaliceal regions and each of them has a ureter[2]. These ureters may be partially duplicated or entirely separated representing complete duplication. Partially duplicated systems are frequently associated with an obstructed and poorly functioning upper pole[3]. Both of these subtypes are the result of premature splitting of the ureteric bud, a remnant of Wolffian duct[2]. Partial duplication is originated from metanephric tissue that has not separated entirely and these systems have several lobes with overlapping collecting tubules. The clinical presentation of the patients depends on age. Recurrent urinary tract infection is seen in pediatric patients and vesicoureteral reflux, recurrent infections, hematuria and abdominal or flank pain are the clinical signs of adult patients. In partial duplex systems, standard surgical treatment is upper pole heminephrectomy for symptomatic patients[3]. In this study, we present a case of partial duplex system treated by laparoscopic upper pole heminephrectomy with excision of upper ureter.

CASE REPORT

A 31-year-old woman presented with right flank pain for a few years. The medical history of the patient was unremarkable. Ultrasonography revealed cystic mass in upper pole of the right kidney suggesting duplicated urinary system. Computed tomography showed right partial duplicated system with hydronephrotic upper pole (Fig 1). Diagnostic ureterorenoscopy confirmed the duplicated system. Retrograde pyelography showed the duplicated system (Fig 2). The double J stent was inserted into the lower pole. The patient was repositioned in the flank position. Peritoneal access was obtained via open techniques near the umbilicus. After the insertion of camera port, two 5-mm ports were placed. At the operation, the ureter was transected from the advent tissue. The ectopic ureter was traced above and below the renal hilum and isolated from the healthy one after the ureter was cut on bifid location and sutured with 4.0 absorbable vicryl suture. The renal hilum was approached, upper pole was identified and the upper pole excised with Harmonic scalpel (Fig 3a and 3b). The specimen of ureter with upper pole is seen in Fig 4. Six weeks after the surgery, the double J stent was
taken under local anesthesia. Intravenous urography demonstrated the final position of the urinary system after three months after the surgery (Fig 5).

**DISCUSSION**

Duplicated collecting system is a common congenital urological abnormality and is characterized by incomplete fusion of lower and upper pole moieties that results in incomplete or complete duplication[4]. The incidence of unilateral duplication is approximately 0.8% in United States. Incomplete duplication is seen three times more often than complete duplications[4]. The investigators believed that this abnormality was autosomal dominant and has the highest prevalence in Caucasian females[3].

The clinical presentation of patients is variable and highly dependent on age[4]. In children, the most common clinical symptom is recurrent urinary tract infection. Vescoureteral reflux and flank pain are usually seen in both children and adults. The
other symptoms are hematuria and stone formation, especially in adults. Urinary incontinence and ureterocele are rarely seen when there is complete duplication and ectopic ureter is implanted into the urethra or vagina. In this study, the patient presented with flank pain for a few years.

Kidney morphology, function and ureter status should be imaged by radiological techniques\[^4\]. Intravenous urography and spiral computed tomography urography are other imaging modalities. Magnetic resonance urography is a good alternative method for children without ionizing radiation. Voiding cystourethrogram may show lower pole reflux\[^2\]. In this study, the patient was diagnosed using spiral computed tomography.

The first reported case of laparoscopic heminephrectomy was published by Jordan and Winslow in 1993 on a pediatric patient\[^5\]. Laparoscopic heminephrectomy in duplex kidneys is more difficult than nephrectomy due to the increased risk of haemorrhage, urine leak, and vascular compromise of the remaining renal moiety. In our case, mean surgical time was 120 minutes. Blood loss was not clinically significant, and the patient was hospitalized for two days. There was no injury to the lower pole urether and the vascular pedicle. Additionally, no intra-operative or post-operative complication occurred.

**CONCLUSION**

In symptomatic patients, surgical treatment can be performed by open, laparoscopic and robotic approaches. Laparoscopy provides an excellent overview of the anatomical structures, with magnification allowing exact pole ablation along the anatomical border when compared to open techniques. Low postoperative pain, short hospital stay and early return to normal daily activities are the advantages of laparoscopic operations. Laparoscopy performed by experienced surgeons is a safe and effective method for patients with duplicated collecting system.
REFERENCES


Case Report

Takayasu Arteritis, Pregnancy and Delivery: Case Report

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¹Clinic for Gynecology and Obstetrics, Clinical Centre of Vojvodina, Branimira Ćosića 37, 21000 Novi Sad, Serbia
²Emergency Centre, Clinical Centre of Vojvodina, Hajduk Veljkova 1-7, University of Novi Sad, Faculty of Medicine, Hajduk Veljkova 3, 21000 Novi Sad, Serbia
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ABSTRACT

Takayasu arteritis (TA) is a rare chronic inflammatory disease affecting major arterial vessels, the aorta and its branches, as well as peripheral blood vessels. Due to numerous cardiovascular complications, the best management for pregnant patients with TA is controversial and challenging for the anesthesiologist and obstetrician. In this case report, we describe a 24-year-old primigravida diagnosed with TA. The patient was admitted to our hospital at 29 weeks of pregnancy complaining of breathlessness, dyspnea, palpitations and fatigue. Upon physical examination, and following electrocardiogram (EKG), chest X-ray and cardiac ultrasound analyses, the patient was diagnosed with heart failure with preserved left-ventricular ejection fraction (HF-PEF). After a two-week treatment, due to a high risk of cardiac and pulmonary complications, we performed a cesarean section (CS) under general anesthesia (GA). Patient evaluation, determining the optimal time and mode of delivery and anesthetic planning are essential to ensure a successful outcome in pregnant patients with Takayasu arteritis.

KEY WORDS: anesthesia, heart failure, pregnancy, Takayasu arteritis

INTRODUCTION

TA is a rare inflammatory disease which is far more prevalent in women than in men (8:1)¹⁻². The incidence of this disease was found to be the lowest in northern Europe (1.26 cases per million), while the highest incidence was found to be in Asians countries, especially in Japan (1 case in every 3000 autopsies)²⁻³. Panarteritis associated with Takayasu’s disease can lead to numerous cardiovascular complications, especially when it is associated with pregnancy. The aim of this case report was to describe the management of pregnant patients with TA and its influence on anesthetic technique.

CASE REPORT

The patient was a 24-year-old female (60 kg and 162 cm), first pregnancy, with a history of hypertension since the age of 17, when the diagnosis of TA affecting the major branches of the aortic arch was initially made. At 11 weeks of pregnancy, severe hypertension was diagnosed, with a 30 mmHg difference in blood pressure (BP) between the left and the right arm (200/120 mmHg and 170/100 mmHg). The patient was started on methyldopa and bisoprolol to control her BP. She also received prednisolone, aspirin and nadroparin.

At 29 weeks of pregnancy, the patient was admitted to the hospital complaining of breathlessness, dyspnea, palpitations and fatigue. She had tachycardia at a rate of 125/min, with a systolic murmur over the aorta, without peripheral edema. The murmur was audible over both carotids and both subclavian arteries.

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Ultrasonography revealed thickening of the left ventricular wall, left ventricular mass index (LVMi) of 131.48 with normal endocavitory dimensions, mitral regurgitation 1+, moderately dilated left atrium, left atrial volume (LAV) of 63 ml; LAV index of 37.8 ml/m², moderate LV diastolic dysfunction of the left ventricle with preserved contractility (LVEF - 63%). There were no changes in the right side of the heart and pleural effusion on the left side.

Chest X-ray showed bilateral infiltrative changes, and functional tests suggested severe bronchial obstruction, forced expiratory volume in 1 second (FEV₁) - 44.4%. A diagnosis of bronchial asthma was suspected.

Biochemical blood analyses showed significantly elevated levels of N-terminal pro brain natriuretic peptide (NTproBNP), 1898 pg/ml, C-reactive protein (CRP) of 23.7. Leukocyte count and other laboratory values were within normal limits.

Control duplex scan of carotid arteries showed moderately worse scores compared with records at 11 weeks of pregnancy. Diffuse concentric thickening of the intima and media arteria carotis communis (ACC) and arteria carotis interna (ACI) was noted bilaterally, with the most severe stenosis of 65 - 70% on the left ACI. On the left subclavian artery, stenosis was detected with pressure gradient of 30 mmHg. The neurological exam was normal.

Diuretics (furosemide) were added as well as aminophylline and berodual spray for antiobstructive therapy. Bisoprolol was replaced with verapamil hydrochloride.

After two weeks, the patient’s clinical condition improved. Due to the high risk of cardiac and pulmonary complications in the advanced stages of pregnancy, we made a decision to perform a CS.

Initially, the delivery was planned under epidural anesthesia (EA). Since the procedure was unsuccessful (we could not identify the epidural space), we reassessed our decision.

Considering that our patient was treated with low molecular weight heparin (nadroparin 0.3 ml/24 hours - 2850 IU) in the last 16 days until 12 hours before surgery, we could not insist on EA, since there was a risk of a haematoma developing. We decided to continue the procedure under GA.

Ranitidine and metoclopramide were administered 30 minutes prior to anesthesia and the patient was preloaded with 500ml Ringer’s solution. Anesthesia was induced with propofol (2.5 mg/kg) and rocuronium (0.5 mg/kg) without succinylcholine. During the intubation, the head was kept in a neutral position to prevent blood vessel extension and cerebrovascular complications. Standard monitoring (5-lead electrocardiogram) non-invasive blood pressure (NIBP), capnografi, pulse oximetry and left lateral position were used. During the anesthesia induction, blood pressure decreased from 160/90 mmHg to 140/80 mmHg. Mean arterial pressure (MAP) during the operation ranged from 90 to 115 mmHg. The left and right arm pressure difference was 15 mmHg. During the CS, the patient was given 1500 ml crystalloid. A male infant was delivered, with an Apgar score of 5/6. Oxytocin was given intravenously, a slow bolus of 5 units followed by an infusion of 10 units. After the CS, she received II units of erythrocyte resuspension. She was stable in the postoperative period and was discharged 5 days after the delivery.

DISCUSSION

TA symptoms depend on the distributions of lesions and presence of complications. The four major complications are hypertension, retinopathy, aneurism formation and aortic regurgitation. Depending on the presence of these complications, the disease can be classified into four stages: Stage I – none of these complications are observed; Stage IIa – patient has only one of these complications in a mild form; Stage IIb – patient has only one of these complications, but in a severe form; Stage III – more than one complication is present[2-4].

Our patient was classified as having stage IIb. Pregnancy does not interfere with disease progression but may cause exacerbation of complications of the disease[2,4].

Hypertension is the most common complication in patients with TA (33 - 83%)[4-5]. It results from reduced elasticity, thickening, fibrosis and vascular occlusion, abnormal function of carotid and aortic baroreceptors, or renovascular changes[4]. Advanced pregnancy is associated with an increase in intravascular volume (40 - 50%), and cardiac output (30 - 40%). These changes in patients with TA can lead to elevated systemic vascular resistance (SVR), exacerbation of hypertension and cerebrovascular hemorrhage[4-6]. High incidence of restricted intrauterine fetal growth (19.7%), abortions (12.4%) and fetal deaths (8.2%) seem to be related to uncontrolled hypertension and aorta and iliac arteries involvement[7].

Heart failure (HF), occurring in 3.9% of all cases, commonly occurs secondary to unregulated hypertension[6-7]. It can also occur if the changes affect coronary arteries, the endocardium or cardiac muscle. Our patient presented us with a dilemma: did she have primary HF or respiratory failure associated with bronchial asthma. Following the criteria for the diagnosis of HF symptoms and signs of the disease, ultrasound changes and significantly elevated values
of NTproBNP, we made a diagnosis of HF with preserved ejection fraction[8].

Delivering the infant in patients with TA should be carefully planned. Vaginal delivery is preferred for patients in stages I and Ila[2]. It should be done under epidural analgesia to reduce catecholamine response to stress.

Operative delivery is preferred for patients with specific obstetric indications and those with advanced complications (stages IIb and III)b[1]. Uncontrolled hypertension is the most common indication for CS[9].

The choice of anesthetic technique depends on each individual case. Regional anesthesia (epidural and combined spinal-epidural anesthesia) for labor and delivery may be advantageous in these patients because of reduced after load and less fluctuation in CO. Consciousness is the best monitoring of cerebral blood flow. Spinal anesthesia should be avoided due to a risk of developing hypotension.

GA involves intubation and extubation, which may be associated with hemodynamic instability and a higher risk of cerebrovascular incidents. MAP should be maintained within +/- 20% of preoperative values[1]. Cerebral blood flow in TA patients is often not correlated with MAP values, so the use of electroencephalogram or transcranial doppler is recommended during GA (not available at our clinic)[2]. NIBP monitoring is preferred due to a risk of developing complications at the point of blood vessel puncture. Furthermore, BP should regularly be monitored in both arms. BP difference between the left and right arm higher than 15 – 20 mmHg is highly associated with subclavian stenosis. Proximal stenosis can lead to “subclavian steal syndrome” and symptoms of vertebra-basilar insufficiency[9].

The use of invasive haemodynamic monitoring depends on the patient’s condition, planned operative procedure and typical practice at the institution where the operation is performed. Fluid resuscitation in patients with HF should be monitored using echocardiography or a central venous catheter[9].

CONCLUSION
Patient evaluation, determining the optimal time and mode of delivery, and anesthetic planning are essential to ensure a successful outcome in pregnant patients with Takayasu arteritis.

REFERENCES
Granulomatosis with Polyangiitis Presented as Isolated Destructive Nasal Mass – Case Report

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Kuwait Medical Journal 2018; 50 (2): 239 - 241

ABSTRACT

Granulomatosis with polyangiitis (GPA), previously known as Wegener’s Granulomatosis, is a relatively rare autoimmune disease. It commonly presents with multiple organ symptoms. Isolated nasal manifestation is a rare form of presentation. Herein, we describe the case of a 19-year-old girl who presented with progressive nasal obstruction. Physical examination revealed a nasal mass involving the nasal septum obstructing the nasal cavity, which appeared on the CT-scan as a destructive mass affecting the nasal septum.

KEY WORDS: nasal mass, nasal septum, vasculitis, wegener’s granuloma

INTRODUCTION

Granulomatosis with polyangiitis (GPA) is an autoimmune multi-systemic disease of rare incidence, characterized by necrotizing granulomatous inflammation and pauci-immune vasculitis in small- and medium-sized blood vessels[1]. It has a relatively rare incidence (3/100,000)[2]. It usually presents with pulmonary, renal and upper airway manifestations. Most of the cases of generalized disease are associated with the presence of cytoplasmic anti-neutrophil cytoplasmic antibodies (c-ANCA). Some cases presented as a limited disease, in which the c-ANCA is usually negative[3,4]. It is not uncommon for patients with GPA to have upper respiratory manifestations of the disease, but being presented with isolated nasal mass without any other disease manifestation is rare and may cause the patient to roam among different clinics and take various medications without definite diagnosis.

CASE REPORT

A 19-year-old girl presented with progressive nasal obstruction for 2 months, associated with headache and decreased sense of smell. She had no history of epistaxis, nasal or post nasal discharge, convulsions, cough, chest pain, or hematuria. On presentation, there was a right side nasal mass destructing the septal cartilaginous and bony parts with liquefying necrosis and gray-brown necrotic material obstructing the nasal airway (Fig 1). Initial laboratory workup showed blood urea nitrogen of 27 mg/dL, creatinine of 0.5 mg/dL, erythrocyte sedimentation rate of 90 mm/h, and normal urine analysis. Chest radiograph was normal as well (Fig 2).

Computed tomography scan showed a destructive mass in the right nasal cavity and involving the nasal septum, with mild contrast enhancement (Fig 3). Then, an incisional biopsy was obtained, which showed necrotizing lesion with vague necrotizing granulomata and focal vascular changes (Fig 4). Other samples sent for microbiology lab for fungi and mycobacterium were all negative. The c-ANCA was requested based on this finding and came to be positive.

Hence, the diagnosis of granulomatosis with polyangiitis was confirmed and the patient was referred to rheumatology team and showed a good response to cyclophosphamide and hydrocortisone.

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DISCUSSION

GPA, previously known as Wegener’s Granulomatosis, was first described by the German pathologist Friedrich Wegener in 1936. In 1931, two patients died from prolonged sepsis with inflammation of blood vessels scattered throughout the body. In 1936, Wegener first described a distinct syndrome in three patients found to have necrotizing granulomas involving the upper and lower respiratory tract. In 1954, seven more patients were described, resulting in a definite criteria\(^5\). It may occur at any age, although patients typically present in the fifth decade\(^6\). Patients with GPA usually present with chronic, non-specific constitutional complaints and recurrent respiratory infection in an adult. Therefore, they commonly

Fig 1: Endoscopic nasal cavity examination showed a destructive nasal mass involving the septum cartilaginous and bony parts with liquefying necrosis and gray-brown necrotic material

Fig 2: Chest X-ray was normal

Fig 3: Computed tomography scan showed a destructive mass in the right nasal cavity and destructing the anterior part of the nasal septum, with mild contrast enhancement.
present after being evaluated in different clinics where they seek help without definite diagnosis. It can manifest in two forms: limited disease without renal manifestations and generalized disease with renal involvement. Also, it can present with involvement of eyes, ENT, musculoskeletal, renal, neurological, cutaneous and cardiac symptoms. According to the modified American College of Rheumatology Criteria for the classification of Wegener’s Granulomatosis, for diagnosis of GPA, patients must have at least two of the following five criteria:

1. Nasal or oral inflammation
2. Abnormal chest radiograph
3. Active urine sediment
4. Granulomatous inflammation and/or necrotizing vasculitis on tissue biopsy
5. Positive enzyme immunoassay for antibodies to serum proteinase

In our patient, the presentation was unusual, in the form of isolated nasal mass with nasal obstruction, without any other disease manifestations. However, the histopathological description is classical for GPA, and therefore c-ANCA was requested and came out positive as further confirmatory clue for the diagnosis.

CONCLUSION

GPA should be considered as one of the differential diagnoses when a patient presents with nasal cavity mass. Early detection of such cases will decrease disease morbidity and eliminate unnecessary intervention and inappropriate management. The workup should include biopsy as well as c-ANCA whenever GPA is to be excluded.

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Complementary bodybuilding: A potential risk for permanent kidney disease

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We report our experience of renal disease associated with bodybuilders who had been on high-protein diet, anabolic androgenic steroids (AASs), and growth hormone (GH) for years. A total of 22 adult males who volunteered information about use of high protein diet and AAS or GH were seen over a six-year period with renal disease. Kidney biopsy revealed focal segmental glomerulosclerosis (FSGS) in eight, nephroangiosclerosis in four, chronic interstitial nephritis in three, acute interstitial nephritis in two, nephrocalcinosis with chronic interstitial nephritis in two, and single patients with membranous glomerulopathy, crescentic glomerulopathy, and sclerosing glomerulonephritis. Patients with FSGS had a longer duration of exposure, late presentation, and worse prognosis. Those with interstitial disease had shorter exposure time and earlier presentation and had improved or stabilized after discontinuation of their practice. There is a need for health education for athletes and bodybuilders to inform them about the risks of renal disease involved with the use of high-protein diet, AAS, and GH.

Increasing prevalence, molecular characterization and antifungal drug susceptibility of serial Candida auris isolates in Kuwait

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Candida auris is an emerging yeast pathogen of global significance. Its multidrug-resistant nature and inadequacies of conventional identification systems pose diagnostic and therapeutic challenges. This study investigated occurrence of C. auris in clinical specimens in Kuwait and its susceptibility to antifungal agents. Clinical yeast strains isolated during 3.5-year period and forming pink-colored colonies on CHROMagar Candida were studied by wet mount examination for microscopic morphology and Vitek 2 yeast identification system. A simple species-specific PCR assay was developed for molecular identification and results were confirmed by PCR-sequencing of rDNA. Antifungal susceptibility testing of one isolate from each patient was determined by Etest. The 280 isolates forming pink-colored colonies on CHROMagar Candida, were identified by Vitek 2 as Candida haemulonii (n = 166), Candida utilis (n = 49), Candida kefyr (n = 45), Candida guilliermondii (n = 9), Candida famata (n = 6) and Candida conglobata (n = 5). Species-specific PCR and PCR-sequencing of rDNA identified 166 C. haemulonii isolates as C. auris (n = 158), C. haemulonii (n = 6) and Candida duobushaemulonii (n = 2). C. auris isolates originated from diverse clinical specimens from 56 patients. Of 56 C. auris isolates tested, all were resistant to fluconazole, 41/56 (73%) and 13/56 (23%) were additionally resistant to voriconazole and amphotericin B, respectively. Eleven (20%) isolates were resistant to fluconazole, voriconazole and amphotericin
PCR array profiling of antiviral genes in human embryonic kidney cells expressing human coronavirus OC43 structural and accessory proteins

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Human coronavirus OC43 (HCoV-OC43) is a respiratory virus that usually causes a common cold. However, it has the potential to cause severe infection in young children and immunocompromised adults. Both SARS-CoV and MERS-CoV were shown to express proteins with the potential to evade early innate immune responses. However, the ability of HCoV-OC43 to antagonise the intracellular antiviral defences has not yet been investigated. The potential role of the HCoV-OC43 structural (M and N) and accessory proteins (ns2a and ns5a) in the alteration of antiviral gene expression was investigated in this study. HCoV-OC43M, N, ns2a and ns5a proteins were expressed in human embryonic kidney 293 (HEK-293) cells before challenge with Sendai virus. The Human Antiviral Response PCR array was used to profile the antiviral gene expression in HEK-293 cells. Over 30 genes were downregulated in the presence of one of the HCoV-OC43 proteins, e.g. genes representing mitogen-activated protein kinases, toll-like receptors, interferons, interleukins, and signaling transduction proteins. Our findings suggest that similarly to SARS-CoV and MERS-CoV, HCoV-OC43 has the ability to downregulate the transcription of genes critical for the activation of different antiviral signaling pathways. Further studies are needed to confirm the role of HCoV-OC43 structural and accessory proteins in antagonising antiviral gene expression.

White blood cell subpopulation changes and prevalence of neutropenia among Arab diabetic patients attending Dasman Diabetes Institute in Kuwait

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BACKGROUND: The effects of diabetes mellitus on the differential white blood cell count are not widely studied in the Arab populations. The objective of this cross-sectional, retrospective study is to assess the influence of chronic diabetes mellitus on white blood cell counts, absolute neutrophil (ANC) and lymphocyte counts (ALC) as well as the prevalence of benign ethnic neutropenia among Arabs attending the Dasman Diabetes Institute (DDI) in Kuwait.
METHODS AND FINDINGS: 1,580 out of 5,200 patients registered in the DDI database qualified for our study. Age, gender, HbA1c and creatinine levels, estimated glomerular filtration rate as well as average WBC, ANC and ALC levels, presence of diabetes-associated complications and anti-diabetic medications were analyzed. Our results showed the mean value of the WBC was 7.6 ± 1.93 x 10⁹/L (95% CI: 2.95-17.15). The mean ANC was 4.3 x 10⁹/L (95% CI: 0.97-10.40) and mean ALC was 2.5 x 10⁹/L (95% CI: 0.29-10.80). Neutropenia (ANC: <1.5 x 10⁹/L) was detected in fifteen patients (0.94%). Six patients (0.4%) fulfilled the definition of lymphopenia (ALC < 1 x10⁹/L). Patients with an HbA1c ≥ 7% and those taking at least 3 anti-diabetic medications showed higher values for ANC and ALC. Patients with diabetes-associated neuropathy or nephropathy displayed higher mean ANC values. Our study was limited by overrepresentation of patients over 50 years old compared to those under 50 as well as selection bias given its retrospective nature.

CONCLUSIONS: Our study showed that patients with poorly controlled diabetes displayed higher ANC and ALC levels. In addition, patients with DM-associated complications showed higher ANC levels. This finding would suggest that DM exerts a pro-inflammatory influence on differential WBC counts. Our study also showed that the prevalence of benign ethnic neutropenia was lower than previously reported in other studies.

Myocardial perfusion abnormalities in asymptomatic type 2 diabetic patients

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OBJECTIVE: The prevalence of coronary artery disease (CAD) is high in patients with diabetes. Because ischemia and infarction are often silent in diabetic patients, diagnosis of CAD occurs inevitably late. It is essential to identify the presence of CAD in diabetic patients to start early treatment. Therefore, the aim of this study was to determine the prevalence of abnormal myocardial perfusion in asymptomatic type 2 diabetic patients using myocardial perfusion imaging.

METHODS: Fifty-nine patients with type 2 diabetes, who did not have any history of CAD, but did have risk factors underwent myocardial perfusion single-photon emission computed tomography (SPECT) imaging using ⁹⁹mTc-tetrofosmin and a 2-day stress-rest protocol. Two nuclear medicine specialists independently interpreted the images. Statistical analysis was performed to determine if there is a correlation between the presence of perfusion abnormalities and the history of diabetes (duration of disease, type of treatment, level of control, and presence and type of complications). The influence of other factors such as age, sex, smoking history, and family history of CAD, with abnormal scans were also studied.

RESULTS: Of the 59 patients, abnormal scans were detected in 22 (37%) including 16 with reversible defects due to stress-induced ischemia. Hence the prevalence was 37%. Duration of diabetes, use of insulin, nephropathy, and neuropathy were significantly associated with abnormal scans (p = 0.048, p = 0.045, p = 0.006, and p = 0.03, respectively). Additionally, positive family history of CAD was highly associated with perfusion abnormalities (p < 0.001). No significant association was found between other risk factors, such as hyperlipidemia and the presence of perfusion defects.

CONCLUSIONS: We found a high prevalence of myocardial perfusion abnormalities in asymptomatic type 2 diabetic patients. Perfusion abnormalities on myocardial perfusion SPECT images were associated with disease duration, insulin use, nephropathy, and neuropathy. Asymptomatic diabetic patients might be candidates with CAD abnormalities that can be studied using myocardial perfusion SPECT.
Forthcoming Conferences and Meetings

Compiled and edited by
Vineetha Elizabeth Mammen

Kuwait Medical Journal 2018; 50 (2): 245 - 256

18th Annual PDG J. Robert Meyers Lions Vision Lecture/Eye & Vision Research Day
Jun 1, 2018
United States / Pennsylvania / Hershey
Contact: Continuing Education, Penn State College of Medicine
Phone: 717-531-6483; Fax: 717-531-5604

2018 International Mediterranean Family Medicine Congress
Jun 3, 2018
Spain / Barcelona
Contact: Elmas Yapici, Organizing Secretariat, Kumgroup Congress & Organization
Phone: +90-5-7061-9537
Email: organizing@imfmc.org

Targeting Therapy of Alzheimer’s and Related Neurodegenerative Diseases
Jun 4, 2018
Bahamas / Nassau
Contact: Conference Manager, Fusion Conferences
Phone: +44-16-3872-4137
Email: admin@fusion-conferences.com

Sleep 2018
Jun 2 - 6, 2018
United States / Maryland / Baltimore
Contact: Associated Professional Sleep Societies
Phone: 630-737-9700; Fax: 630-737-9789
Email: info@sleepmeeting.org

Allergic Skin Disease
Jun 4 - 5, 2018
United Kingdom / London
Contact: Continuing Professional Development, Imperial College London
Phone: +44-20-7589-5111

Anaesthetists as Educators: An Introduction
Jun 5, 2018
United Kingdom / London
Contact: Royal College of Anaesthetists
Phone: +44-20-7092-1500; Fax: +44-20-7092-1730
Email: info@rcoa.ac.uk

Infectious Diseases and Sexual Health - London School of Paediatrics
Jun 5, 2018
United Kingdom / London
Contact: Andrea Torok, Organizer, Royal Society of Medicine
Phone: +44-20-7290-2986
Email: paediatrics@rsm.ac.uk

16th World Congress on Menopause: Midlife Health in the 21st Century
Jun 6 - 9, 2018
Canada / British Columbia / Vancouver
Contact: Ms Lee Tomkins, Executive Director, International Menopause Society
Phone: 011-44-17-2688-4221
Email: leetomkinsims@btinternet.com

Paediatric Allergy
Jun 6 - 7, 2018
United Kingdom / London
Contact: Continuing Professional Development, Imperial College London
Phone: +44-20-7589-5111

2018 Medical Careers: The Advisor’s Perspective
Jun 7, 2018
United Kingdom / London
Contact: Jemma Hemsworth, Organizer, Royal Society of Medicine
Phone: +44-20-7290-3919
Email: schools@rsm.ac.uk

Blended Introduction to Critical Care Ultrasound
Jun 7 - 8, 2018
United States / Florida / St. Petersburg
Contact: Casey Green, Business Development Supervisor, Gulfcoast Ultrasound Institute, Inc
Phone: 727-363-4500; Fax: 727-363-0811
Email: learn@gcus.com

Blended Introduction to Emergency Ultrasound
Jun 7 - 8, 2018
United States / Florida / St. Petersburg
Contact: Casey Green, Business Development Supervisor, Gulfcoast Ultrasound Institute, Inc
Phone: 727-363-4500; Fax: 727-363-0811
Email: learn@gcus.com
Forthcoming Conferences and Meetings
June 2018

**Blended Trauma and Acute Care Sonography**
Jun 7, 2018  
*United States / Florida / St. Petersburg*  
Contact: Casey Green, Business Development Supervisor, Gulfcoast Ultrasound Institute, Inc  
Phone: 727-363-4500; Fax: 727-363-0811  
Email: learn@gcus.com

**Harold Hopkins Symposium**
Jun 7, 2018  
*United Kingdom / London*  
Contact: Faye Kelleher, Organizer, Royal Society of Medicine  
Phone: +44-20-7290-2987  
Email: urology@rsm.ac.uk

**Medical CBT: 10-Minute Techniques for Real Doctors (Cognitive Behavior Therapy)**  
Jun 7 - 8, 2018  
*Canada / Ontario / Ottawa*  
Contact: Greg Dubord, Md, CME Director, CBT Canada  
Phone: 877-466-8228  
Email: info@cbt.ca

**Blended Ultrasound-Guided Nerve Blocks for the Emergency Physician**
Jun 8, 2018  
*United States / Florida / St. Petersburg*  
Contact: Casey Green, Business Development Supervisor, Gulfcoast Ultrasound Institute, Inc  
Phone: 727-363-4500; Fax: 727-363-0811  
Email: learn@gcus.com

**Blended Ultrasound-Guided Vascular Access**
Jun 8, 2018  
*United States / Florida / St. Petersburg*  
Contact: Casey Green, Business Development Supervisor, Gulfcoast Ultrasound Institute, Inc  
Phone: 727-363-4500; Fax: 727-363-0811  
Email: learn@gcus.com

**Healthcare Safety Investigations Branch: Update Meeting**
Jun 8, 2018  
*United Kingdom / London*  
Contact: Stacey Warner, Organizer, Royal Society of Medicine  
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**Singapore Hepatology Conference / Best of EASL 2018**  
Jun 8 - 9, 2018  
*Singapore / Singapore*  
Contact: Conference Manager, Singapore Hepatitis Conference PTE Ltd  
Email: info@shc-sg.com

**Starting a Point of Care Ultrasound Program**
Jun 8, 2018  
*United States / Florida / St. Petersburg*  
Contact: Casey Green, Business Development Supervisor, Gulfcoast Ultrasound Institute, Inc  
Phone: 727-363-4500; Fax: 727-363-0811  
Email: learn@gcus.com

**7th Asian Conference on Hepatitis and AIDS**
Jun 9 - 10, 2018  
*China / Beijing*  
Contact: Kun-Chieh Wu, Project Manager, Virology Education  
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Email: kun-chief@vironet.com

**9th World Congress of the World Federation of Pediatric Intensive and Critical Care Societies**
Jun 9 - 13, 2018  
*Singapore / Singapore*  
Contact: Josh Margo, Mr, Kenes Group  
Phone: 011-97-2-3972-7450  
Email: jmargo@kenes.com

**17th Biennial Society for Medical Decision Making European Conference**
Jun 10 - 12, 2018  
*Netherlands / Leiden*  
Contact: Society for Medical Decision Making  
Phone: 908-359-1184  
Fax: 908-450-1119  
Email: info@smdm.org

**41st European Congress of Cytology**
Jun 10 - 14, 2018  
*Spain / Madrid*  
Contact: Kenes Group, Kenes Group  
Phone: 011-34-91-361-2600  
Email: ecc2018@kenes.com

**11th International Conference on Acute Cardiac Care**
Jun 11 - 12, 2018  
*Israel / Tel Aviv*  
Contact: Bronia Tiger, ISAS International Seminars  
Phone: +972-2-652-0574; Fax: +972-2-652-0558  
Email: confer@isas.co.il

**Nutrition, the Immune System and Health**
Jun 11, 2018  
*United Kingdom / London*  
Contact: Hatty Grant, Organizer, Royal Society of Medicine  
Phone: +44-20-7290-2984  
Email: food@rsm.ac.uk
Child Health Festival: How to Advocate for Children, Influence Policy & Change Practice
Jun 12, 2018
United Kingdom / London
Contact: Andrea Torok, Organizer, Royal Society of Medicine
Phone: +44-20-7290-2986
Email: paediatrics@rsm.ac.uk

29th Congress of Union of the European Phoniatricians (UEP)
Jun 13 - 16, 2018
Finland / Helsinki
Contact: Ahmed Geneid, Dr, UEP
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50th Jubilee Meeting of the European Pancreatic Club
Jun 13 - 16, 2018
Germany / Berlin
Contact: EPC 2018 Team, INTERPLAN Congress, Meeting and Event Management AG
Phone: +49-89-5482-3462
Email: epc2018@interplan.de

Applied Therapeutics for Palliative Medicine: An Advanced Update for Senior Clinicians
Jun 13, 2018
United Kingdom / London
Contact: Hatty Grant, Organizer, Royal Society of Medicine
Phone: +44-20-7290-2984
Email: palliative@rsm.ac.uk

EULAR 2018 - Annual European Congress of Rheumatology
Jun 13 - 16, 2018
Netherlands / Amsterdam
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Sonography Principles & Instrumentation Registry Review
Jun 13, 2018
United States / Florida / St. Petersburg
Contact: Casey Green, Business Development Supervisor, Gulfcoast Ultrasound Institute, Inc
Phone: 727-363-4500; Fax: 727-363-0811
Email: learn@gcus.com

2nd International Conference on Zika Virus and Aedes Related Infections
Jun 14 - 17, 2018
Estonia / Tallinn
Contact: Conference Secretariat, Target Conferences
Phone: +972-3-517-5150
Email: zika@target-conferences.com

5th World Congress of Dermoscopy
Jun 14 - 16, 2018
Greece / Thessaloniki
Contact: John Antoniou, Mr., ERA Ltd
Phone: 011-30-210-363-4944; Fax: 011-30-210-363-4690
Email: jantoniou@era.gr

Society for Vascular Medicine 29th Annual Scientific Sessions
Jun 13 - 16, 2018
United States / Illinois / Chicago
Contact: Society for Vascular Medicine
Phone: 847-686-2232
Fax: 847-686-2251
Email: info@vascularmed.org

2018 Pacific Northwest Endovascular Conference
Jun 15, 2018
United States / Washington / Seattle
Contact: Complete Conference Management
Phone: 888-334-7495 or 305-279-2263
Fax: 305-279-8221
Email: questions@ccmcme.com

Brain Injury
Jun 15, 2018
United Kingdom / London
Contact: Ruth Cloves, Organizer, Royal Society of Medicine
Phone: +44-20-7290-2985
Email: cns@rsm.ac.uk

Exercise Medicine
Jun 15, 2018
United Kingdom / London
Contact: Beilul Kahsai, Organizer, Royal Society of Medicine
Phone: +44-20-7290-3859
Email: sports@rsm.ac.uk
Medical CBT: 10-Minute Techniques for Real Doctors (Cognitive Behavior Therapy)
Jun 15 - 16, 2018
Canada / British Columbia / Nelson, Bc
Contact: Greg Dubord, MD, CME Director, CBT Canada
Phone: 877-466-8228
Email: info@cbt.ca

31st International College of Neuropsychopharmacology (CINP) World Congress
Jun 16 - 19, 2018
Austria / Vienna
Contact: Central Office, CINP
Phone: 011-44-13-5524-4930; Fax: 011-44-13-5524-9959
Email: woc2018reghot@mci-group.com

36th World Ophthalmology Congress of the International Council of Ophthalmology
Jun 16 - 19, 2018
Spain / Barcelona
Contact: Secretariat, MCI Suisse SA
Phone: 011-41-22-339-9728; Fax: 011-41-22-339-9631
Email: education@rcseng.ac.uk

31st International College of Neuropsychopharmacology (CINP) World Congress
Jun 16 - 19, 2018
Austria / Vienna
Contact: Central Office, CINP
Phone: 011-44-13-5524-4930; Fax: 011-44-13-5524-9959
Email: woc2018reghot@mci-group.com

Systematic Training in Acute Illness Recognition and Treatment for Surgery
Jun 16, 2018
United Kingdom / London
Contact: Education Team, Royal College of Surgeons of England
Email: education@rcseng.ac.uk

Advanced Peripheral Nerve Ultrasound: Diagnostic & Interventional Applications
Jun 21 - 22, 2018
United States / Florida / St. Petersburg
Contact: Casey Green, Business Development Supervisor, Gulfcoast Ultrasound Institute, Inc
Phone: 727-363-4500; Fax: 727-363-0811
Email: learn@gcus.com

Clinical Cases in Dermatology
Jun 21, 2018
United Kingdom / London
Contact: Dermatology Section, Royal Society of Medicine
Phone: +44-20-7290-3942
Email: dermatology@rsm.ac.uk

Intermediate Skills in Laparoscopic Surgery
Jun 19 - 20, 2018
United Kingdom / London
Contact: Education Team, Royal College of Surgeons of England
Email: education@rcseng.ac.uk

20th International Immunocompromised Host Society (ICHS) Symposium
Jun 17 - 19, 2018
Greece / Athens
Contact: William Kirkpatrick, ICHS Secretariat, ICHS
Email: ichs.kirkpatrick@gmail.com

Global Contraception
Jun 19, 2018
United Kingdom / London
Contact: Amy Stratton, Organizer, Royal Society of Medicine
Phone: +44-20-7290-2980
Email: globalhealth@rsm.ac.uk

Intermediate Skills in Laparoscopic Surgery
Jun 19 - 20, 2018
United Kingdom / London
Contact: Education Team, Royal College of Surgeons of England
Email: education@rcseng.ac.uk

Cardia: Cardiac Arrhythmia, Sudden Death, Inherited Cardiovascular Disease, Athletes
Jun 21 - 22, 2018
United States / California / Stanford
Contact: Dianna Ziehm, CME Conference Coordinator, Stanford Health Care
Phone: 650-724-7166
Email: dziehm@stanford.edu

Clinical Cases in Dermatology
Jun 21, 2018
United Kingdom / London
Contact: Dermatology Section, Royal Society of Medicine
Phone: +44-20-7290-3942
Email: dermatology@rsm.ac.uk

Intermediate Skills in Laparoscopic Surgery
Jun 19 - 20, 2018
United Kingdom / London
Contact: Education Team, Royal College of Surgeons of England
Email: education@rcseng.ac.uk

2018 Vascular Annual Meeting
Jun 20 - 23, 2018
United States / Massachusetts / Boston
Contact: Society for Vascular Surgery
Phone: 800-258-7188 or 312-334-2300

32nd International Computer Assisted Radiology & Surgery (CARS) Congress & Exhibition
Jun 20 - 23, 2018
Germany / Berlin
Contact: Mrs. Franziska Schweikert, Conference Manager, CARS Conference Office
Phone: +49-77-4292-2434
Email: office@cars-int.org

12th Asian & Oceanian Epilepsy Congress
Jun 21 - 24, 2018
Indonesia / Bali
Contact: Secretariat, International League against Epilepsy / International Bureau for Epilepsy
Phone: 011-353-1-205-6720
Email: bali@epilepsycongress.org

Definitive Surgical Trauma Skills
Jun 21 - 22, 2018
United Kingdom / Manchester
Contact: Education Team, Royal College of Surgeons of England
Email: education@rcseng.ac.uk
14th International Regional Stress & Behavior Neuroscience & Biopsychiatry Conference (North America)
Jun 22 - 23, 2018
United States / Florida / Miami Beach
Contact: Na Nutsa, Secretary, International Stress and Behavior Society (ISBS)
Phone: 240-899-9571
Email: isbs.congress@gmail.com

2nd Annual International Congress on Oncology Pathology™: Towards Harmonization of Pathology & Oncology Standards
Jun 23, 2018
United States / New York / New York
Contact: Physicians’ Education Resource, LLC
Phone: 609-378-3701
Fax: 609-257-0705
Email: info@mceconferences.com

26th Annual Primary Care Summer CME Conference
Jun 25 - 29, 2018
United States / South Carolina / Kiawah Island
Contact: Barbara Ejes, Continuing Education Company
Phone: 386-447-6831
Email: barbara@cmemeeting.org

Geriatrics, Psychiatry and Palliative Medicine for Primary Care
Jun 22 - 24, 2018
United States / North Carolina / Asheville
Contact: MCE Conferences, MCE Conferences, MCE Conferences
Phone: 888-533-9031
Fax: 888-533-9031
Email: info@mceconferences.com

Clinical Anesthesia Update
Jun 26 - 29, 2018
United States / Colorado / Boulder
Contact: Northwest Seminars
Phone: 800-222-6927
Fax: 509-547-1265
Email: info@northwestseminars.com

2nd Annual European Congress on Genitourinary Malignancies™
Jun 22 - 23, 2018
Czech Republic / Prague
Contact: Physicians’ Education Resource, LLC
Phone: 609-378-3701
Fax: 609-257-0705
Email: info@gotoper.com

Royal College of Anaesthetists CPD Study Days
Jun 26 - 29, 2018
United Kingdom / London
Contact: Royal College of Anaesthetists
Phone: +44-20-7092-1500
Fax: +44-20-7092-1730
Email: info@rcoa.ac.uk

Society for Nuclear Medicine & Molecular Imaging 2018 Annual Meeting
Jun 23 - 26, 2018
United States / Pennsylvania / Philadelphia
Contact: Society of Nuclear Medicine & Molecular Imaging
Phone: 703-708-9000
Fax: 703-708-9015

Topics in Emergency Medicine: Trauma
Jun 27 - 30, 2018
United States / Florida / Clearwater Beach
Contact: Northwest Seminars
Phone: 800-222-6927
Fax: 509-547-1265
Email: info@northwestseminars.com

Musculoskeletal Ultrasound in Hemophilia
Jun 27 - 29, 2018
United States / California / San Diego
Contact: Marlene Zepeda, Continuing Medical Education, UC San Diego
Phone: 858-534-3940
Email: ocme@ucsd.edu

Innovation in Medicine 2018: Royal College of Physicians Annual Conference
Jun 25 - 26, 2018
United Kingdom / London
Contact: Royal College of Physicians
Phone: +44-20-3075-1649

2nd Annual International Congress on Oncology Pathology™: Towards Harmonization of Pathology & Oncology Standards
Jun 23, 2018
United States / New York / New York
Contact: Physicians’ Education Resource, LLC
Phone: 609-378-3701
Fax: 609-257-0705
Email: info@mceconferences.com

2018 Asia Pacific AIDS & Co-Infections Conference
Jun 28 - 30, 2018
China / Hong Kong
Contact: Virology Education
Phone: +31-30-230-7142
2018 Updates in **Kidney Transplant and Donation**
Jun 28, 2018
*United States / Virginia / Charlottesville, VA*
Contact: Andrea Zimmerman, University of Virginia Health System
Email: alm6f@virginia.edu

**HBS 2018: Heart and Brain Symposium 2018**
Jun 28 - 30, 2018
*United States / Illinois / Chicago*
Contact: Heart and Brain Secretariat, Kenes Group
Phone: +359-2-808-2110
Email: reg_hbs18@kenes.com

**2018 Pulmonary Hypertension** Association (PHA)
International Pulmonary Hypertension Conference & Scientific Sessions
Jun 29 - Jul 1, 2018
*United States / Florida / Orlando*
Contact: PHA
Phone: 301-565-3004; Fax: 301-565-3994
Email: pha@phassociation.org

**Endocrinology** for Primary Care
Jun 29 - Jul 1, 2018
*United States / South Carolina / Myrtle Beach*
Contact: MCE Conferences, MCE Conferences, MCE Conferences
Phone: 888-533-9031; Fax: 858-777-5588
Email: info@mceconferences.com

**The Traveller: Infectious and Tropical Diseases**
Jun 29, 2018
*United Kingdom / London Infectious Disease*
Contact: Emergency Medicine Section, Royal Society of Medicine
Phone: +44-20-7290-3935
Email: emergency@rsm.ac.uk

**25th Biennial Congress of the European Association for Cancer Research (EACR)**
Jun 30 - Jul 3, 2018
*Netherlands / Amsterdam*
Contact: Kathryn Wass, Office and Conference Series Manager, EACR
Phone: 011-44-11-5951-5114
Email: kathryn.wass@nottingham.ac.uk

**Patient Safety, Drug Abuse, Psychiatry & Pharmacogenomics**
Jun 30 - Jul 7, 2018
*United States / Washington / Seattle*
Contact: University Learning Systems
Phone: 800-940-5860
Fax: 716-529-0550
Email: info@universitylearning.com

**18th European Congress on Biotechnology**
Jul 1 - 4, 2018
*Switzerland / Geneva*
Contact: Congress Team, TFI Group
Phone: 011-44-20-7808-5171
Email: ecb2018@tfigroup.com

**2018 UK Radiological & Radiation Oncology**
Congress: Disease & Diversity
Jul 2 - 4, 2018
*United Kingdom / Liverpool*
Contact: Congress Organizers, Profile Productions Ltd.
Phone: +44-20-3725-5840; Fax: +44-84-4507-0578
Email: jointcongress@profileproductions.co.uk

**Child Public Health and Social Paediatrics**
Jul 2 - 3, 2018
*United Kingdom / London*
Contact: Continuing Professional Development, Imperial College London
Phone: +44-20-7589-5111

**Medical CBT: 10-Minute Techniques for Real Doctors** *(Cognitive Behavior Therapy)*
Jul 2 - 4, 2018
*Canada / Ontario / Collingwood*
Contact: Greg Dubord, MD, CME Director, CBT Canada
Phone: 877-466-8228
Email: info@cbt.ca

**Adolescent Health**
Jul 4 - 5, 2018
*United Kingdom / London*
Contact: Continuing Professional Development, Imperial College London
Phone: +44-20-7589-5111

**Dementia and Radiology**
Jul 5, 2018
*United Kingdom / London*
Contact: Emily Amos, Organizer, Royal Society of Medicine
Phone: +44-20-7290-3937
Email: radiology@rsm.ac.uk

**5th International Congress on Naturopathic Medicine**
Jun 6 - 8, 2018
*United Kingdom / London*
Contact: Conference Secretariat, International Congress on Naturopathic Medicine
Phone: +44-17-4582-8400
Email: secretariat@icnmnaturopathy.eu
2018 Federation of European **Neurosciences** Societies Forum
Jul 7 - 11, 2018
**Germany** / Berlin
Contact: Ron Marcovici, Mr., Kenes Group
Phone: 011-41-2-2908-0488
Email: rmarcovici@kenes.com

**Hypnosis** in Practice & Theory – Towards a Synthesis of Academic & Clinical Protocols
Jul 7 - 8, 2018
**United Kingdom** / London
Contact: Verity Cotton, Organizer, Royal Society of Medicine
Phone: +44-20-7290-3947
Email: hypnosis@rsm.ac.uk

40th Annual **Diagnostic Imaging** on Cape Cod
Jul 9 - 13, 2018
**United States** / Massachusetts / Chatham
Contact: Department of Radiology, Penn Medicine
Phone: 800-789-7366

9th Annual Essentials in **Primary Care** Summer CME Conference
Jul 9 - 13, 2018
**Canada** / Florida / Palm Coast
Contact: Barbara Ejnes, Mr., Continuing Education Company
Phone: 386-447-6831
Email: barbara@cmemeeeting.org

Topics in **Emergency Medicine**
Jul 9 - 13, 2018
**Canada** / Hawaii / Honolulu
Contact: Northwest Seminars
Phone: 800-222-6927
Fax: 509-547-1265
Email: info@northwestseminars.com

47th Annual Scientific Meeting of the Society for Academic **Primary Care**
Jul 10 - 12, 2018
**United Kingdom** / London
Contact: Secretariat, Society for Academic Primary Care
Phone: +44-18-6533-1839
Email: office@sapc.ac.uk

19th Annual Summer Conference on **Women’s Health**
Jul 11 - 14, 2018
**United States** / Hawaii / Big Island
Contact: Symposia Medicus
Phone: 800-327-3161 or 925-969-1789

25th International Meeting on **Advanced Spine Techniques**
Jul 11 - 14, 2018
**United States** / California / Los Angeles Neurology, Orthopedics
Contact: Scoliosis Research Society
Phone: 414-289-9107; Fax: 414-276-3349
Email: info@srs.org

43rd Annual Meeting of the Society for **Pediatric Dermatology**
Jul 11 - 14, 2018
**United States** / California / Lake Tahoe Dermatology
Contact: Society for Pediatric Dermatology
Phone: 317-202-0224; Fax: 317-205-9481
Email: info@pedsderm.net

Challenges in **Mental Healthcare** for the Primary Care Provider
Jul 11 - 14, 2018
**United States** / California / Napa
Contact: Symposia Medicus
Phone: 800-327-3161 or 925-969-1789

13th Annual Scientific Meeting of the Society of **Cardiovascular Computed Tomography**
Jul 12 - 15, 2018
**United States** / Texas / Grapevine
Contact: Society of Cardiovascular Computed Tomography
Phone: 800-876-4195 or 703-766-1706
Email: info@scct.org

22nd Annual Meeting of the Society for **Behavioral Neuroendocrinology** Joint Meeting with ICN
Jul 15 - 18, 2018
**Canada** / Ontario / Toronto
Contact: Society for Behavioral Neuroendocrinology
Phone: 847-517-7225; Fax: 847-517-7229
Email: info@sbn.org

Success with Failure: Strategies for the Evaluation & Treatment of **Heart Failure**
Jul 15 - 17, 2018
**Canada** / Oregon / Mt. Hood
Contact: Charlene Tri, Mayo Clinic
Phone: 800-283-6296
Email: cvcme@mayo.edu

2018 Focus on **Women’s Health** CME Conference
Jul 16 - 19, 2018
**United States** / South Carolina / Kiawah Island
Contact: Customer Service, Southern Medical Association
Phone: 800-423-4992 or 205-945-1840
Fax: 205-945-1830
Email: customerservice@sma.org
Forthcoming Conferences and Meetings June 2018

2018 Pan Pacific Lymphoma Conference
Jul 16 - 20, 2018
United States / Hawaii / Maui
Contact: Brenda Ram, CMP, CHCP, Continuing Education Coordinator, University of Nebraska Medical Center
Phone: 402-559-9250; Fax: 402-559-5915
Email: bram@unmc.edu

Medical CBT: 10-Minute Techniques for Real Doctors (Cognitive Behavior Therapy)
Jul 22 - 29, 2018
Spain / Barcelona
Contact: Greg Dubord, MD, CME Director, CBT Canada
Phone: 877-466-8228
Email: info@cbt.ca

10th Annual International Workshop on HIV Pediatrics
Jul 20 - 21, 2018
Netherlands / Amsterdam
Contact: Virology Education
Phone: +31-30-230-7142
Email: info@virology-education.com

2018 Peripheral Nerve Society (PNS) Annual Meeting
Jul 22 - 25, 2018
United States / Maryland / Baltimore
Contact: PNS Executive Office
Phone: 952-545-6284
Email: info@pnsociety.com

26th Annual Update in Orthopaedic Surgery Conference
Jul 22 - 26, 2018
United States / Hawaii / Maui
Contact: Joseph Federl, Conference Manager, CMX Travel Travel & Meetings
Phone: 781-829-9696; Fax: 781-735-0558
Email: cmxtravel@cmxtravel.com

6th Scientific Meeting of the World Society for Pediatric & Congenital Heart Surgery / 18th International Symposium on Congenital Heart Disease
Jul 22 - 26, 2018
United States / Florida / Orlando
Contact: Suzanne Anderson, Conference Coordinator, Johns Hopkins All Children’s Hospital
Phone: 727-767-2565; Fax: 727-767-8601
Email: suzanne.anderson@jhmi.edu

Society of Neurointerventional Surgery 15th Annual Meeting
Jul 23 - 27, 2018
United States / California / San Francisco
Contact: Society of Neurointerventional Surgery
Phone: 703-691-2272; Fax: 703-537-0650

10th Diabetes Complications Conference & Grand Rounds
Jul 24 - 25, 2018
Malaysia / Kuching
Contact: Suaidah, Ms., National Diabetes Institute (NADI) Malaysia
Phone: +60-3-7876-1676; Fax: +60-3-7876-1679
Email: suaidah.nadi16@gmail.com

20th Annual Summer Conference on Pediatrics
Jul 25 - 28, 2018
United States / California / Lake Tahoe
Contact: Symposia Medicus
Phone: 800-327-3161 or 925-969-1789

Topics in Emergency Medicine
Jul 25 - 28, 2018
United States / Oregon / Portland
Contact: Northwest Seminars
Phone: 800-222-6927; Fax: 509-547-1265
Email: info@northwestseminars.com

Blended Introduction to Adult Echocardiography
Jul 26 - 27, 2018
United States / Florida / St. Petersburg
Contact: Casey Green, Business Development Supervisor, Gulfcoast Ultrasound Institute, Inc
Phone: 727-363-4500; Fax: 727-363-0811
Email: learn@gcus.com

Blended Introduction to Carotid Duplex/Color Flow Imaging
Jul 26, 2018
United States / Florida / St. Petersburg
Contact: Casey Green, Business Development Supervisor, Gulfcoast Ultrasound Institute, Inc
Phone: 727-363-4500; Fax: 727-363-0811
Email: learn@gcus.com
Diabetes Asia 2018 Conference  
Jul 26 - 29, 2018  
Malaysia / Kuching  
Contact: Suaidah, Ms., National Diabetes Institute (NADI) Malaysia  
Phone: +60-3-7876-1676; Fax: +60-3-7876-1679  
Email: suaidah.nadi16@gmail.com

Blended Introduction to Peripheral Vascular Duplex/Color Flow Imaging  
Jul 27, 2018  
United States / Florida / St. Petersburg  
Contact: Casey Green, Business Development Supervisor, Gulfcoast Ultrasound Institute, Inc  
Phone: 727-363-4500; Fax: 727-363-0811  
Email: learn@gcus.com

Blended Introduction to Transcranial Doppler Ultrasound  
Jul 27, 2018  
United States / Florida / St. Petersburg  
Contact: Casey Green, Business Development Supervisor, Gulfcoast Ultrasound Institute, Inc  
Phone: 727-363-4500; Fax: 727-363-0811  
Email: learn@gcus.com

31st Annual in Vitro Fertilization & Embryo Transfer  
Jul 30 - Aug 1, 2018  
United States / California / San Diego  
Contact: Bermellyn Imamura, Continuing Medical Education, UC San Diego  
Phone: 858-534-3940  
Email: ocme@ucsd.edu

25th Annual Summer Conference on Obstetrics and Gynecology  
Aug 1 - 4, 2018  
United States / Florida / Naples  
Contact: Symposia Medicus  
Phone: 800-327-3161 or 925-969-1789

Relevant Topics in Anesthesia  
Aug 1 - 4, 2018  
United States / California / San Diego  
Contact: Northwest Seminars  
Phone: 800-222-6927; Fax: 509-547-1265  
Email: info@northwestseminars.com

70th Annual Meeting of the Pacific Dermatologic Association (PDA)  
Aug 2 - 5, 2018  
Mexico / Cabo San Lucas  
Contact: PDA  
Phone: 888-388-8815  
Email: info@pacificderm.org

35th Annual Primary Care Summer Conference  
Aug 3 - 5, 2018  
United States / California / San Diego  
Contact: Scripps Conference Services & CME  
Phone: 858-678-6400  
Email: med.edu@scrippshealth.org

Ultrasound-Guided Vascular Access  
Aug 3, 2018  
United States / Florida / St. Petersburg  
Contact: Casey Green, Business Development Supervisor, Gulfcoast Ultrasound Institute, Inc  
Phone: 727-363-4500; Fax: 727-363-0811  
Email: learn@gcus.com

Medical CBT: 10-Minute Techniques for Real Doctors (Cognitive Behavior Therapy)  
Aug 4 – 11, 2018  
Spain / Barcelona  
Contact: Greg Dubord, MD, CME Director, CBT Canada  
Phone: 877-466-8228  
Email: registrar@cbt.ca

Current Topics in Anesthesia  
Aug 5 - 9, 2018  
United States / Oregon / Sunriver  
Contact: Northwest Seminars  
Phone: 800-222-6927  
Fax: 509-547-1265  
Email: info@northwestseminars.com

Hospitalist and Emergency Procedures Course - Long Beach  
Aug 5, 2018  
United States / California / Long Beach  
Contact: Joseph Esherick, President, Hospital Procedures Consultants  
Phone: 805-339-0225; Fax: 805-339-0375  
Email: jesherick@hospitalprocedures.org

14th Global Conference on Ageing  
Aug 8 - 10, 2018  
Canada / Ontario / Toronto Geriatrics  
Contact: Ms. Savannah Duchen, Events Management Officer, International Federation on Ageing  
Phone: 416-342-1655  
Email: sduchen@ifa-fiv.org

Current Topics in Emergency Medicine  
Aug 13 - 17, 2018  
United States / Montana / Glacier National Park  
Contact: Northwest Seminars  
Phone: 800-222-6927; Fax: 509-547-1265  
Email: info@northwestseminars.com
Introduction to **Musculoskeletal Ultrasound**
Aug 13 - 15, 2018
*United States / Florida / St. Petersburg*
Contact: Casey Green, Business Development Supervisor, Gulfcoast Ultrasound Institute, Inc
Phone: 727-363-4500; Fax: 727-363-0811
Email: learn@gcus.com

Introduction to **Musculoskeletal Ultrasound** with Optional Interventional Cadaver Lab
Aug 13 - 15, 2018
*United States / Florida / St. Petersburg*
Contact: Casey Green, Business Development Supervisor, Gulfcoast Ultrasound Institute, Inc
Phone: 727-363-4500
Fax: 727-363-0811
Email: learn@gcus.com

See the Line **Concussion and Awareness**
Aug 15, 2018
*United Kingdom / London*
Contact: Natalie Wakabayashi, Continuing Professional Development, Schulich Medicine and Dentistry
Phone: 519-661-2111 Ext. 89201
Email: natalie.wakabayashi@schulich.uwo.ca

Advanced & Interventional **MSK Ultrasound**
Aug 16 - 17, 2018
*United States / Florida / St. Petersburg*
Contact: Casey Green, Gulfcoast Ultrasound Institute
Phone: 727-363-4500
Fax: 727-363-4500
Email: learn@gcus.com

Advanced/Interventional **MSK Ultrasound** with Regenerative Medicine Track
Aug 16 - 17, 2018
*United States / Florida / St. Petersburg*
Contact: Casey Green, Business Development Supervisor, Gulfcoast Ultrasound Institute, Inc
Phone: 727-363-4500
Fax: 727-363-4500
Email: learn@gcus.com

**23rd Annual Challenges in Critical Care: A Multidisciplinary Approach**
Aug 24, 2018
*United States / Pennsylvania / Hershey*
Contact: Continuing Education, Penn State College of Medicine
Phone: 717-531-6483; Fax: 717-531-5604

**13th European Congress on Epileptology**
Aug 26 - 30, 2018
*Austria / Vienna Neurology*
Contact: Congress Secretariat, International League against Epilepsy / International Bureau for Epilepsy
Phone: 011-353-1-205-6720
Email: vienna@epilepsycongress.org

**ICS 2018: 48th Annual Meeting of the International Continence Society**
Aug 28 - 31, 2018
*United States / Pennsylvania / Philadelphia*
Contact: Stephanie Orzech, Kenes Group on Behalf of ICS
Phone: +972 3-972-7955
Email: sorzech@kenes.com

**2018 Minimally Invasive Surgery Week**
Aug 29 - Sep 1, 2018
*United States / New York / New York*
Contact: Society of Laparoendoscopic Surgeons
Phone: 305-665-9959
Email: info@sls.org

**Society for Paediatric Anaesthesia in New Zealand and Australia (SPANZA) 2018 Annual Conference**
Aug 29 - Sep 2, 2018
*United States / Australia / Darwin*
Contact: Spanza Secretariat, Will Organise
Phone: +61-2-4973-6573
Fax: +61-2-4973-6609
Email: spanza@willorganise.com.au

**13th International Hepato-Pancreato-Biliary Association World Congress**
Sep 3 - 7, 2018
*Switzerland / Geneva*
Contact: MCI Suisse SA
Email: ihpba2018@mci-group.com

**2018 Foodmicro Conference**
Sep 3 - 6, 2018
*Germany / Berlin*
Contact: Astrid Wilch, MCI Deutschland GmbH
Phone: 011-49-30-204-590
Fax: 011-49-30-204-5950
Email: foodmicro@mci-group.com
2018 Tissue Engineering International & Regenerative Medicine Society (TERMIS) World Congress
Sep 4 - 7, 2018
Japan / Kyoto
Contact: Congress Management Office, C/O Japan Convention Service, Inc.
Phone: +81-6-6221-5933; Fax: +81-6-6221-5938
Email: termis-wc2018@convention.co.jp

Clinical Anesthesia Update
Sep 10 - 14, 2018
United States / California / Yosemite
Contact: Northwest Seminars
Phone: 800-222-6927; Fax: 509-547-1265
Email: info@northwestseminars.com

Introduction to Emergency Medicine Ultrasound
Sep 10 - 12, 2018
United States / Florida / St. Petersburg
Contact: Casey Green, Business Development Supervisor, Gulfcoast Ultrasound Institute, Inc.
Phone: 727-363-4500; Fax: 727-363-4500
Email: learn@gcus.com

Topics in Emergency Medicine: Emphasis on Pediatrics
Sep 10 - 13, 2018
United States / Nevada / Las Vegas
Contact: Northwest Seminars
Phone: 800-222-6927; Fax: 509-547-1265
Email: info@northwestseminars.com

Introduction to Critical Care Ultrasound
Sep 11 - 12, 2018
United States / Florida / St. Petersburg
Contact: Casey Green, Business Development Supervisor, Gulfcoast Ultrasound Institute, Inc.
Phone: 727-363-4500; Fax: 727-363-0811
Email: learn@gcus.com

17th World Congress on Pain
Sep 12 - 16, 2018
United States / Massachusetts / Boston
Contact: International Association for the Study of Pain
Phone: 202-856-7400; Fax: 202-856-7401

19th Annual Fall Conference on Integrative Medicine in Women’s Health
Sep 12 - 15, 2018
United States / Arizona / Sedona
Contact: Symposia Medicus
Phone: 800-327-3161 or 925-969-1789

20th Annual Meeting of the European Pressure Ulcer Advisory Panel
Sep 12 - 14, 2018
Italy / Rome
Contact: Adina Markova, European Pressure Ulcer Advisory Panel
Phone: +420-251-019-379
Email: office@epuap.org

37th Annual European Society of Regional Anaesthesia & Pain Therapy Congress: ESRA 2018
Sep 12 - 15, 2018
Ireland / Dublin
Contact: ESRA Congress Secretariat, Kenes Group on Behalf of ESRA
Phone: +41-22-908-0488
Email: tsimantov@kenes.com

Current Topics in Healthcare 2018
Sep 12 - 14, 2018
United States / Nevada / Las Vegas
Contact: University Learning Systems
Phone: 800-940-5860; Fax: 716-529-0550
Email: info@universitylearning.com

1st Conference on Liver Disease in Africa
Sep 13 - 15, 2018
Kenya / Nairobi
Contact: Virology Education
Phone: +31-30-230-7142
Email: info@virology-education.com

Advanced Emergency Medicine & Critical Care Ultrasound
Sep 13 - 14, 2018
United States / Florida / St. Petersburg
Contact: Casey Green, Business Development Supervisor, Gulfcoast Ultrasound Institute, Inc.
Phone: 727-363-4500; Fax: 727-363-0811
Email: learn@gcus.com

Medicine24
Sep 13 - 14, 2018
United Kingdom / Glasgow
Contact: Wilma Paterson, Coordinator, Royal College of Physicians and Surgeons of Glasgow
Phone: +44-14-1227-3212
Email: wilma.paterson@rcpsg.ac.uk

17th Biennial Meeting of the International Gynecologic Cancer Society
Sep 14 - 16, 2018
Japan / Kyoto
Contact: Josh Margo, Kenes Group
Phone: +972-3-972-7450
Email: jmargo@kenes.com
6th Annual UCLA Review of *Clinical Neurology*
Sep 14 - 16, 2018
*United States / California / Los Angeles*
Contact: Continuing Medical Education, University of California, Los Angeles
Phone: 310-794-2620; Fax: 310-794-2624

Medical CBT: 10-Minute Techniques for Real Doctors
(*Cognitive Behavior Therapy*)
Sep 14 - 15, 2018
*Canada / British Columbia / Fort St. John*
Contact: Greg Dubord, MD, CME Director, CBT Canada
Phone: 877-466-8228
Email: registrar@cbt.ca

Societies for *Pediatric Urology* 2018 Pediatric Urology Fall Congress
Sep 14 - 16, 2018
*United States / Georgia / Atlanta*
Contact: Societies for Pediatric Urology
Phone: 978-927-8330; Fax: 978-524-0498

Blended *Pediatric Emergency & Critical Care Ultrasound*
Sep 15, 2018
*United States / Florida / St. Petersburg*
Contact: Casey Green, Business Development Supervisor, Gulfcoast Ultrasound Institute, Inc
Phone: 727-363-4500; Fax: 727-363-0811
Email: learn@gcus.com

16th World Congress of the International Society for *Diseases of the Esophagus* (ISDE)
Sep 16 - 19, 2018
*Austria / Vienna*
Contact: International Conference Services Ltd.
Phone: 604-681-2153; Fax: 604-681-1049
Email: isde2018@icsevents.com

Current *Anesthesia Practice*
Sep 17 - 20, 2018
*United States / Arizona / Sedona*
Contact: Northwest Seminars
Phone: 800-222-6927; Fax: 509-547-1265
Email: info@northwestseminars.com

Medical CBT: 10-Minute Techniques for Real Doctors
(*Cognitive Behavior Therapy*)
Sep 17 - 18, 2018
*Canada / British Columbia / Vancouver*
Contact: Greg Dubord, MD, CME Director, CBT Canada
Phone: 877-466-8228
Email: info@cbt.ca

Challenges in *Obstetrics & Gynecology*
Sep 18 - 27, 2018
*Spain / Barcelona*
Contact: Symposium Medicus
Phone: 800-327-3161 or 925-969-1789

*Eurospine 2018*
Sep 19 - 21, 2018
*Spain / Barcelona*
Contact: Liesa Wessely, Organizing Secretariat, Mondial Congress & Events
Phone: +43-1-58-8040
Email: eurospine2018@mondial-congress.com

*Musculoskeletal Ultrasound* Registry Review Course
Sep 20 - 21, 2018
*United States / Florida / St. Petersburg*
Contact: Casey Green, Business Development Supervisor, Gulfcoast Ultrasound Institute, Inc
Phone: 727-363-4500; Fax: 727-363-0811
Email: learn@gcus.com

Relevant Topics in *Anesthesia*
Sep 20 - 23, 2018
*United States / South Carolina / Hilton Head Island*
Contact: Northwest Seminars
Phone: 800-222-6927
Fax: 509-547-1265
Email: info@northwestseminars.com

*Advanced Radiology Life Support (ARLS)*
Sep 22, 2018
*United States / Minnesota / Rochester (MN)*
Contact: Department of Radiology CME Office, Mayo Clinic
Phone: 507-284-3317
Email: radiologymce@mayo.edu

*Hospitalist and Emergency Procedures* Course - Seattle
Sep 23, 2018
*United States / Washington / Seattle*
Contact: Joseph Escherick, President, Hospital Procedures Consultants
Phone: 805-339-0225
Fax: 805-339-0375
Email: jesherick@hospitalprocedures.org

*Anesthesia Update*
Sep 24 - 28, 2018
*United States / Wyoming / Jackson Hole*
Contact: Northwest Seminars
Phone: 800-222-6927
Fax: 509-547-1265
Email: info@northwestseminars.com
1. DIARRHOEAL DISEASE

Diarrhoeal disease is the second leading cause of death in children under five years old, and is responsible for killing around 525,000 children every year. Diarrhoea can last several days, and can leave the body without the water and salts that are necessary for survival. In the past, for most people, severe dehydration and fluid loss were the main causes of diarrhoea deaths. Now, other causes such as septic bacterial infections are likely to account for an increasing proportion of all diarrhoea-associated deaths. Children who are malnourished or have impaired immunity as well as people living with HIV are most at risk of life-threatening diarrhoea.

Diarrhoea is defined as the passage of three or more loose or liquid stools per day (or more frequent passage than is normal for the individual). Frequent passing of formed stools is not diarrhoea, nor is the passing of loose, “pasty” stools by breastfed babies.

Diarrhoea is usually a symptom of an infection in the intestinal tract, which can be caused by a variety of bacterial, viral and parasitic organisms. Infection is spread through contaminated food or drinking-water, or from person-to-person as a result of poor hygiene.

Interventions to prevent diarrhoea, including safe drinking-water, use of improved sanitation and hand washing with soap can reduce disease risk. Diarrhoea should be treated with oral rehydration solution (ORS), a solution of clean water, sugar and salt. In addition, a 10-14 day supplemental treatment course of dispersible 20 mg zinc tablets shortens diarrhoea duration and improves outcomes.

There are three clinical types of diarrhoea:
• acute watery diarrhoea – lasts several hours or days, and includes cholera;
• acute bloody diarrhoea – also called dysentery; and
• persistent diarrhoea – lasts 14 days or longer.

KEY FACTS
• Diarrhoeal disease is the second leading cause of death in children under five years old. It is both preventable and treatable.
• Each year diarrhoea kills around 525,000 children under five.
• A significant proportion of diarrhoeal disease can be prevented through safe drinking-water and adequate sanitation and hygiene.
• Globally, there are nearly 1.7 billion cases of childhood diarrhoeal disease every year.
• Diarrhoea is a leading cause of malnutrition in children under five years old.

Scope of diarrhoeal disease
Diarrhoeal disease is a leading cause of child mortality and morbidity in the world, and mostly results from contaminated food and water sources. Worldwide, 780 million individuals lack access to improved drinking-water and 2.5 billion lack improved sanitation. Diarrhoea due to infection is widespread throughout developing countries.

In low-income countries, children under three years old experience on average three episodes of diarrhoea every year. Each episode deprives the child of the nutrition necessary for growth. As a result, diarrhoea is a major cause of malnutrition, and malnourished children are more likely to fall ill from diarrhoea.
Dehydration

The most severe threat posed by diarrhoea is dehydration. During a diarrhoeal episode, water and electrolytes (sodium, chloride, potassium and bicarbonate) are lost through liquid stools, vomit, sweat, urine and breathing. Dehydration occurs when these losses are not replaced.

The degree of dehydration is rated on a scale of three.

1. Severe dehydration (at least two of the following signs):
   - Lethargy/unconsciousness
   - Sunken eyes
   - Unable to drink or drink poorly
   - Skin pinch goes back very slowly (≥2 seconds)
2. Some dehydration (two or more of the following signs):
   - Restlessness, irritability
   - Sunken eyes
   - Drinks eagerly, thirsty
3. No dehydration (not enough signs to classify as some or severe dehydration).

Causes

Infection: Diarrhoea is a symptom of infections caused by a host of bacterial, viral and parasitic organisms, most of which are spread by faeces-contaminated water. Infection is more common when there is a shortage of adequate sanitation and hygiene and safe water for drinking, cooking and cleaning. Rotavirus and Escherichia coli, are the two most common etiological agents of moderate-to-severe diarrhoea in low-income countries. Other pathogens such as cryptosporidium and shigella species may also be important. Location-specific etiologic patterns also need to be considered.

Malnutrition: Children who die from diarrhoea often suffer from underlying malnutrition, which makes them more vulnerable to diarrhoea. Each diarrhoeal episode, in turn, makes their malnutrition even worse. Diarrhoea is a leading cause of malnutrition in children under five years old.

Source: Water contaminated with human faeces, for example, from sewage, septic tanks and latrines, is of particular concern. Animal faeces also contain microorganisms that can cause diarrhoea.

Other causes: Diarrhoeal disease can also spread from person-to-person, aggravated by poor personal hygiene. Food is another major cause of diarrhoea when it is prepared or stored in unhygienic conditions. Unsafe domestic water storage and handling is also an important risk factor. Fish and seafood from polluted water may also contribute to the disease.

Prevention and treatment

Key measures to prevent diarrhoea include:
- Access to safe drinking-water;
- Use of improved sanitation;
- Hand washing with soap;
- Exclusive breastfeeding for the first six months of life;
- Good personal and food hygiene;
- Health education about how infections spread; and
- Rotavirus vaccination.

Key measures to treat diarrhoea include the following:
- Rehydration: with oral rehydration salts (ORS) solution. ORS is a mixture of clean water, salt, and sugar. It costs a few cents per treatment. ORS is absorbed in the small intestine and replaces the water and electrolytes lost in the faeces.
- Zinc supplements: zinc supplements reduce the duration of a diarrhoea episode by 25% and are associated with a 30% reduction in stool volume.
- Rehydration: with intravenous fluids in case of severe dehydration or shock.
- Nutrient-rich foods: the vicious circle of malnutrition and diarrhoea can be broken by continuing to give nutrient-rich foods – including breast milk – during an episode, and by giving a nutritious diet – including exclusive breastfeeding for the first six months of life – to children when they are well.
- Consulting a health professional, in particular for management of persistent diarrhoea or when there is blood in stool or if there are signs of dehydration.

WHO response

WHO works with Member States and other partners to:
- Promote national policies and investments that support case management of diarrhoea and its complications as well as increasing access to safe drinking-water and sanitation in developing countries;
- Conduct research to develop and test new diarrhoea prevention and control strategies in this area;
- Build capacity in implementing preventive interventions, including sanitation, source water improvements, and household water treatment and safe storage;
- Develop new health interventions, such as the rotavirus immunization; and
- Help to train health workers, especially at community level.

2. EPILEPSY

Epilepsy is a chronic disorder of the brain that affects people of all ages worldwide. It is one of
the world’s oldest recognized conditions. Fear, misunderstanding, discrimination and social stigma have surrounded epilepsy for centuries. This stigma continues in many countries today and can impact on the quality of life for people with the disorder and their families.

**KEY FACTS**

- Epilepsy is a chronic disorder of the brain that affects people of all ages.
- Approximately 50 million people worldwide have epilepsy, making it one of the most common neurological diseases globally.
- Nearly 80% of the people with epilepsy live in low- and middle-income countries.
- People with epilepsy respond to treatment approximately 70% of the time.
- About three fourths of people with epilepsy living in low- and middle-income countries do not get the treatment they need.
- In many parts of the world, people with epilepsy and their families suffer from stigma and discrimination.

**Signs and symptoms**

Epilepsy is defined as having two or more unprovoked seizures. Seizures are brief episodes of involuntary movement that may involve a part of the body (partial) or the entire body (generalized), and are sometimes accompanied by loss of consciousness and control of bowel or bladder function.

Seizures are a result of excessive electrical discharges in a group of brain cells. This can happen in different parts of the brain. Seizures can vary from the briefest lapses of attention or muscle jerks to severe and prolonged convulsions. Seizures can also vary in frequency, from less than one per year to several per day.

Characteristics of seizures vary and depend on where in the brain the disturbance first starts, and how far it spreads. Temporary symptoms occur, such as loss of awareness or consciousness, and disturbances of movement, sensation (including vision, hearing and taste), mood, or other cognitive functions.

People with seizures tend to have more physical problems (such as fractures and bruising from injuries related to seizures), as well as higher rates of psychological conditions, including anxiety and depression. Similarly, the risk of premature death in people with epilepsy is up to three times higher than the general population, with the highest rates found in low- and middle-income countries and rural versus urban areas. A great proportion of the causes of death related to epilepsy in low- and middle-income countries are potentially preventable, such as falls, drowning, burns and prolonged seizures.

**Rates of disease**

Approximately 50 million people currently live with epilepsy worldwide. The estimated proportion of the general population with active epilepsy (i.e. continuing seizures or with the need for treatment) at a given time is between 4 and 10 per 1000 people. However, some studies in low- and middle-income countries suggest that the proportion is much higher, between 7 and 14 per 1000 people. Close to 80% of people with epilepsy live in low- and middle-income countries.

Globally, an estimated 2.4 million people are diagnosed with epilepsy each year. In high-income countries, annual new cases are between 30 and 50 per 100 000 people in the general population. In low- and middle-income countries, this figure can be up to two times higher. The higher figure in low- and middle-income countries is likely due to the increased risk of endemic conditions such as malaria or neurocysticercosis; the higher incidence of road traffic injuries; birth-related injuries; and variations in medical infrastructure, availability of preventive health programmes and accessible care.

**Causes**

Epilepsy is not contagious. The most common type of epilepsy, which affects 6 out of 10 people with the disorder, is called idiopathic epilepsy and has no identifiable cause.

Epilepsy with a known cause is called secondary epilepsy, or symptomatic epilepsy. The causes of secondary (or symptomatic) epilepsy include:

- brain damage from prenatal or perinatal injuries (e.g. a loss of oxygen or trauma during birth, low birth weight);
- congenital abnormalities or genetic conditions with associated brain malformations;
- a traumatic head injury;
- a stroke that restricts the amount of oxygen to the brain;
- an infection of the brain such as meningitis, encephalitis, neurocysticercosis;
- certain genetic syndromes; or
- a brain tumor.

**Treatment**

Epilepsy can be treated easily and affordably with inexpensive daily medication that costs as little as US$ 5 per year. Recent studies in both low- and middle-income countries have shown that up to 70% of children and adults with epilepsy can be successfully
treated (i.e. their seizures completely controlled) with anti-epileptic medicines. Furthermore, after 2 to 5 years of successful treatment and being seizure-free, drugs can be withdrawn in about 70% of children and 60% of adults without subsequent relapse. It is possible to diagnose and treat most people with epilepsy at the primary healthcare level without the use of sophisticated equipment. Surgical therapy might be beneficial to patients who respond poorly to drug treatments.

Despite these facts, about three fourths of people with epilepsy in low- and middle-income countries may not receive the treatment they need. This is called the “treatment gap”. Contributors to the high treatment gap are many and include:

- the lack or severe shortage of appropriately trained staff. According to the WHO 2017 Neurology Atlas, the median number of neurologists in low-income countries is 0.1 per 100,000, compared with 7.1 per 100,000 in high-income countries;
- the low availability of anti-epileptic medicines. A recent study found the average availability of generic antiepileptic medicines in the public sector facilities of low- and middle-income countries to be less than 50%;
- the cost of medication. The above study estimated that epilepsy treatment with the lowest-price generic anti-epileptic medicine cost the lowest-paid worker the equivalent of 2.7 and 5.2 days’ wages in the public and private sectors respectively; and
- the lack of public awareness and cultural beliefs.

**Prevention**

Idiopathic epilepsy is not preventable. However, preventive measures can be applied to the known causes of secondary epilepsy.

- Preventing head injury is the most effective way to prevent post-traumatic epilepsy.
- Adequate perinatal care can reduce new cases of epilepsy caused by birth injury.
- The use of drugs and other methods to lower the body temperature of a feverish child can reduce the chance of febrile seizures.
- Central nervous system infections are common causes of epilepsy in tropical areas. Elimination of parasites and education on how to avoid infections can be effective ways to reduce epilepsy in these environments.

**Social and economic impacts**

Epilepsy accounts for 0.6%, of the global burden of disease, a time-based measure that combines years of life lost due to premature mortality and time lived in less than full health. Epilepsy has significant economic implications in terms of health care needs, premature death and lost work productivity. An Indian study conducted in 1998 calculated that the cost per patient of epilepsy treatment was as high as 88.2% of the country’s per capita Gross National Product (GNP), and epilepsy-related costs, which included medical costs, travel, and lost work time, exceeded $2.6 billion/year (2013 USD). (1)

The discrimination and social stigma that surround epilepsy in some parts of the world are often more difficult to overcome than the seizures themselves. People living with epilepsy can be targets of prejudice. The stigma of the disorder can discourage people from seeking treatment for symptoms, so as to avoid becoming identified with the disorder.

**Human rights**

People with epilepsy can experience reduced access to health and life insurance, withholding of the opportunity to obtain a driving license, and barriers to enter certain occupations. In many countries legislation reflects centuries of misunderstanding about epilepsy. For example:

- In both China and India, epilepsy is commonly viewed as a reason for prohibiting or annulling marriages.
- In the United Kingdom, laws which permitted the annulment of a marriage on the grounds of epilepsy were not amended until 1971.
- In the United States of America, until the 1970s, it was legal to deny people with seizures access to restaurants, theatres, recreational centres and other public buildings.

Legislation based on internationally accepted human rights standards can prevent discrimination and rights violations, improve access to health-care services, and raise the quality of life for people with epilepsy.

**WHO response**

WHO and its partners recognize that epilepsy is a major public health concern. As part of an initiative established in 1997, WHO, the International League Against Epilepsy (ILAE) and the International Bureau for Epilepsy (IBE) are carrying out a global campaign – “Out of the Shadows” – to provide better information and raise awareness about epilepsy and strengthen public and private efforts to improve care and reduce the disorder’s impact.

This, as well as other WHO projects on epilepsy, have shown that there are simple, cost-effective ways to treat epilepsy in resource-poor settings, thereby significantly reducing treatment gaps. For example, a project carried out in China resulted in treatment gap reductions of 13% over 1 year and significant improvements in access to care for people with epilepsy.
Projects which aim to reduce the treatment gap and morbidity of people with epilepsy, to train and educate health professionals, to dispel stigma, to identify potential prevention strategies, and to develop models integrating epilepsy control into local health systems are ongoing in many countries.

In particular, the WHO Programme on Reducing the Epilepsy Treatment Gap and the Mental Health Gap Action Programme (mhGAP) sought to achieve these goals in Ghana, Mozambique, Myanmar and Viet Nam. These projects combined several innovative strategies. They focused on expanding the skills of primary care and non-specialist health professionals at the community level to diagnose, treat and follow up people with epilepsy. The Programme also included strengthening of health systems to increase sustainable access to antiepileptic medicines, reinforcing referral systems and ensuring better monitoring of epilepsy in health information systems. It included activities to raise awareness about epilepsy and to support people with epilepsy and their families.

Recognising the need to improve access to epilepsy care and reduce stigmatisation, the World Health Assembly in 2015 adopted a resolution, WHA68.20: Global burden of epilepsy and the need for coordinated action at the country level to address its health, social and public knowledge implications. This resolution urges governments to formulate, strengthen and implement national policies and legislation to promote access to care and protect the rights of people living with epilepsy. It emphasizes the importance of training non-specialist health care providers in order to reduce epilepsy treatment gaps.

Transmission
Foodborne trematodiases are zoonoses, i.e. they are naturally transmissible from vertebrate animals to people and vice versa. Direct transmission is however not possible, as the relevant causative parasites become infective only after having completed complex life-cycles that usually involve stages in intermediate, non-human hosts.

People become infected by eating raw fish, crustaceans or vegetables that harbour the parasite larvae.

Foodborne trematodiases are most prevalent in East Asia and South America.

Foodborne trematodiases result in severe liver and lung disease.

Safe and efficacious medicines are available to prevent and treat foodborne trematodiases.

Prevention and management of food-borne trematodes requires cross-sectoral collaboration on the human-animal and ecosystems interface.

3. FOODBORNE TREMATODIASES

Foodborne trematodiases are caused by trematode worms (“flukes”), among them the species affecting humans with potentially severe outcomes, are Clonorchis, Opisthorchis, Fasciola and Paragonimus.

People become infected through the consumption of raw or undercooked food: fish, crustaceans and vegetables that harbour the minute larval stages of the parasites (see Table 1).

Epidemiology and burden
The true burden of disease associated with these infections is unclear. For example, paragonimiasis is known to be transmitted in the central and western Africa, but information regarding its epidemiological status is limited.

Estimates from the WHO Foodborne disease burden Epidemiology Reference Group (FERG) (2015) identified the 4 species of food borne trematodes as important causes of disability with an estimated annual total of 200 000 illnesses and more than 7 000 deaths, resulting in > 2 million disability-adjusted life-years (DALYs) (1) globally.

Clonorchiasis and opisthorchiasis are confined to

KEY FACTS
• Foodborne trematodiases cause 2 million life years lost to disability and death worldwide every year.
Asia, while paragonimiasis can be found in Africa, Asia and Latin America. Fascioliasis is a global disease, affecting a significant number of countries throughout the world. Although cases of foodborne trematodes have been reported from more than 70 countries worldwide, countries in Asia and Latin America are the worst affected.

Within countries, transmission is often restricted to limited areas and reflects behavioural and ecological patterns, such as people’s food habits, methods of food production and preparation, and the distribution of intermediate hosts. Information on the epidemiological status of foodborne trematode infections in Africa is largely missing.

The economic impact of foodborne trematodiases is significant, and is linked to losses in the livestock and aquaculture industries due to reduced animal productivity, as well as to restrictions on exports and reduced consumer demand.

Symptoms

The public health burden attributable to foodborne trematodiases is predominantly due to morbidity rather than mortality.

Early and light infections often pass unnoticed, as they are asymptomatic or only scarcely symptomatic. Conversely, if the worm load is high, general malaise is common and severe pain can occur, especially in the abdominal region, and this occurs most frequently in the case of fascioliasis.

Chronic infections are invariably associated with severe morbidity. Symptoms are mainly organ-specific and reflect the final location of the adult worms in the body.

In clonorchiasis and opisthorchiasis, the adult worms lodge in the smaller bile ducts of the liver, causing inflammation and fibrosis of the adjacent tissues with a potential to cause cholangiocarcinoma, a severe and fatal form of bile duct cancer. Both C. sinensis and O. viverrini, but not O. felineus, are classified as carcinogenic agents.

In fascioliasis, the adult worms lodge in the larger bile ducts and the gall bladder, where they cause inflammation, fibrosis, blockage, colic pain and jaundice. Liver fibrosis and anaemia are also frequent.

In paragonimiasis, the final location of the worms is the lung tissue. They cause symptoms that can be confounded with tuberculosis: chronic cough with blood-stained sputum, chest pain, dyspnoea (shortness of breath) and fever. Migration of the worms is possible: cerebral locations are the most severe.

Prevention and control

Control of foodborne trematodiases aims to reduce the risk of infection and at controlling associated morbidity.

Like other diseases including an animal cycle, for the control of food-borne trematodes, an approach which links animal, human and environmental aspects should be used.

Unhygienic preparation and storage can lead to the contamination of food, and the consumption of raw fish and seafood is a main risk factor for contracting these parasites.

The preservation of the parasites’ biological cycles is also closely linked with water and sanitation. Unprocessed human and animal faecal waste used as manure or even deliberately as fish feed can contaminate (drinking) water, leading to a continuous cycle of infections.

Therefore, veterinary public health measures and food safety practices and education are recommended to reduce the risk of infection. While, to control morbidity, WHO recommends improved access to treatment using safe and effective anthelminthic medicines (drugs that expel the worms).

Treatment can be offered through preventive chemotherapy or individual case management. Preventive chemotherapy involves a population-based approach where everyone in a given region or area is given medicines, irrespective of their infection status. It is recommended in areas where large numbers of people are infected. A vigilant use of this preventive treatment is recommended due to rarely observed side effects. A cost-effective and risk minimizing strategy is to define at-risk populations based on consumption patterns of raw fish and focus on these for medication.

Individual case-management involves the treatment of people with confirmed or suspected infection (see Table 2): this approach is more appropriate where cases are less clustered and where health facilities are available.
WHO response

WHO’s work on foodborne trematodiases is part of an integrated approach to the control of neglected tropical diseases, and includes:

- development of strategic directions and recommendations;
- support for mapping in endemic countries;
- support for pilot interventions and control programmes in endemic countries;
- support for monitoring and evaluation of implemented activities; and
- documentation of the burden of foodborne trematodiases and the impact of implemented interventions.

WHO promotes the inclusion of foodborne trematodiases among the targets of preventive chemotherapy interventions, with the aim of ensuring that their worst consequences (cancer of the bile duct and others) are fully prevented.

WHO has also negotiated an agreement with Novartis Pharma AG whereby the company donates triclabendazole for the treatment of human fascioliasis and paragonimiasis. The medicines are shipped free of charge to ministries of health that apply for them. Several countries have taken advantage of this opportunity. In 2016, about 600 000 individuals were reported to have received treatment for foodborne trematodiases worldwide.

In contrast, donations of praziquantel have not yet been secured.

In May 2017, an expert consultation to accelerate the control of foodborne trematode infections will be held by the WHO Regional Office for the Western Pacific in Korea to discuss programmatic actions, operational research, monitoring & evaluation and surveillance of these diseases.

(1) Disability adjusted life years (DALY) are used in health economics as a measure of disease impact. One DALY is equal to one year of “healthy life lost” due to a disease. They are calculated as the sum of years of life lost to death (YLL) and to disability (YLD) for people living with the health condition or its consequences.
4. HERPES SIMPLEX VIRUS

KEY FACTS

- The herpes simplex virus, or herpes, is categorized into 2 types: herpes simplex virus type 1 (HSV-1) and herpes simplex virus type 2 (HSV-2).
- HSV-1 is mainly transmitted by oral-to-oral contact to cause oral herpes (which can include symptoms known as “cold sores”), but can also cause genital herpes.
- HSV-2 is a sexually transmitted infection that causes genital herpes.
- Both HSV-1 and HSV-2 infections are lifelong.
- An estimated 3.7 billion people under age 50 (67%) have HSV-1 infection globally.
- An estimated 417 million people aged 15-49 (11%) worldwide have HSV-2 infection.
- Most oral and genital herpes infections are asymptomatic.
- Symptoms of herpes include painful blisters or ulcers at the site of infection.
- Herpes infections are most contagious when symptoms are present but can still be transmitted to others in the absence of symptoms.
- Infection with HSV-2 increases the risk of acquiring and transmitting HIV infection.

Introduction

Infection with the herpes simplex virus, commonly known as herpes, can be due to either herpes simplex virus type 1 (HSV-1) or herpes simplex virus type 2 (HSV-2). HSV-1 is mainly transmitted by oral to oral contact to cause infection in or around the mouth (oral herpes). HSV-2 is almost exclusively sexually transmitted, causing infection in the genital or anal area (genital herpes). However, HSV-1 can also be transmitted to the genital area through oral-genital contact to cause genital herpes.

Both oral herpes infections and genital herpes infections are mostly asymptomatic but can cause mild symptoms or painful blisters or ulcers at the site of infection.

- Herpes simplex virus - type 1 (HSV-1)
- Herpes simplex virus - type 2 (HSV-2)

Herpes simplex virus type 1 (HSV-1)

HSV-1 is a highly contagious infection, which is common and endemic throughout the world. Most HSV-1 infections are acquired during childhood, and infection is lifelong. The vast majority of HSV-1 infections are oral herpes (infections in or around the mouth, sometimes called orolabial, oral-labial or oral-facial herpes), but a proportion of HSV-1 infections are genital herpes (infections in the genital or anal area).

Scope of the problem

In 2012, an estimated 3.7 billion people under the age of 50, or 67% of the population, had HSV-1 infection. Estimated prevalence of the infection was highest in Africa (87%) and lowest in the Americas (40-50%).

With respect to genital HSV-1 infection, 140 million people aged 15-49-years were estimated to have genital HSV-1 infection worldwide in 2012, but prevalence varied substantially by region. Most genital HSV-1 infections are estimated to occur in the Americas, Europe and Western Pacific, where HSV-1 continues to be acquired well into adulthood. In other regions, for example in Africa, most HSV-1 infections are acquired in childhood, before the age of sexual debut.

Signs and symptoms

Oral herpes infection is mostly asymptomatic, and the majority of people with HSV-1 infection are unaware they are infected. Symptoms of oral herpes include painful blisters or open sores called ulcers in or around the mouth. Sores on the lips are commonly referred to as “cold sores.” Infected persons will often experience a tingling, itching or burning sensation around their mouth, before the appearance of sores. After initial infection, the blisters or ulcers can periodically recur. The frequency of recurrences varies from person to person.

Genital herpes caused by HSV-1 can be asymptomatic or can have mild symptoms that go unrecognized. When symptoms do occur, genital herpes is characterised by 1 or more genital or anal blisters or ulcers. After an initial genital herpes episode, which may be severe, symptoms may recur, but genital herpes caused by HSV-1 often does not recur frequently.

Transmission

HSV-1 is mainly transmitted by oral-to-oral contact to cause oral herpes infection, via contact with the HSV-1 virus in sores, saliva, and surfaces in or around the mouth. However, HSV-1 can also be transmitted to the genital area through oral-genital contact to cause genital herpes.

HSV-1 can be transmitted from oral or skin surfaces that appear normal and when there are no symptoms present. However, the greatest risk of transmission is when there are active sores.

Individuals who already have HSV-1 oral herpes infection are unlikely to be subsequently infected with HSV-1 in the genital area.

In rare circumstances, HSV-1 infection can be transmitted from a mother with genital HSV-1 infection to her infant during delivery.
Possible complications

Severe disease

In immunocompromised people, such as those with advanced HIV infection, HSV-1 can have more severe symptoms and more frequent recurrences. Rarely, HSV-1 infection can also lead to more severe complications such as encephalitis or keratitis (eye infection).

Neonatal herpes

Neonatal herpes can occur when an infant is exposed to HSV in the genital tract during delivery. This is a rare condition, occurring in an estimated 10 out of every 100,000 births globally, but can lead to lasting neurologic disability or death. The risk for neonatal herpes is greatest when a mother acquires HSV infection for the first time in late pregnancy. Women who have genital herpes before they become pregnant are at very low risk of transmitting HSV to their infants.

Psychosocial impact

Recurrent symptoms of oral herpes may be uncomfortable and can lead to some social stigma and psychological distress. With genital herpes, these factors can have an important impact on quality of life and sexual relationships. However, in time, most people with either kind of herpes adjust to living with the infection.

Treatment

Antiviral medications, such as acyclovir, famciclovir, and valacyclovir, are the most effective medications available for people infected with HSV. These can help to reduce the severity and frequency of symptoms, but cannot cure the infection.

- WHO guidelines for the treatment of Genital Herpes Simplex Virus

Prevention

HSV-1 is most contagious during an outbreak of symptomatic oral herpes, but can also be transmitted when no symptoms are felt or visible. People with active symptoms of oral herpes should avoid oral contact with others and sharing objects that have contact with saliva. They should also abstain from oral sex, to avoid transmitting herpes to the genitals of a sexual partner. Individuals with symptoms of genital herpes should abstain from sexual activity whilst experiencing any of the symptoms.

People who already have HSV-1 infection are not at risk of getting it again, but they are still at risk of acquiring herpes simplex virus type 2 (HSV-2) genital infection (see below).

The consistent and correct use of condoms can help to prevent the spread of genital herpes. However, condoms can only reduce the risk of infection, as outbreaks of genital herpes can occur in areas not covered by a condom.

Pregnant women with symptoms of genital herpes should inform their health care providers. Preventing acquisition of a new genital herpes infection is particularly important for women in late pregnancy, as this is when the risk for neonatal herpes is greatest.

Additional research is underway to develop more effective prevention methods against HSV infection, such as vaccines. Several candidate HSV vaccines are currently being studied.

Herpes simplex virus type 2 (HSV-2)

HSV-2 infection is widespread throughout the world and is almost exclusively sexually transmitted, causing genital herpes. HSV-2 is the main cause of genital herpes, which can also be caused by herpes simplex virus type 1 (HSV-1). Infection with HSV-2 is lifelong and incurable.

Scope of the problem

Genital herpes caused by HSV-2 is a global issue, and an estimated 417 million people worldwide were living with the infection in 2012. Prevalence of HSV-2 infection was estimated to be highest in Africa (31.5%), followed by the Americas (14.4%). It was also shown to increase with age, though the highest numbers of people newly-infected were adolescents.

More women are infected with HSV-2 than men; in 2012 it was estimated that 267 million women and 150 million men were living with the infection. This is because sexual transmission of HSV is more efficient from men to women than from women to men.

Signs and symptoms

Genital herpes infections often have no symptoms, or mild symptoms that go unrecognized. Most infected people are unaware that they have the infection. Typically, about 10-20% of people with HSV-2 infection report a prior diagnosis of genital herpes.

When symptoms do occur, genital herpes is characterised by one or more genital or anal blisters or open sores called ulcers. In addition to genital ulcers, symptoms of new genital herpes infections often include fever, body aches, and swollen lymph nodes.

After an initial genital herpes infection with HSV-2, recurrent symptoms are common but often less severe than the first outbreak. The frequency of outbreaks tends to decrease over time. People infected with HSV-2 may experience sensations of mild tingling or shooting pain in the legs, hips, and buttocks before the occurrence of genital ulcers.
Transmission
HSV-2 is mainly transmitted during sex, through contact with genital surfaces, skin, sores or fluids of someone infected with the virus. HSV-2 can be transmitted from skin in the genital or anal area that looks normal and is often transmitted in the absence of symptoms.

In rare circumstances, HSV-2 infection can be transmitted from a mother to her infant during delivery.

Possible complications
HSV-2 and HIV
HSV-2 and HIV have been shown to influence each other. HSV-2 infection increases the risk of acquiring a new HIV infection by approximately three-fold. In addition, people with both HIV and HSV-2 infection are more likely to spread HIV to others. HSV-2 is amongst the most common infections in people living with HIV, occurring in 60-90% of HIV-infected persons.

Infection with HSV-2 in people living with HIV (and other immunocompromised individuals) often has a more severe presentation and more frequent recurrences. In advanced HIV disease, HSV-2 can lead to more serious, but rare, complications such as meningoencephalitis, esophagitis, hepatitis, pneumonitis, retinal necrosis, or disseminated infection.

Neonatal herpes
Neonatal herpes can occur when an infant is exposed to HSV in the genital tract during delivery. This is a rare condition, occurring in an estimated 10 out of every 100,000 births globally, but can lead to lasting neurologic disability or death. The risk for neonatal herpes is greatest when a mother acquires HSV infection for the first time in late pregnancy. Women who have genital herpes before they become pregnant are at very low risk of transmitting HSV to their infants.

Psychosocial impact
Recurrence symptoms of genital herpes may be painful and the infection can lead to social stigma and psychological distaste. These factors can have an important impact on quality of life and sexual relationships. However, in time, most people with herpes adjust to living with the infection.

Treatment
Antivirals, such as acyclovir, famciclovir, and valacyclovir are the most effective medications available for people infected with HSV. These can help to reduce the severity and frequency of symptoms, but cannot cure the infection.

WHO guidelines for the treatment of Genital Herpes Simplex Virus

Prevention
Individuals with genital HSV infection should abstain from sexual activity whilst experiencing symptoms of genital herpes. HSV-2 is most contagious during an outbreak of sores, but can also be transmitted when no symptoms are felt or visible.

The consistent and correct use of condoms can help reduce the risk of spreading genital herpes. However, condoms only provide partial protection, as HSV can be found in areas not covered by a condom. Medical male circumcision can provide men life-long partial protection against HSV-2, in addition to HIV and human papillomavirus (HPV).

Pregnant women with symptoms of genital herpes should inform their health care providers. Preventing acquisition of a new genital herpes infection is particularly important for women in late pregnancy, as this is when the risk for neonatal herpes is greatest.

Additional research is underway to develop more effective prevention methods against HSV infection, such as vaccines or topical microbicides (compounds which can be applied inside the vagina or rectum to protect against sexually transmitted infections).

WHO response to herpes (HSV-1 and HSV-2)
WHO and partners are working to accelerate research to develop new strategies for prevention and control of genital and neonatal HSV-1 and HSV-2 infections. Such research includes the development of HSV vaccines and topical microbicides. Several candidate vaccines and microbicides are currently being studied.

5. MATERNAL MORTALITY

KEY FACTS
• Every day, approximately 830 women die from preventable causes related to pregnancy and childbirth.
• 99% of all maternal deaths occur in developing countries.
• Maternal mortality is higher in women living in rural areas and among poorer communities.
• Young adolescents face a higher risk of complications and death as a result of pregnancy than other women.
• Skilled care before, during and after childbirth can save the lives of women and newborn babies.
• Between 1990 and 2015, maternal mortality worldwide dropped by about 44%.
• Between 2016 and 2030, as part of the Sustainable Development Goals, the target is to reduce the global maternal mortality ratio to less than 70 per 100 000 live births.

Maternal mortality is unacceptably high. About 830 women die from pregnancy- or childbirth-related complications around the world every day. It was estimated that in 2015, roughly 303 000 women died during and following pregnancy and childbirth. Almost all of these deaths occurred in low-resource settings, and most could have been prevented.1

In sub-Saharan Africa, a number of countries halved their levels of maternal mortality since 1990. In other regions, including Asia and North Africa, even greater headway was made. Between 1990 and 2015, the global maternal mortality ratio (the number of maternal deaths per 100 000 live births) declined by only 2.3% per year between 1990 and 2015. However, increased rates of accelerated decline in maternal mortality were observed from 2000 onwards. In some countries, annual declines in maternal mortality between 2000–2010 were above 5.5%.

The Sustainable Development Goals and the Global Strategy for Women’s, Children’s and Adolescents’ Health

Seeing that it is possible to accelerate the decline, countries have now united behind a new target to reduce maternal mortality even further. One target under Sustainable Development Goal 3 is to reduce the global maternal mortality ratio to less than 70 per 100 000 births, with no country having a maternal mortality rate of more than twice the global average.

Where do maternal deaths occur?

The high number of maternal deaths in some areas of the world reflects inequities in access to health services, and highlights the gap between rich and poor. Almost all maternal deaths (99%) occur in developing countries. More than half of these deaths occur in sub-Saharan Africa and almost one third occur in South Asia. More than half of maternal deaths occur in fragile and humanitarian settings.

The maternal mortality ratio in developing countries in 2015 is 239 per 100 000 live births versus 12 per 100 000 live births in developed countries. There are large disparities between countries, but also within countries, and between women with high and low income and those women living in rural versus urban areas.

The risk of maternal mortality is highest for adolescent girls under 15 years old and complications in pregnancy and childbirth is a leading cause of death among adolescent girls in developing countries.2,3

Women in developing countries have, on average, many more pregnancies than women in developed countries, and their lifetime risk of death due to pregnancy is higher. A woman’s lifetime risk of maternal death – the probability that a 15 year old woman will eventually die from a maternal cause – is 1 in 4900 in developed countries, versus 1 in 180 in developing countries. In countries designated as fragile states, the risk is 1 in 54; showing the consequences from breakdowns in health systems.

Why do women die?

Women die as a result of complications during and following pregnancy and childbirth. Most of these complications develop during pregnancy and most are preventable or treatable. Other complications may exist before pregnancy but are worsened during pregnancy, especially if not managed as part of the woman’s care. The major complications that account for nearly 75% of all maternal deaths are:4

• severe bleeding (mostly bleeding after childbirth)
• infections (usually after childbirth)
• high blood pressure during pregnancy (pre-eclampsia and eclampsia)
• complications from delivery
• unsafe abortion.

The remainder are caused by or associated with diseases such as malaria, and AIDS during pregnancy.

How can women’s lives be saved?

Most maternal deaths are preventable, as the healthcare solutions to prevent or manage complications are well known. All women need access to antenatal care in pregnancy, skilled care during childbirth, and care and support in the weeks after childbirth. Maternal health and newborn health are closely linked. It was estimated that approximately 2.7 million newborn babies died in 20155, and an additional 2.6 million are stillborn6. It is particularly important that all births are attended by skilled health professionals, as timely management and treatment can make the difference between life and death for both the mother and the baby.

Severe bleeding after birth can kill a healthy woman within hours if she is unattended. Injecting oxytocin immediately after childbirth effectively reduces the risk of bleeding.

Infection after childbirth can be eliminated if good hygiene is practiced and if early signs of infection are recognized and treated in a timely manner.

Pre-eclampsia should be detected and appropriately managed before the onset of convulsions (eclampsia) and other life-threatening complications. Administering drugs such as magnesium sulfate for
pre-eclampsia can lower a woman’s risk of developing eclampsia.

To avoid maternal deaths, it is also vital to prevent unwanted and too-early pregnancies. All women, including adolescents, need access to contraception, safe abortion services to the full extent of the law, and quality post-abortion care.

**Why do women not get the care they need?**

Poor women in remote areas are the least likely to receive adequate health care. This is especially true for regions with low numbers of skilled health workers, such as sub-Saharan Africa and South Asia. Globally in 2015, births in the richest 20 per cent of households were more than twice as likely to be attended by skilled health personnel as those in the poorest 20 per cent of households (89 per cent versus 43 per cent). This means that millions of births are not assisted by a midwife, a doctor or a trained nurse.

In high-income countries, virtually all women have at least four antenatal care visits, are attended by a skilled health worker during childbirth and receive postpartum care. In 2015, only 40% of all pregnant women in low-income countries had the recommended antenatal care visits.

Other factors that prevent women from receiving or seeking care during pregnancy and childbirth are:

- poverty
- distance
- lack of information
- inadequate services
- cultural practices.

To improve maternal health, barriers that limit access to quality maternal health services must be identified and addressed at all levels of the health system.

**WHO response**

Improving maternal health is one of WHO’s key priorities. WHO works to contribute to the reduction of maternal mortality by increasing research evidence, providing evidence-based clinical and programmatic guidance, setting global standards, and providing technical support to Member States.

In addition, WHO advocates for more affordable and effective treatments, designs training materials and guidelines for health workers, and supports countries to implement policies and programmes and monitor progress.

During the United Nations General Assembly 2015, in New York, UN Secretary-General Ban Ki-moon launched the Global Strategy for Women’s, Children’s and Adolescents’ Health, 2016-2030. The Strategy is a road map for the post-2015 agenda as described by the Sustainable Development Goals and seeks to end all preventable deaths of women, children and adolescents and create an environment in which these groups not only survive, but thrive, and see their environments, health and wellbeing transformed.

As part of the Global Strategy and goal of Ending Preventable Maternal Mortality, WHO is working with partners towards:

- addressing inequalities in access to and quality of reproductive, maternal, and newborn health care services;
- ensuring universal health coverage for comprehensive reproductive, maternal, and newborn health care;
- addressing all causes of maternal mortality, reproductive and maternal morbidities, and related disabilities; and
- strengthening health systems to collect high quality data in order to respond to the needs and priorities of women and girls; and
- ensuring accountability in order to improve quality of care and equity.