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KUWAIT MEDICAL JOURNAL

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Editorial

Medical Science - What Science?

Belle M Hegde

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“The fact that we live at the bottom of a deep gravity well, on the surface of a gas covered planet going around a nuclear fireball 90 million miles away and think this to be normal is obviously some indication of how skewed our perspective tends to be.”

Douglas Adams

We talk and write about medical science, evidence based medicine, epidemiological evidence, randomized controlled studies, treatment guidelines, and some medical people even get Nobel for their “so called” discoveries. Do any, or all, of these stand up to a strict audit and admissible as evidence in a court of law? I wonder? I think I have had a reasonably long association with this phenomenon ever since I joined the medical school in 1956. I have been expressing my thoughts cogently in one place at any time in the past. Time has now come to give expression to my despair, so that those of my colleagues who are not sure of what I am about to write might clarify their thoughts, or those few who are angry with me can express their anger giving valid reasons. Either way, there can be progress.

Somehow or the other, the western reductionist science has got into this mess and got itself locked in its own closed box from where it finds it hard to get out now. Is this world made up of bouncing particles looking like golf balls which together try and make this world? What is the big bang? What was there before the big bang? If the universe is expanding what is it expanding to? Did all the money that went down the drain at the CERN reactor bring out the basic building block of this universe the (God) dem particle? When is the “Theory of Everything” coming out, if ever? Western science is good at describing small things inside the universe like how long does it take for the earth to go round the sun once, and how long does the Mars take to rotate in its axis etc. But, when it comes to the crucial question of the nature of this universe, science is both blind and mute.

For a keen observer, life teaches many lessons which science cannot comprehend. How did we explain the various relationships of the forces in this universe? When we look at a beautiful rainbow, or watch the birds talk to each other with love we can understand that and enjoy them, but science can never explain or measure them. It is so naive to think that a few cells in our brain can comprehend the beauty of the full moon! In short, life teaches us that we can comprehend much more than what we can grasp with our senses and sense based science. Finally, we must admit that science is conceived by man; therefore, science is only a perception.

Medicine basically is an art based on the western reductionist imperfect science. Lately we have been trying to say that western medicine is a science and has therefore, to be true. Recent studies have shown that medicine for his work on brain function had this to say about it: “The center most part of the brain with which consciousnesses is presumably associated with
are simply not understood. They are far beyond our comprehension, that no one that I know of has been able to imagine their nature.”

“Medicine is not science,” wrote Clifford and Donald Miller from Washington University, Seattle and London, UK in their article by the same name in the European Journal of Person Centered Health Care[1]. They go on to state that “science, in the sense of the conventional conception of the scientific method applied in chemistry and physics, is not the only route to and is limited in the extent to which and the fields in which it and it alone can deliver, reliable knowledge.

There is an urgent need for a fundamental reappraisal of the nature of knowledge and how it is and how it can better be obtained. The practice of medicine is largely observational and functions without the level of certainty essential to science.” Evidence-based medicine has serious crippling flaws. We need “evidence-informed” individualized care. Cohort studies like the RCTs do not apply to individuals. Statistically significant changes in a heterogeneous cohort cannot and should not be applied to a unique dynamic human being. That is where modern western medicine has lost its track resulting in the medical establishment, thereby becoming one of the leading causes of death and disability!

Writing in his classic Bad Medicine-Doctors Harming Society since Hippocrates, Professor David Wootton so beautifully shows how we doctors have never audited our methods and have been responsible for so much unnecessary deaths almost from the time of Hippocrates[2]. A recent audit of the scene now was done by Hillary Butler in London in 2010, which showed that the present western medicine has become a Corporate Monstrosity on the public. People from outside like Professor Ivan Illich, Karl Popper, Paul Feyerabend, David Wootton, Norlin Hadler, Sherwin Nulund and many others have been warning us but their sane voices get drowned in the din of the claptrap, cacophony, and the expensive brain washing of the medical profession by the very powerful pharma lobby that wants to keep it going the way it is to keep their till moving. Hippocrates was dead right when he wrote that a doctor “cures rarely, comforts mostly but should console always.”

We doctors seem to have sold our soul to the devil for money, having lost our divine healing powers by getting and spending money. Our lives seem to exist by money, for money and of money! We have fully believed the industry’s false propaganda that we have the power to cure always, save people from the jaws of death, give a new heart where extensive coronary artery disease seems to have restricted the blood supply to the major portion of the heart muscle, transplant new lungs for the diseased ones, take over the function of the kidney, liver and what have you. I am surprised, that we have even fallen for the false propaganda, that by screening the whole healthy population, we will be able to catch diseases (young!) in their asymptomatic stages and start drugging them to keep them away from the ravages of many complications, despite the fact many large studies have shown that treating any disease in its asymptomatic stage is not going to help! Little do we realize that we have NOT BEEN able to reduce the death rate nor have been able to eradicate a single infectious disease with the help of the highly touted vaccinations, except smallpox that was achieved with low tech Indian system of vaccination known for “times out of mind”. Rather, the fact is that at any time anywhere when doctors went on strike, the death and disability rates fell down precipitously. We have been over diagnosing, over treating and doing interventions when they were not needed. When do we learn that we have a hollow science to back us?

Many of the RNI (resident non-Indian) readers and some editors do not believe what I say unless I supply western data. While I have been extolling the virtues of coconut oil for at least four decades, Indian intelligensia is slowly waking up to that reality after USA started praising coconut oil as the best fat for man. Robert Lanza and Bob Bermer, in their classic, Biocentrism, have this to say:

“But most of these comprehensive theories (of science) fail to take into account one crucial factor: we are creating them. It is the biological creature that fashions them, that makes the observations, and that gives names to things. And there lies the great expanse of our oversight, that science has not confronted the one thing that is at once most familiar and most mysterious-conscious awareness or consciousness.”

That is why the ether of the last century, relativity of Einstein, and the string theory of this century have all fallen by the wayside. The much touted “Theory of Everything” has been eluding our great scientists for a long time. How does one construct physical laws so very accurately to make biological life possible on this planet? Even if the so called Big Bang were to be a miniscule part, more powerful it would have rushed out too fast for life on earth. If the strong nuclear force were to be less by a microscopic fraction, atomic nuclei would not hold together. If the gravitational force were reduced by “even a hair’s breadth” our Sun and stars would not have ignited! Who, other than man, (scientist) designed them? While evolution is mainly environmental we still hold on to Darwinism. Darwin and his father in law, Erasmus, did eventually believe that Lamarck, who propagated the environmental evolution theory, was right.

While the hard sciences like physics have such shaky foundation what about the purely statistical science of medicine? We need to understand that this very universe does come into existence because of our
consciousness. Now do not jump to the conclusion that science is all bad. Far from it! It is neither all good as is commonly believed. Science simply is curiosity. It is the scientists that could be good or bad. The inner secrets of science are not shared outside a small group. The idea of science is enmeshed in philosophy, myths, in theories, in smugness, in heroism, even in superstition, in fear, and in hindsight what actually happens inside is rarely told openly, feel Harry Collins and Trevor Pinch, the two physicists who have written a book comparing science to The Golem\(^3\). Golem is a creature of mythology. It could, if uncontrolled, destroy the master. In the Yiddish culture, a Golem is a “metaphor for any lumbering fool who neither knows his own strength nor the extent of his own clumsiness and ignorance.”

I agree with those two physicists fully. Anything that does not change is not science. Having now understood science as it is, let us put our heads together to see if it could be made safer, powerful and more useful to society. Otherwise, using wrong medical science might (is already) endanger human life on this planet negating all efforts (by whom) to construct a world precariously balanced for human existence.

“One thing I have learned in a long life: that all our science, measured against reality, is primitive and childlike -- and yet it is the most precious thing we have.”

Albert Einstein

REFERENCES

Challenge of Diabetes Control in Patients with Rheumatic Diseases

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ABSTRACT

Patients who are suffering of rheumatic diseases are at great risk for the development of diabetes mellitus; also diabetic patients who develop rheumatic disorders are liable to have fluctuating blood glucose. New onset diabetes, new onset hyperglycemia, uncontrolled pre-existing diabetes, difficulties in life style modifications, and acute complications of diabetes such as diabetic ketoacidosis and hypoglycemia; all of these present a major challenge in the management of patients with rheumatic diseases. There are multiple risk factors which contribute to this challenge. Some of the risk factors are related to the rheumatic disease itself, such as inflammatory cytokines, disease associated renal impairment, physical disability and gastroparesis. Drugs utilized for the treatment of rheumatic diseases (e.g., steroids, calcineurin inhibitors and hydroxychloroquine) impose a great risk in relation to diabetes. The role of non-pharmacological and pharmacological approach in the control of diabetes is essential and can deal well with the challenge.

INTRODUCTION

It is well known that the pathophysiology of type 2 diabetes (T2DM) is complex, but has two dominating factors, insulin resistance (which is mainly due to obesity and physical inactivity), and deficient insulin production[1].

Insulin resistance is highly likely to develop in patients with systemic inflammatory diseases like rheumatoid arthritis (RA)[2-3], systemic lupus erythematosus (SLE)[4-5], and ankylosing spondylitis[6]. There are several mechanisms that could contribute to altered insulin sensitivity which are important in patients with RA or SLE, and they provide insights into the pathogenesis of insulin resistance associated with inflammation. Inflammatory cytokines like tumor necrosis factor-alpha (TNF-α) can induce insulin resistance and suppression of Glut4 expression by inhibiting insulin receptor (IRS) autophosphorylation[7] or by inducing serine phosphorylation of IRS-1[8]. Interleukin-6 also inhibits insulin signal transduction in hepatocytes[9]. Leptin produced by adipose tissue may contribute to insulin resistance through phosphorylation of serine residues of IRS-1[10].

Some patients with SLE may develop autoantibodies against insulin receptors causing type B insulin resistance[11]. Blockade of insulin action results in hyperglycemia, hypercatabolism, severe acanthosis nigricans, and hyperandrogenism in women[12]. Some SLE patients present with severe hypoglycemia because of stimulatory autoantibodies against insulin receptors[13]. These findings and other data raised the idea that diabetes in rheumatic patients is challenging regarding diabetes control and lines of management. In this review, the risk factors contributing to the problem as well as the proper management will be discussed in detail.

DISEASE RELATED RISK FACTORS

There are some risk factors which augment the likelihood of insulin resistance in systemic inflammatory disorders which include abnormal fat distribution and lack of physical activity[14].

Vitamin D deficiency has been shown to affect insulin secretion in both humans and animal models. Also, accumulating evidence suggests the role of vitamin D deficiency in the pathogenesis of insulin resistance including several vitamin-D-related gene polymorphisms and vitamin-D-related metabolic and immune pathways[15]. It is documented that patients with SLE[16] as well as those patients with

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RA[17] have multiple risk factors for vitamin D deficiency. Inflammatory rheumatic diseases are frequently complicated by subclinical or overt renal manifestations. This is well-known for the connective tissue diseases and vasculitis in which renal disease can be of significant prognostic value and therapeutic implication. However, RA and spondylo-arthritis can also be associated with direct renal manifestation or with secondary renal AA-amyloidosis. The clinician should be aware of the different glomerular (i.e., nephritic or nephritic syndrome, rapidly progressive renal disease) and tubulo-interstitial syndromes[18].

A scleroderma renal crisis in the course of systemic sclerosis can potentially result in end-stage renal disease (ESRD) within days[19]. Lupus nephropathy belongs to the most severe clinical manifestations of SLE. In 40 - 60% of patients, impairment in renal function is stated on diagnosis and in 10 -25% of them, the disease progresses to the ESRD. There is ample of evidence that the kidney is involved very early in the course of SLE and the occurrence of low-level proteinuria and hematuria may be associated with a significant renal disease[20]. In humans, renal glucose production, contributes approximately 25% to systemic glucose production whereas renal glucose uptake accounts for 20% of systemic glucose removal. This indicates the important role of the human kidney in glucose homeostasis[21]. Handling of glucose by the kidney is altered in T2DM renal gluconeogenesis and renal glucose uptake are increased in both the post-absorptive and postprandial states, and renal glucose reabsorption is increased[22]. Exogenous insulin is normally metabolized by the kidney. However, when there is impairment of kidney function, the half-life of insulin is prolonged because of lower levels of degradation[23]. Clearance of many oral drugs is decreased by kidney disease and this results in prolonged exposure to higher levels of the drug or its metabolites and potentially leads to adverse side effects including hypoglycemia. The greatest risk for this to occur is in patients with moderate to severe chronic kidney disease (CKD stages 3 – 5) affecting drugs like 1st generation sulfonylureas[24] and α-glucosidase inhibitors and their metabolites which are cleared by the kidney[25]. With metformin there is a risk of development of lactic acidosis, even in patients with mild impairment of kidney function, resulting from the accumulation of the drug and its metabolites[26].

Gastroparesis is one of the manifestations of some rheumatologic diseases. SLE, sclerosis, dermatomyositis and polymyositis may present with gastroparesis[27]. Gastric emptying accounts for at least 35% of the variance in the initial rise as well as the peak blood glucose levels after an oral glucose load in both healthy individuals and patients with T2DM. Pharmacological slowing of gastric emptying by morphine reduces the postprandial glycemic response to a mixed meal in T2DM patients, whilst acceleration of gastric emptying by erythromycin (a motilin agonist) increases postprandial blood glucose concentrations. In type 1 diabetic (T1DM) patients the glycemic response to a meal, and therefore the requirement for exogenous insulin, is also critically dependent on the rate of gastric emptying. Here, when emptying is slower, the insulin requirement to achieve euglycemia is less[28].

Another important effect of rheumatic diseases on diabetes control is the effect of impaired functional capacity of patients with rheumatic diseases. A reduced level of physical performance has been found to be associated with RA. Patients with RA have been shown to have reduced muscle strength and aerobic capacity. A reduction in muscle strength and endurance can be due to several factors, such as the intra-articular and extra-articular inflammatory process, side-effects of medication, inactivity, reflex inhibition due to pain and joint swelling, reduced proprioception and the loss of mechanical stability around the joint[29]. At the same time those patients who have peripheral neuropathy as a part of RA, SLE, sicca syndrome and vasculitis[30], are at great risk of exercise induced injuries. That is why lifestyle modification is affected in a bad way[31]. Also, impaired movement and flexibility in patients with ankylosing spondylitis (AS) will interfere with physical activity needed to control blood glucose[32].

**DRUG RELATED RISK FACTORS**

Drugs used in the treatment of rheumatic diseases can affect blood glucose control. Glucocorticoids (GC), hydroxychloroquine, immune-suppressant drugs and NSAIDs, all are involved in compromised blood glucose control.

GC remain a mainstay of therapy for many inflammatory conditions and immunomodulators requiring therapeutic protocols. As recently as 1998, a survey of patients in the American Rheumatism Association Medical Information System database showed that 50% of patients were on long term GC therapy[33].

The association between GC therapy and the development of diabetes was established in the 1960s[34]. The diabetogenic effect of GC includes reduction in insulin synthesis[35] and insulin sensitivity[36]. Also, increased hepatic gluconeogenesis[37] and central obesity[38] may contribute to diabetogenic effect of GC. Impaired glucose tolerance (IGT) occurs in up to 90% of patients with Cushing’s syndrome, but only 10% to 29% of these patients develop frank diabetes mellitus (DM)
Predictors of development of new onset diabetes in users of GC include ethnicity (non-Caucasian), age > 40 years-old, family history of DM, hepatitis C virus infection, IGT (before starting GC) and obesity. Similarly, total GC dose and duration of therapy are strong predictors of diabetes induction. Loss of glycemic control during GC use is particularly due to impaired postprandial glucose metabolism, whereas fasting plasma glucose (FPG) levels are, if any, usually only mildly elevated. It is known that diabetic ketoacidosis and hyperosmolar non-ketotic syndrome have been reported as a result of GC treatment.

Among the other immunosuppressive drugs used in the treatment of rheumatic diseases, are calcineurin inhibitors. Cyclosporine A (CSA) is a fungal metabolite used as an immunosuppressant to treat some of the rheumatic diseases. CSA was first reported to be effective in RA in an open-label study in 1979. Subsequently, a number of controlled studies demonstrated its efficacy as either monotherapy or in combination with other disease-modifying antirheumatic drugs (DMARDs) in ameliorating disease activity and retarding radiological progression in both early and refractory RA. CSA has proven efficacy in treatment of severe SLE and lupus nephritis. In a review article, Kitahara et al summarized four randomized double-blind controlled studies of tacrolimus in RA and showed significant improvement of disease activity using American College of Rheumatology (ACR) criteria in terms of ACR20, ACR50 and ACR70 and it was first reported to be useful in severe SLE in 1997. Recently, tacrolimus was found to be more effective and safer than intravenous cyclophosphamide (CPD) as an induction therapy for Chinese lupus nephritis patients. In Japan, tacrolimus was approved for the treatment of RA in 2005. The incidence of diabetes in previously non-diabetic renal transplant recipients who receive CSA has been reported to be from 2% to 46%. However, CSA is usually given in concert with GC, which are diabetogenic themselves and may have an additive or synergistic effect. In post-transplantation patients receiving tacrolimus, the cumulative incidence of post-transplantation diabetes was 52.4% at one month and 57.1% at three and six months.

Calcineurin inhibitors induced diabetes involves beta cell dysfunction as cAMP and calcium-induced activity of the human insulin gene is mediated by cAMP-responsive element binding protein and blocked by both tacrolimus and CSA at concentrations that inhibit calcineurin phosphatase activity. The immunosuppressive effects of CSA and tacrolimus are thought to be secondary to inhibition of calcineurin. It is suggested that inhibition of human insulin gene transcription by the immunosuppressants is clinically important and may contribute to their diabetogenic effect.

In recipients of pancreas transplants, the calcineurin inhibitors cyclosporine and tacrolimus have been shown to cause reversible toxicity to islet cells. Also, increased insulin resistance at the level of skeletal muscles may be blamed for the diabetogenic effect of calcineurin inhibitors.

It is important to identify the risk factors of calcineurin inhibitors induced diabetes which include family history of diabetes, age, history of IFG / IGT, ethnicity, overweight / obesity, physical inactivity, hypertension, dyslipidemia, hepatitis C infection and drug regimen of immunosuppression as addition of GC to calcineurin inhibitors increases the risk of new onset diabetes mellitus.

Other drugs used in the treatment of rheumatic diseases with an impact on blood glucose level are hydroxychloroquine and non-steroidal anti-inflammatory drugs (NSAIDs).

Hydroxychloroquine is an antimalarial drug commonly used to treat RA and SLE since 1950s. Studies addressing the effect of hydroxychloroquine on diabetes have shown reduced risk of development of diabetes. Hydroxychloroquine has been shown to lower glycated hemoglobin levels in patients with T2DM who have suboptimal glucose control. There was lower mean glucose level among participants in the Baltimore Lupus Cohort while they were taking hydroxychloroquine, as well as a protective effect of hydroxychloroquine on abnormal glucose tolerance testing. Even those rheumatic patients with or without diabetes mellitus treated with hydroxychloroquine may develop hypoglycemia. The anti-diabetic effect of hydroxychloroquine is attributed to reduced insulin resistance, reduced intracellular insulin degradation and increased intracellular insulin accumulation. Another possible anti-diabetic mechanism is due to enhanced insulin secretion with chronic use of hydroxychloroquine.

Those diabetic patients on sulfonylurea treatment receiving NSAIDs for rheumatic diseases are at risk of hypoglycemia. In addition, it has also long been known that high doses of salicylates lower plasma glucose concentrations. The mechanism of hypoglycemic effect of NSAIDs has been referred to their blocking effect on KATP (flufenamic acid) through an extracellular mechanism and thus increased insulin secretion. As some NSAIDs synergistically inhibit KATP activity together with sulphonylureas, the risk of NSAID-induced hypoglycemia should be considered when sulphonylurea compounds are co-administered. Improved insulin resistance may contribute to the hypoglycemic effect of NSAIDs as recent studies indicate that insulin resistance in
diabetics results from hepatic activation of inhibitory kappa B kinase (IKK-β) and nuclear factor-kappa B and high doses of salicylates inhibit IKK-β activity and might therefore, ameliorate insulin resistance and improve glucose tolerance in T2DM patients[23].

Through their anti-inflammatory effect, anti-TNF therapy improve insulin sensitivity and reverse defects in the insulin signaling cascade in RA patients with active disease and high insulin resistance[74]. Abatacept is a biological drug used in the treatment of RA[73]. Rituximab[76-78] is another biological treatment used in the treatment of RA and ANCA-associated vasculitides and was found to be effective in SLE on off-label use. Both of them can improve insulin sensitivity by a similar mechanism as anti-TNF.

MANAGEMENT OF HYPERGLYCEMIA IN PATIENTS WITH RHEUMATIC DISEASES

Screening for diabetes and monitoring of blood sugar

First of all, we should emphasize that the aforementioned risk factors affecting blood glucose levels in rheumatic patients should be considered in designing the program of diabetes treatment.

The presence of risk factors for diabetes should be probed in patients with systemic rheumatic diseases before starting immunosuppressive drugs. The fasting plasma glucose (FPG) should be documented. In patients with normal FPG levels, the updated International Consensus Guidelines recommend performing a 75-g OGTT to detect the presence of IGT[79]. Screening for new onset diabetes in rheumatic patients should include an evaluation of the glucose metabolism status by FPG and / or oral glucose tolerance test (OGTT). A recent large study (N = 889) has underlined the low sensitivity of FPG in detecting glucose metabolism abnormalities in patients with RA[73]. Screening for new onset diabetes in rheumatic patients should include an evaluation of the glucose metabolism status by FPG and / or oral glucose tolerance test (OGTT). An FPG screening performed on patients with ESRD [80] as well as RA patients with active disease and high insulin resistance[74], Abatacept is a biological drug used in the treatment of RA[73]. Rituximab[76-78] is another biological treatment used in the treatment of RA and ANCA-associated vasculitides and was found to be effective in SLE on off-label use. Both of them can improve insulin sensitivity by a similar mechanism as anti-TNF.

The ADA diagnostic criteria of diabetes are fasting glucose, after treating low blood glucose until they recover their blood sugar. Self-monitoring of blood glucose (SMBG) may be as high as 6 - 8 times daily in case of T1DM patients or in those patients who are on basal / bolus insulin regimen (at least prior to meals and snacks), occasionally post-prandially, at bedtime, prior to exercise, when they suspect low blood glucose, after treating low blood glucose until they are normoglycemic, and prior to critical tasks such as driving[87]. Check blood glucose ≥ 2 times daily on starting medications causing hyperglycemia such as GC and calcineurin inhibitors, while on using drugs known to cause hypoglycemia (sulfonylurea, meglitinides, hydroxychloroquine and NSAIDs, especially when given in patients taking sulfonylurea), at times when symptoms of hypoglycemia occur or at times when hypoglycemia has previously occurred[88]. The follow-up of the overall glucose control is carried-out through HBA1c which has to be checked every three months[76].

Lifestyle modification

Making lifestyle changes for persons with diabetes can be challenging. However, to achieve metabolic control for many persons with diabetes, changes in nutrition and physical activity are essential. In the past, nutrition and exercise recommendations have been rigid and have allowed for little flexibility; however, there is no longer a set of guidelines that applies to all persons with diabetes. By individualizing treatment and focusing on metabolic outcomes, health care professionals can assist persons with diabetes to make lifestyle changes and to achieve metabolic goals[89].

As mentioned before, impaired exercise tolerance, flexibility and biomechanical efficiency in rheumatoid arthritis patients will interfere with the exercise program needed for diabetic patients. To improve glycemic control, assist with weight maintenance, and reduce risk of CVD, studies recommend at least 150 min / week of moderate-intensity aerobic physical activity (40 - 60% of \( V_{O_{2max}} \)) and / or at least 90 min / week of vigorous aerobic exercise (> 60% of \( V_{O_{2max}} \) or > 70% of maximum heart rate). The physical activity should be distributed over at least three days / week and with no more than two consecutive days without physical activity[89]. Exercise
should be continuous in nature and could include activities such as walking, swimming or cycling. People with T2DM should be encouraged to perform resistance exercise three times a week, targeting all major muscle groups, progressing to three sets of 8 - 10 repetitions at a weight that cannot be lifted more than 8 - 10 times. As mentioned before, reduced level of physical performance has been found to be associated with RA. Patients with RA have been shown to have reduced muscle strength and aerobic capacity. In addition to that, acutely, inflamed joints should be rested to prevent exacerbation of symptoms.

Osteoarthritis (OA) can result in decreased muscle strength in the peri-articular muscles, decreased flexibility, weight gain, and diminished aerobic capacity. Recent studies have shown that patients with OA are able to tolerate weight bearing exercises such as walking. That is why engagement in proper exercise activity may be compromised. In general, a health professional experienced in arthritis exercise prescription can determine which of these exercises will help the patient. Swimming may be a good exercise choice in diabetic patient with RA and ankylosing spondylitis. In case of OA, health-care providers typically counsel them to do activities that are low impact, not painful, and have low risk of joint injury. Swimming, walking, and strength-training are good examples of this type of activity.

Exercise induced hypoglycemia may occur many hours post exercise. That is why close glucose monitoring before, during and after exercise is needed. ADA guidelines suggested that added carbohydrate should be ingested if pre-exercise glucose levels are < 5.6 mmol/l (100 mg/dl). Drugs used for treatment of rheumatic diseases can increase risk of exercise induced hypoglycemia. Therefore, patients taking drugs that increase hypoglycemic risk like insulin or a secretagogue like NSAIDs or hydroxychloroquine may need to take additional carbohydrate before physical activity and / or reduce doses of insulin or secretagogue to avoid hypoglycemia. Rheumatic patients suffering from peripheral vascular disease due to vasculitis or suffering from peripheral neuropathy are exposed to increased risk of injury and infection in the feet. Peripheral neuropathy can also affect balance, placing the patient at greater risk of falls. Some types of exercise such as treadmill walking should be avoided. Adequate footwear and regular screening for blisters is a must for these individuals, especially with weight-bearing activities. Non-weight-bearing exercises such as cycling, swimming and upper limb resistance training may minimize damage or infection.

The other face of the coin in lifestyle modification in the treatment of diabetes is dietary modifications. The dietary recommendations in diabetes management include dietary carbohydrate from fruits, vegetables, whole grains, legumes, and low-fat milk, limited saturated fat to <7% of total calories, minimized intake of transfat, protein intake covering 15 - 20% of energy and fiber intake should reach the recommendations of dietary fiber (14 g fiber / 1,000 kcal) and foods containing whole grains (one-half of grain intake). Gastroparesis with delayed gastric emptying may be a presenting picture in some rheumatic diseases. Dietary recommendations include ingesting multiple small meals, favoring liquids over solids, avoiding indigestible solids as high fiber diet, and consuming low-fat and low soluble fiber meals. These recommendations are able to compensate for the gastric motor impairment in gastroparesis. Although other lines of treatment for gastroparesis are beyond the scope of this review, they include prokinetics as metoclopramide, erythromycin, domperidone, betahanechol and pyridostigmine. Other available treatments include Injection of botulinum toxin into the pylorus reducing phasic contractions and tone by preventing unopposed cholinergic contractile activity and gastric electrical stimulator implantation. Another problem which is not uncommon in rheumatic patient is renal impairment in which lower protein intake, retards the progression of advanced renal disease. Current recommendations from the NKF K / DOQI based on evidence from animal studies suggest a protein intake of 0.8 to 1.0 g per kg per day. In patient with chronic renal failure on dialysis, protein recommendations are 1.2 - 1.4 g/kg/day.

**MANAGEMENT OF SPECIFIC RISK FACTORS**

**Steroid induced diabetes**

Lifestyle modification (as a first step for treatment of diabetes) may not be a good option for steroid induced diabetes. As the rheumatic condition for which the patient is receiving a GC may prevent him or her from exercising, at least in the acute phase of the illness. In addition, though the exact mechanism is not known, GC increase hunger, and so decreasing food intake is not easy. Studies showed that metformin and the thiazolidinedione pioglitazone were unable to mitigate the effects of GC on glucose tolerance, whereas the thiazolidinedione troglitazone prevented GC-induced hyperglycemia by enhancing GC clearance. Because of liver toxicity, however, troglitazone is no longer available for treatment in humans.

Corticosteroid dose reduction has been shown to significantly improve glucose tolerance. However, any dose reduction should be weighed against the risk of acute rejection. A steroid sparing regimen or steroid avoidance regimen should be tailored to each individual patient.
Glucagon like peptide-1 analogues are promising treatment for steroid induced diabetes because of their effect on postprandial blood glucose. One case report demonstrated good efficacy of the GLP-1 receptor agonist exenatide in a patient with Cushing’s disease, whereas in other case reports steroid diabetes was effectively treated in a number of patients with exenatide or liraglutide. Moreover, in a proof-of-principle study in healthy volunteers, exenatide infusion prevented islet-cell dysfunction and hyperglycemia induced by short-term glucocorticoid treatment. Similarly, dipeptidyl peptidase-4 inhibitors have been tried in the treatment of steroid induced diabetes with success. The fact that GLP-1 (but not dipeptidyl peptidase-4 inhibitors) delays gastric emptying makes GLP-1 not a good choice for patients with gastroparesis.

The meglitinide drug repaglinide has been proven to be effective in improving glucose and meal induced insulin secretion as well as on controlling for postprandial glucose excursion. This mechanism makes it a good option in treating steroid induced diabetes being given preprandial. Also, sulphonylurea drugs (avoiding long acting drugs such as glibipride, except if fasting plasma glucose is high) can be used.

If the random or 1- to 2-hour post-meal plasma glucose is lower than 220 mg/dl, a single oral agent should be used, but if the random or 1- to 2-hour post-meal plasma glucose is 220 to 300 mg/dl, two oral agents should be used. Those patients who have random or 1- to 2-hour post-meal plasma glucose is higher than 300 mg/dl, especially with frank symptoms of diabetes, have to start insulin. Although smaller doses of GC potentially could allow for a therapeutic response to oral agents, the doses required for most current therapeutic uses induce more potent insulin resistance than is amenable to non-insulin therapy. That is why insulin treatment is directed mainly to prandial coverage. As compared with patients who have T1DM or T2DM, patients who have steroid-induced diabetes often require only prandial insulin.

With higher doses of steroids or in patient with pre-existing diabetes, basal insulin is needed, but typically this amount is only 30% of the total daily insulin need (versus 50% for usual diabetes dosing).

Glucose toxicity or hyperglycemia-induced resistance to insulin also might result in higher insulin dosing needs at the onset of therapy; once glucose levels are controlled, patients often need less insulin.

Regular insulin generally is recommended for people consuming between-meal snacks, high-protein or high-fat meals, or those who may have delayed gastric emptying. The rapid-acting insulin analogues are more appropriate for the person who does not snack between meals and consumes more carbohydrate-based meals. It has been found that a practical initial insulin dose is 0.1 U/kg/meal. For high doses of steroid (i.e., 60 - 80 mg of prednisone per day), this amount might underestimate insulin need, but the dose base can be adjusted rapidly, if needed, after a review of glycemic response and the amount of supplemental insulin needed during the first several days of insulin therapy. Supplemental insulin is a correction dose of insulin that is used to correct for pre-meal hyperglycemia. Initially, the recommendation is that for every 50 mg/dl of glucose level between 200 – 300 mg/dl, an additional 0.04 U/kg/meal of insulin is added to the base and for every 50 mg/dl of glucose level above 300 mg/dl, an additional 0.08 U/kg/meal of insulin is added to the base. On tapering of steroid dose, the dose of insulin typically needs to be decreased as steroid doses are tapered, with intermediate insulin being the first that should be discontinued, then prandial. Alternate-day steroid regimens can be challenging with regard to insulin dosing needs, because the “off” days require a significant decrease in dose, if not frank cessation of insulin, to prevent hypoglycemia. While treating steroid induced diabetes we should put a target of less than 7% regarding HBA1c, 70 – 130 mg/dl for pre-prandial capillary plasma glucose and less than180 mg/dl for postprandial capillary plasma glucose.

Calcineurin inhibitors induced diabetes

For the management of immunosuppression in order to both minimize the risk of developing new onset diabetes and improve established new onset diabetes, calcineurin inhibitors should not be the first choice. Try to start with immunosuppressive drugs that are not diabetogenic. Steroid free regimens (steroids potentiate the diabetogenic effect of calcineurin inhibitors) are preferred. Similarly, reduction of steroid dose, if essential, has been shown to significantly improve glucose tolerance. Also, cyclosporine is less diabetogenic than tacrolimus which makes it feasible to shift patients who develop new onset diabetes or have their diabetes worsened while on tacrolimus treatment from tacrolimus to cyclosporine. Similarly, reducing the dose of tacrolimus can dramatically improve glucose control in tacrolimus induced diabetes or worsened glucose control. Other studies support the beneficial effect of reduction of tacrolimus dose on glucose control as it was found that the addition of mycophenolate or azathioprine to tacrolimus containing immunosuppressive regimens had reduced risk of diabetes due to reduction of tacrolimus dose. While selecting the immunosuppressive regimen, you should weigh the risk-benefit ratio.

Lifestyle modification still presents the first step in the treatment of calcineurin inhibitors induced diabetes, but exercise programs may be affected by musculoskeletal disability caused by the original diseases for which calcineurin inhibitors are initiated.
Metformin is initiated in association with lifestyle modification\[87\], but it is to be noted that it should be avoided in patients with impaired renal function who have GFR < 60 ml/min\[122\].

Second step for those patients who do not come under control using the first step will include addition of other oral antidiabetic drugs. Sulphonylurea drugs are good option, but first generation sulphonylurea and long-acting second generation sulphonylurea, glyburide, are better to be avoided in elderly and in patients with impaired renal function because of increased risk of hypoglycemia\[123\,124\]. The “non-sulfonylureas” meglitinides are insulin secretagogues with a mechanism of action similar to that of the sulphonylureas. Nonetheless, they have a more rapid onset and shorter duration of action and seemingly lower risks of hypoglycemia and weight gain\[125\]. These agents are best suited for patients whose food intake is erratic and for elderly patients.

As insulin resistance may have a role in calcineurin inhibitors induced diabetes, thiazolidinedione, pioglitazone, may be effective in treatment of calcineurin inhibitors induced diabetes. However, because of increased risk of female fractures\[126\] as salt and water retention\[125\] are major problems in many rheumatic patients with osteoporosis, cardiac or renal troubles, it is not a good choice.

The dipeptidyl peptidase-4 (DPP-IV) inhibitors (sitagliptin, vildagliptin, linagliptin and saxagliptin) have recently been approved for clinical use. When taken orally, they effectively raise blood concentrations of endogenous active GLP-1. That is why they decrease appetite, maintain body weight, increase beta cell mass and improve fasting and postprandial plasma glucose\[127\]. All of these advantages make DPP-IV inhibitors very good choice in the treatment of calcineurin inhibitors induced diabetes.

Glucagon like peptide-1 analogues (GLP-1) have similar effect to DPP-IV inhibitors when given subcutaneously, but they affect mainly postprandial blood glucose and they have an added effect on slowing gastric emptying\[128\]. Also, they present a good treatment choice for calcineurin inhibitors induced diabetes.

Diabetologist should take care of possible drug-drug interaction. Cyclosporine is a CYP 3A4 inhibitor. That is why it can potentiate the action of repaglinide which is metabolized by CYP 3A4. Co-administration of cyclosporine and repaglinide has also been shown to enhance the blood glucose lowering effect of repaglinide and increase the risk of hypoglycemia\[129\].

Proceed to the third step if hyperglycemia is not properly controlled. Combination of three oral drugs is warranted or insulin is added\[130\]. Although oral hypoglycemic agents may be effective in many patients with corticosteroid or cyclosporine or tacrolimus-induced new onset diabetes, insulin therapy may be necessary in as many as 40% of patients\[131\] when HbA1c is very high (e.g., ≥ 9.0%)\[131\].

As initial therapy, unless the patient is markedly hyperglycemic (random plasma glucose ≥ 16.7 - 19.4 mmol/l or ≥ 300 - 350 mg/dl; HbA1c ≥ 10.0 - 12.0%; and / or symptomatic) a “basal”insulin alone is typically added to drugs in step 2. The starting dose is 0.2 unit/kg basal insulin (e.g., NPH, insulin glargine or detemir)\[132\]. More complex insulin regimen including basal-bolus insulin is needed in patients who are symptomatic or markedly hyperglycemic. Prandial insulin (e.g., lispro, aspart and glulisine) regimen should be adapted to patient dietary and exercise habits\[130\]. While stepping up in the treatment of hyperglycemia in patients taking calcineurin inhibitors, our target of glucose control is similar to that in corticosteroid treated patients\[87\].

Renal impairment

In rheumatic patients who have pre-dialysis chronic kidney disease (CKD), the measure of HbA1c is likely reflective of glucose control similar to that in a population of patients without kidney disease. Therefore, a target goal of < 7.0% may be applied to this patient group\[133\]. But in patients with end-stage renal disease HbA1c has low sensitivity in follow-up of glucose control\[85\]. Glycated albumin (GA) was shown to better identify sub-optimal glycemic control than HBA1c in patients with advanced CKD for whom intensified treatment may offer improved outcomes. Also, elevated GA concentrations, in contrary to HbA1c, is predictive of mortality and hospitalization in dialysis patients with diabetes\[134\]. SMBG is a good tool for follow-up of chronic glycemic control in patients with CKD even in advanced setting. Fasting blood glucose levels < 140 mg/dl, < 200 mg/dl one hour after meal in T1DM and T2DM that are on hemodialysis are considered acceptable\[135\]. Oral anti-diabetic drugs can be used to control hyperglycemia, but we should know that the clearance of both sulphonylureas and their metabolites is highly dependent on kidney function, and severe prolonged episodes of hypoglycemia as a result of sulphonylurea use have been described in dialysis patients\[133\]. In patients with stage 3-5 CKD, first-generation sulphonylureas (chlorpropamide and tolbutamide) should be avoided. Out of the second-generation sulphonylureas, glipizide is the recommended drug because its metabolites are not active, and there is a lower potential for development of hypoglycemia\[136\]. Also, metformin is contraindicated in male patients with a serum creatinine ≥ 1.5 mg/dl and in female patients with serum creatinine ≥ 1.4 mg/dl\[137\]. While acarbose, a disaccharidase inhibitor, is not recommended in patients with a GFR < 26 ml/min/1.73 m², the other disaccharidase inhibitor, miglitol, should
not be used in patients with GFR < 25 ml/min/1.73 m² [138].

Pioglitazone, a thiazolidinedione, is a drug metabolized by the liver and can be given to diabetic patients even with advanced renal disease without dose modification. However, it should be kept in mind that it can increase fluid retention [139].

The new drugs that are available for the treatment of type 2 diabetes such as DPP-4 inhibitors (sitagliptin, saxagliptin and vildagliptin) can be given in case of renal impairment even in severe form but with dose modifications, but linagliptin can be given without dose modification [139]. Another group of new drugs (glucagon like peptide-1) including exanitide and lixilaglutide are used with caution, as exanitide is contraindicated if GFR < 30 ml/min/1.73 m² while lixilaglutide is contraindicated if GFR < 60 ml/min/1.73 m² [139].

In patients with impairment of kidney function, the half-life of insulin is prolonged because of lower levels of degradation [23]. Therefore, in the presence of impaired renal function, patients require less insulin with reduction of insulin requirements by 50% in T1DM and T2DM diabetics [140]. Both human insulin and insulin analogues can be used safely in patients with renal impairment [141]. Correction of hypovitaminosis-D in cases of CKD will improve insulin resistance and diabetes control [15].

Gastroparesis

It is a common clinical observation that diabetic patients with gastroparesis may also exhibit erratic postprandial blood sugar values. Indeed, loss of good glycemic control in a previously well-regulated diabetic should raise concern for gastroparesis [142]. Gastric stasis impairs delivery of nutrients and oral hypoglycemic medications to the small intestine for absorption. Postprandial hypoglycemia or hyperglycemia may develop depending on how the delivery of nutrients corresponds with the peak absorption of the medication [142].

In patients with T1DM, acute hyperglycemia to blood glucose levels of 288 - 360 mg/dl elicits delays in both liquid and solid gastric emptying [143]. Therefore, intensification of therapies to correct hyperglycemia may facilitate the actions of and increase the benefits of other treatments in managing the patient with diabetic gastroparesis. In T2DM patients, oral hypoglycemic medications often are ineffective and can contribute to swings in blood glucose levels because of the temporal mismatch between nutrient absorption and medication [142]. Oral drugs that act on insulin resistance (pioglitazone, a thiazolidinedione) and glucose dependent insulin secretion (DPP-4 inhibitors) are less likely to cause hypoglycemia and do not impair gastric motility [113, 125]. Addition of basal insulin glargine or neutral protamine hagedorn (NPH) to target a mean fasting plasma glucose concentration of 100 mg/dl facilitates attainment of HbA1c values of < 7% in patients who were inadequately controlled with oral hypoglycemic agents [144]. The use of a premixed formulation requires relatively strict adherence to meal timing and composition, and assumes that nutrients will be available within a given time frame to avoid hypoglycemia. Because of these restrictions, premixed insulin may be a poor choice for individuals with delayed or unpredictable gastric emptying [142]. For many T1DM patients, a long-acting preparation such as insulin glargine may be administered daily with preprandial injections of short acting or regular insulin formulas. However, in those with gastroparesis, postprandial hypoglycemic episodes can occur when the glucose-lowering effects of preprandial short-acting insulin precedes delivery of nutrients into the small intestine for digestion and absorption [142]. As a consequence, some persons with delayed gastric emptying may need regular insulin dosing during or even after meal ingestion. Postprandial administration also allows the patient to reduce the insulin dose, if vomiting prevented consumption of the entire meal. That is why in these patients monitoring 2-h postprandial blood glucose levels may be useful [142]. Some patients benefit from use of improved insulin pumps which can be set to provide a constant basal insulin infusion 24 h a day. These individuals then administer bolus regular insulin injections prior to, during, or after meals [142]. In selected cases, jejunostomy feedings may minimize extreme glycemic fluctuations. Additional insulin may be needed for those receiving nocturnal enteral nutrition to correct for the additional calories and to prevent overnight hyperglycaemia [142].

CONCLUSION

Rheumatic diseases can present a challenge in the treatment of hyperglycemia in known diabetic patients or in patients with new onset diabetes. Insulin resistance associated with rheumatic diseases, disease related renal impairment, gastroparesis or drugs used in the treatment of rheumatic diseases are all responsible for difficult control of hyperglycemia in this group of patients. Proper management of hyperglycemia in patients with rheumatic diseases depends on good understanding of pathogenesis of diabetes and rheumatic diseases, co-morbidities of rheumatic diseases, pharmacokinetics and pharmacodynamics of drugs used in the treatment of both hyperglycemia and rheumatic diseases.

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Original Article

Contribution of Advanced Magnetic Resonance Imaging Techniques in Diagnosis of Breast Lesions

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ABSTRACT

Objectives: To determine the diagnostic contribution of diffusion weighted imaging (DWI) and magnetic resonance spectroscopy (MRS) identified either with mammography, ultrasonography or conventional enhanced magnetic resonance imaging (MRI) to cases with palpable breast lesions or for routine control

Design: Prospective study

Setting: Department of Radiology, Celal Bayar University, Turkey

Subjects and Methods: Fifty female patients who applied to the clinic between November 2009 and April 2010 with different indications were included. We applied conventional breast MRI with the routine sequences. We added DWI and BREASE (MRS). After MRI examination postprocessing applications were applied.

 Intervention: Analysis of contribution of advanced techniques in breast lesions diagnosis

Main Outcome Measure: Determining the value of DWI and MRS of breast lesions, which may be useful in improving the specificity.

Results: Fifty-two breast lesions in 37 cases were evaluated. In DWI when cut off apparent coefficient diffusion (ACD) value was accepted as 1.44 x10.3 mm²/sn, the sensitivity was found to be 91.3% and the specificity was 62.1% in discriminating malignant and benign lesions. When the lesions which have choline peak at 3.2 ppm were accepted as malignant and lesions which do not have choline peak were accepted as benign lesions in spectroscopic examination, the specificity was 80%, the sensitivity was 31.8%, negative predictive value (NPV) was 44.4% and positive predictive value (PPV) was found to be 70%.

Conclusions: Our specificity was compatible with that in the literature but sensitivity and negative ppv were lower than reported in the literature. According to ADC values, the findings in our study were compatible with the literature.

KEY WORDS: breast cancer, diffusion magnetic resonance imaging, magnetic resonance spectroscopy, mammography

INTRODUCTION

The traditional imaging approaches to assess breast lesions have limitations in sensitivity and specificity. Since mammography (MM), ultrasonography (US), and even contrast-enhanced magnetic resonance imaging (MRI) are unable to reliably distinguish between malignant and benign tissues, the final diagnosis of cancer is most often based on histopathology. Contrast-enhanced MRI of the breast has been shown to detect breast cancers with a very high degree of sensitivity ranging from 95% to 100%. However the major limitation of dynamic breast MRI is the false-positive enhancement of benign breast lesions which causes a relatively low specificity ranging from 37% to 97%, which is a potential reason for increased number of biopsies. About 75% of the breast tumors detected by MM as well as about 50% of contrast enhancing lesions as detected by MRI are benign at histology[1]. Diffusion weighted imaging (DWI) and magnetic resonance spectroscopy (MRS) offer a non-invasive possibility of differentiating malignant and benign lesions.

DWI is an advanced MRI technique based on the diffusion signal of tissues, which reflects the amount of random motion of water molecules into tissues due to thermal agitation (Brownian motion)[1-4]. Proton (1H) MRS is an in vivo method of providing biochemical information about the investigated tissue. It is widely used in brain and prostate imaging. The diagnostic
value of MRS in breast imaging is typically based on the detection of elevated levels of choline compounds such as phosphocholine and glycerophosphocholine[6,7]. Previous ex vivo MRS studies have shown elevated levels of choline, which are markers of active tumor[6,7]. The appearance of phosphocholine in the spectrum is due mainly to increased choline kinase activity and increased catabolism mediated by increased phospholipase C activity[6].

In this study, we tried to determine the value of DWI and MRS of breast lesions, which may be useful in improving the specificity.

SUBJECTS AND METHODS
Between November 2009 and April 2010, 50 different female patients who were examined with MM and US who had lesions evaluated as BI-RADS 4 and BI-RADS 5 were included in the study. These patients were evaluated by contrast enhanced MRI. Ten patients with no focal lesions and three patients with motion artifacts were excluded from the study. A total of 52 lesion in 37 patients included in the study were evaluated.

The study was approved by the institutional review board of our institute. All participants gave written informed consent. Conventional breast MRI was performed with 1.5 Tesla Magnetic Resonance Imaging device (Signa HDx; General Electric, Milwaukee, WI, USA) and a dedicated 8-channel high definition breast coil. All patients were examined in the prone position. The breasts were slightly compressed from the lateral sides by the compression paddles, taking care not to apply too much pressure on the tissue.

The routine sequences were axial Short TI Inversion Recovery (STIR), sagittal Fast Spin Echo (FSE) Fat Saturated T2-weighted (W), sagittal 3D VIBRANT (Post-contrast Fat Saturated TIW gradient echo sequence). For the dynamic series two pre-contrast, and six post-contrast series with a temporal resolution of about one minute (depending on the size of breast and number of images per sequence) were done.

The other parameter values for DWI were as follows: DWI with \( b = 0 \) s/mm\(^2\) and \( b = 600 \) s/mm\(^2\) values were applied in the axial plane prior to application of contrast material. The other parameter values for DWI were as follows: Sequence EPI, TR / TE 7900 ms / 88.9 ms (minimum TE), FOV 36 - 40 mm, matrix 192 x 192, slice thickness / interval: 5 mm / 1 mm, NEX 16, rBW 250 kHz, scan time 261s. After the acquisition, all data were transferred to a Workstation (Advantage Windows 4.4). During post-processing, black and white Apparent Diffusion Coefficient (ADC) maps were generated and ADC values of normal breast tissue for each patient and mass lesions which were visualized were measured. The ADC values of breast tissue were obtained from the fibroglandular areas, trying to omit the fatty tissue in the region of interest (ROI). For breasts with a dominant fatty pattern a small ROI was used to minimize the inclusion of fat which may artificially reduce the ADC value. For the mass lesions the ROI was placed over the tumor, trying to avoid areas of hemorrhage or necrosis. Sizes of the ROI varied between 10 - 100 mm\(^2\).

MRS examination was performed following the dynamic contrast enhanced sequence, in order to be sure to examine the enhancing lesion. ROI was placed by one of two radiologists (SO or IB), taking care to encompass the lesion in the voxel. The data was collected from a single rectangular volume of interest. The voxel size was determined depending on the size of the lesion, trying to exclude any fat tissue. The voxel size ranged between 3 - 8 cm\(^3\). The proton spectrum was collected with BREASE sequence; a breast-specific, single-voxel spectroscopy application designed for ease-of-use and enhanced visualization (GE Healthcare). (Repetition time (TR): 2000 msec, echo time (TE): 155 msec, number of excitations (NEX): 32, imaging time: 4 min and 48 sec, voxel thickness: 20 mm). Saturation bands on four sides of the voxel and the automatic shimming were used. The lesions were evaluated according to the presence or absence of choline peak.

Results were evaluated statistically by using SPSS 16.0 for Windows version. Sensitivity, specificity, positive and negative predictive values, likelihood ratios, pretest and post-test possibilities were calculated for every test. For every calculated ADC value, receiver operating characteristic (ROC) was analyzed and a cut-off value was determined.

In premenopausal cases in order to avoid false positive results, the evaluation was performed in the 7th and 17th days of cycle. In patients who were using neo-adjuvant chemotherapy, MRI examinations were applied in the 3rd - 6th months after therapy.

RESULTS
Fifty-two lesions in 50 patients were evaluated in this study. The exact diagnoses were obtained either with typical radiological findings or with histopathological results. The ages of the patients ranged between 26 – 76 years, the average being 46.83 years. The average dimension was 16.48 mm in benign lesions, and 23 mm in malignant lesions.

Nine additional lesions which could not have been detected by MM and US were determined by contrast-enhanced breast MRI. No additional lesion was determined by DWI in the patients. Lesions were classified according to the histopathological results (n = 26), typical radiological (n = 8) and follow-up findings (n = 18) (Table 1). Number of malignant lesion was 23,
lesions malignant type curves (type 3) were obtained from contrast-enhanced dynamic breast MRI. In one patient with one lesion who had gadolinium allergy

Table 1: The distribution of lesions according to typical radiologic findings and histopathological results

<table>
<thead>
<tr>
<th>Lesion</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malignant Lesion</td>
<td>23</td>
</tr>
<tr>
<td>Invasive ductal carcinoma</td>
<td>19</td>
</tr>
<tr>
<td>Invasive ductal carcinoma + Invasive lobular carcinoma</td>
<td>2</td>
</tr>
<tr>
<td>Invasive ductal carcinoma + Invasive lobular carcinoma in situ</td>
<td>1</td>
</tr>
<tr>
<td>Mixed invasive ductal carcinoma + Pleomorphic invasive lobular carcinoma</td>
<td>1</td>
</tr>
<tr>
<td>Benign Lesion</td>
<td>29</td>
</tr>
<tr>
<td>Enhanced normal breast focus stable in follow up</td>
<td>8</td>
</tr>
<tr>
<td>Post-op tissue stable in follow up</td>
<td>6</td>
</tr>
<tr>
<td>Mastitis</td>
<td>2</td>
</tr>
<tr>
<td>Infected galactocele</td>
<td>2</td>
</tr>
<tr>
<td>Simple cyst</td>
<td>2</td>
</tr>
<tr>
<td>Abscess</td>
<td>1</td>
</tr>
<tr>
<td>Hemorrhagic cyst</td>
<td>1</td>
</tr>
<tr>
<td>Post-op hemorrhagic fat necrosis</td>
<td>1</td>
</tr>
<tr>
<td>Fat necrosis</td>
<td>1</td>
</tr>
</tbody>
</table>

In 16 lesions benign type signal / time curves (type 1), in 12 lesions intermediate type (type 2) and in 15 benign lesion was 29. The percentage and numbers of benign-malignant results of pathological results are shown in Table 2.

In 16 lesions benign type signal / time curves (type 1), in 12 lesions intermediate type (type 2) and in 15 benign lesion was 29. The percentage and numbers of benign-malignant results of pathological results are shown in Table 2.

Table 2: Percentage and numbers of benign-malignant diagnosis based on pathological results

<table>
<thead>
<tr>
<th>Distribution of pathological results</th>
<th>Frequency</th>
<th>Percentage</th>
<th>Current percentage</th>
<th>Cumulative percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benign</td>
<td>29</td>
<td>55.8</td>
<td>55.8</td>
<td>55.8</td>
</tr>
<tr>
<td>Malignant</td>
<td>23</td>
<td>44.2</td>
<td>44.2</td>
<td>100.0</td>
</tr>
<tr>
<td>Total</td>
<td>52</td>
<td>100.0</td>
<td>100.0</td>
<td></td>
</tr>
</tbody>
</table>

Table 3: The discrimination of lowest and highest average ADC values

<table>
<thead>
<tr>
<th>Lesion</th>
<th>The lowest average ADC value (x 10^3 mm^2/sec)</th>
<th>The highest average ADC value (x 10^-3 mm^2/sec)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Invasive ductal Ca (n = 19)</td>
<td>0.92</td>
<td>1.90</td>
</tr>
<tr>
<td>Invasive ductal Ca + Invasive lobular Ca (n = 2)</td>
<td>0.98</td>
<td>1.15</td>
</tr>
<tr>
<td>Enhanced normal breast focus stable in follow up (n = 8)</td>
<td>1.41</td>
<td>2.37</td>
</tr>
<tr>
<td>Fibroadenoma (n = 6)</td>
<td>1.23</td>
<td>2.11</td>
</tr>
<tr>
<td>Post-op tissue stable in follow up (n = 5)</td>
<td>1.19</td>
<td>1.6</td>
</tr>
<tr>
<td>Mastitis (n = 2)</td>
<td>1.27</td>
<td>2.11</td>
</tr>
<tr>
<td>Infected galactocele (n = 2)</td>
<td>1.10</td>
<td>1.21</td>
</tr>
<tr>
<td>Simple cyst (n = 2)</td>
<td>2.03</td>
<td>2.14</td>
</tr>
<tr>
<td>Normal breast tissue (n = 91)</td>
<td>1.09</td>
<td>2.43</td>
</tr>
</tbody>
</table>

Table 4: The discrimination of choline peak according to the lesions

<table>
<thead>
<tr>
<th>Choline peak</th>
<th>Malignant lesions</th>
<th>Benign lesions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Choline peak</td>
<td>Invasive ductal Ca (n = 4)</td>
<td>Enhanced normal breast focus stable in follow up (n = 2)</td>
</tr>
<tr>
<td></td>
<td>Invasive ductal carcinoma + Invasive lobular carcinoma in situ (n = 1)</td>
<td>Simple cyst (n = 2)</td>
</tr>
<tr>
<td></td>
<td>Mixed invasive ductal carcinoma + Pleomorphic invasive lobular carcinoma (n = 1)</td>
<td>Fibroadenoma (n = 1)</td>
</tr>
<tr>
<td></td>
<td>Invasive ductal carcinoma + Invasive lobular carcinoma (n = 1)</td>
<td>Post-op tissue stable in follow up (n = 1)</td>
</tr>
<tr>
<td>No Choline</td>
<td>Invasive ductal Ca (n = 14)</td>
<td>Enhanced normal breast focus stable in follow up (n = 6)</td>
</tr>
<tr>
<td></td>
<td>Invasive ductal carcinoma + Invasive lobular carcinoma (n = 1)</td>
<td>Fibroadenoma (n = 6)</td>
</tr>
<tr>
<td></td>
<td>Mixed invasive ductal carcinoma + Pleomorphic invasive lobular carcinoma (n = 1)</td>
<td>Post-op tissue stable in follow up (n = 5)</td>
</tr>
<tr>
<td></td>
<td>Mixed invasive ductal carcinoma + Pleomorphic invasive lobular carcinoma (n = 1)</td>
<td>Mastitis (n = 2)</td>
</tr>
<tr>
<td></td>
<td>Hemorrhagic cyst (n = 1)</td>
<td>Infected galactocele (n = 2)</td>
</tr>
<tr>
<td></td>
<td>Fat necrosis (n = 1)</td>
<td></td>
</tr>
</tbody>
</table>

Fig. 1: The cut-off value of ADC values in 23 malignant and 29 benign lesions.
lesions malignant type curves (type 3) were obtained from contrast-enhanced dynamic breast MRI. In one patient with one lesion who had gadolinium allergy, and one patient with two lesions in lactation period, non-enhanced breast MRI was applied. In three lesions which were simple cysts and one lesion which had hemorrhagic decay products (because of ferromagnetic artifacts), dynamic enhancement curves could not be obtained.

In DWI, there was visual and quantitative discrimination of all ADC values is shown in Table 3.

Fig. 2 (a - e) : 48-year-old female patient with right breast invasive ductal carcinoma, a-b: CC-MLO MM images, there is a nodular opacity in lower outer quadrant of right breast (Arrows). c: In US image, hypoechoic, irregular contoured, solid mass is seen (Arrow). d-e: Post-contrast T1W and subtraction images. The lesion is enhanced and also another enhanced component of the lesion is seen (Arrows).

In DWI, there was visual and quantitative diffusion restriction in a total of 23 cases, 20 malignant and 3 benign lesions. In twenty-three lesions with malignant diagnosis, lowest ADC value was $0.92 \times 10^{-3}$ mm$^2$/sec and the highest ADC value was $1.90 \times 10^{-3}$ mm$^2$/sec. The average of all malignant values was $1.14 \pm 0.18 \times 10^{-3}$ mm$^2$/sec. In 29 lesions clinically and histopathologically diagnosed as benign, the lowest ADC value was $1.10 \times 10^{-3}$ mm$^2$/sec and the highest value; $2.37 \times 10^{-3}$ mm$^2$/sec. The average of all values was detected as $1.58 \pm 0.36 \times 10^{-3}$ mm$^2$/sec. The discrimination of all ADC values is shown in Table 3.
The cut-off value of ADC values for 23 malignant and 29 benign lesions was calculated as $1.44 \times 10^{-3} \text{mm}^2/\text{sec}$ in ROC analysis (Fig. 1). For this cut-off value, the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of 52 lesions were 91.3%, 62.1%, 60.4% and 40.4% respectively. The difference between the ADC values of malignant-benign lesions and cysts was statistically significant ($p = 0.000$). When the cut-off ADC was accepted as $1.09 \times 10^{-3} \text{mm}^2/\text{sec}$ for 100% specificity, the sensitivity of malignant lesion was calculated as 48%, PPV and NPV were calculated as 33.1% and 67.5% respectively.

In proton MRS, the lesion was classified according to the presence of choline peak at 3.2 ppm. Out of the 52 lesions, 13 lesions (n = 7 malignant, n = 6 benign lesions) had choline peaks and 39 lesions (n = 16 malignant, n = 23 benign lesions) did not have choline peaks (Table 4). The discrimination of choline peak percentage is shown in Table 5. Case samples of our study are shown in Fig. 2 - 6).

**DISCUSSION**

Breast cancer has a high morbidity and mortality worldwide. For this reason it is an important source of interest and anxiety for clinicians and researchers. In recent years, with development of techniques in MM, breast US and breast MRI, the proportion of malignancy determination has risen. With the increase of these early diagnostic techniques, alternative

<table>
<thead>
<tr>
<th>Choline Peak</th>
<th>Frequency</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative</td>
<td>39</td>
<td>75.0</td>
</tr>
<tr>
<td>Positive</td>
<td>13</td>
<td>25.0</td>
</tr>
<tr>
<td>Total</td>
<td>52</td>
<td>100.0</td>
</tr>
</tbody>
</table>
surgical methods to mastectomy have taken over\cite{9,10}. After the digital MM has been put into routine use, it is reported that the proportion of lesion determinations in breasts with high density has increased\cite{11}. Also, with the use of high resolution probes in US, with the developments in spatial and temporal resolution in breast MRI, the sensitivity of diagnostic techniques has risen\cite{12,13}. It is reported that, breast MRI is a problem solving method in some cases with dense breast parenchyma, in evaluating patients with silicon implants, in diagnosis of primary focus of occult breast carcinoma, in preoperative evaluation of multifocal and multicuscent breast carcinomas which cannot be determined with MM and US and in demonstration of intraductal component of breast carcinoma. In these cases MM and breast US techniques remain insufficient for the diagnosis\cite{14}.

MM is the most effective method in the approach of breast disease investigations. Other diagnostic methods are used as complementary to MM when needed. The
Fig. 4 (a - f): 52-year-old female patient with fibroadenoma (diagnosed with tru-cut biopsy). a: In CC position MM image, there is an asymmetric density with indistinct contour in her right breast (Arrow). b: In US examination, there is a solid, hypoechoic, microlobulated contoured lesion (Arrow). c: Post-contrast, fat saturated T1W MRI image shows slight enhancement in the lesion (Arrow). There are enhanced septums. However in subtracted image there is no enhancement (Circle). d: Type 1 (benign type) enhancement curve is seen. e: In DWI image, there is no significant diffusion restriction (Arrow). ADC value: 1544.38 mm²/sec. f: In MRS, choline peak is not seen.

usage of MM is for two different purposes; diagnosis and malignancy screening. In fact, the specificity of MM is low and biopsy is needed in order to make discrimination between benign and malignant lesions, which have been determined by MM. Only 10 - 35% of the biopsies that are done according to mammographic findings yielded the final diagnosis of malignancy[15].

The usage of gray scale US additional to MM, especially after the developments in US technology, helps in solid-cystic lesion discrimination, guides aspiration biopsies and also helps to discriminate benign and malignant lesions[16,17].

MRI has been in use from the 1980’s. In the first application, longitudinal relaxation time (T1), transverse relaxation time (T2) and hydrogen spin densities were used[18]. MRI should be done necessarily with the application of contrast material containing gadopentetate dimeglumine (Gd DTPA). By this way, it provides high sensitivity in diagnosis.
Fig. 5 (a - g): 27-year-old female patient in lactation period. She had fever, pain, swelling and erythema in her right breast. The findings were diagnosed as infected galactocele. Non-enhanced MRI examination was performed. a: In STIR sequence there are increased signals (Arrows), b: In T1W sequence, there are heterogeneous signals compatible with increased signals in STIR image (Arrow), c: In right breast T2W images, there are lobulated contoured, with low signal cystic lesions compatible with galactocele (Arrows). d: In left breast T2W, there are dilated ductal structures compatible with lactation period. e: In b = 600 DWI and ADC images, there are restricted diffusion, ADC value: 1101.05 mm²/sec (Arrows). f: In one area of infected breast there is no choline peak. g: There is choline peak.
of breast cancer and lesion discrimination. Enhanced breast MRI has been used in the control and diagnosis of breast cancer for more than 15 years\cite{19-22}. According to the technical and diagnostic criteria in breast MRI application, the sensitivity varies between 83 - 100% and the specificity varies between 29 - 100%\cite{19,21,22}. Breast MRI has disadvantages such as long examination time. Moreover, difficulties can be seen in characterization of lesion determination from time to time. The diagnostic criteria of conventional breast MRI evaluation include lesion morphologies, enhancement dynamics of the lesions and T2 signal features. As the findings in benign and malignant lesions overlap, it is reported that the specificity of MRI can decrease to 40 - 80\%\cite{23-29}. Recently, enhanced dynamic breast MRI is accepted as a very sensitive imaging method in breast cancer diagnosis. In selected cases, it is offered as a complementary diagnostic modality\cite{26,27}. When MRI is used together with MM and US, it is a very powerful method in imaging and characterization of breast masses.

DWI is an advanced MRI technique based on the diffusion signal of tissues, which reflects the amount of random motion of water molecules into tissues due to thermal agitation (Brownian motion)\cite{24-24}. DWI was first introduced for and has become one of the primary

Fig. 6 (a - b) : 39-year-old female patient with mixed invasive ductal-invasive lobular carcinoma (Arrows). a: Pre-chemotherapy MRI and MRS images are seen. There is choline a peak at 3.23 ppm. b: After 6 cure chemotherapy, the size of the lesion got smaller and choline peak disappeared.
imaging modalities of acute cerebral infarction. However, it is being used for other clinical applications to the entire body, with great promise for the detection and characterization of tumors of the other organs like ovaries, pancreas, prostate and breasts[2,4,28,29]. It helps to investigate breast masses by providing information about the biological behavior of the tumor[3]. There are several studies evaluating the breast masses using DWI in the literature[2,4,28,29]. DWI provides qualitative and quantitative information related to the tumor cellularity. ADC is a quantitative measurement reflecting the free motion of water molecules which is inversely proportional to the tumor cellular density[30].

Previous studies report that DWI is a useful technique for the discrimination of benign and malignant lesions[2,4,28,29]. Malignant lesions with tightly packed cells, has reduced extracellular space and diffusion of water is decreased. On the contrary benign lesions with a larger extracellular space, water molecules are more mobile, and the ADC value is higher[31].

When various studies in the literature were evaluated, ADC values found to change with the use of different b values. Sinha et al reported that with b = 400 value study, ADC values in malignant lesions are 1.60 ± 0.36 ×10⁻³ mm²/sec[4]; Kinoshita et al reported that with b = 700 study, ADC values in malignant lesions are 1.22 ± 0.19 ×10⁻³ mm²/sec[28]; in the Woodhams et al study with b = 750 study, ADC values in malignant lesions are 1.12 ± 0.24 ×10⁻³ mm²/sec[29] and in Guo et al study with b = 1000, ADC values in malignant lesions are 0.97 ± 0.20 ×10⁻³ mm²/sec[29]. In our study DWI was carried out with b = 600. In malignant lesions ADC values were evaluated as 1.14 ± 0.18 ×10⁻³ mm²/sec and this was compatible with the values reported in the literature. All the studies in the literature including our study revealed that DWI is a useful method in discrimination of benign lesions from malignant ones[31].

Choline is a biochemical measure of metabolism, indicating the rate of cellular membrane turnover and proliferation. Currently, there is molecular evidence of increased choline metabolism in breast cancer cells. In the evaluation of MRS, the presence of composite choline was used as an indicator of malignancy, whereas its absence indicated a benign process. This hypothesis is consistent with the high phosphocoline content in human breast cancer cells, which was found to be ten times higher than that of normal mammary epithelial cells in previous studies[7].

Previous investigators have reported sensitivities of 70 - 100%, specificities of 67 - 100% and PPV of 82 - 100% for breast MR spectroscopy[32,38]. The results of the previous studies in comparison to our results are presented in Table 2. Several studies have shown that the broad composite resonance at 3.2 ppm, which includes contributions from choline, phosphocholine, glycerophosphocholine, myo-inositol and taurine is a unique marker for malignancy.

In our study, when the lesions with positive choline peak are evaluated as malignant, and lesions without choline peak were evaluated as benign, sensitivity, specificity, NPV and PPV results were calculated as 31.8%, 80%, 44.4% and 70% respectively. Whereas, specificity of our study was compatible and sensitivity and PPV results were lower than the results in the literature.

User-dependent technical reasons, lesion size dependent limiting factors, and genetic content of the lesions may cause false-negative results in MRS examinations. Additionally heavy fatty and water contents of the breast may make shimming difficult. In single voxel MRS, only one lesion can be evaluated at a time and this increases the examination time. All these reasons are limitations of this method.

The sensitivity of MRS of breast is detected true-positive (malignant lesions with choline peak). The sensitivity is limited by false-negative (malignant lesion without choline peak) results. In various studies in the literature; Cecil et al[31] (4 cases), Yeung et al[34] (2 cases), Kvidsted et al[35] (2 cases), Jagannathan et al[36] (6 cases) and Roebuck et al[33] (3 cases) the outcomes were false-negative results. All these results were mostly based on technical reasons. In our study, we think that incompatible results in the literature were based on technical and user dependent reasons. In cases with correct selection of the sample volume, although there was appropriate spectroscopic curve, choline peak might not be obtained. We think that this result was based on the content of the lesion.

Thirty-seven cases included in our study, where all the examinations were complete, the prevalence of malignant lesion was calculated as 59.4%. In this group, when US and MM examinations were evaluated together, the sensitivity was 95.4% and specificity was 66.6%. When US and conventional MRI were evaluated together, sensitivity was 100% and specificity was 66%. When US, MM and conventional MRI results were evaluated together, sensitivity was 100% and specificity was 0.2%. The sensitivity and the specificity results were same when US, MM, conventional and advanced MRI examinations were evaluated together.

CONCLUSION

With all the findings of our study in diagnosis of malignant lesions, conventional examinations, especially conventional MRI and DWI have important contributions. However, MRS examination has provided insufficient contribution to the diagnosis and more studies with larger patient series should be done for further evaluation.
REFERENCES

Original Article

Effect of Highly Active Antiretroviral Therapy (HAART) on Body Mass Index (BMI), PCV, CD4+ T Cell Count and Albumin of HIV Seropositive Women in Nigeria

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¹Department of Chemical Pathology, University of Benin Teaching Hospital, Benin, Nigeria
²Department of Basic Sciences, Benson Idahosa University, Edo, Nigeria

Kuwait Medical Journal 2014; 46 (4): 312 - 318

ABSTRACT

Objectives: To establish the effect of highly active antiretroviral therapy (HAART) on some parameters of HIV seropositive women in their reproductive ages in both follicular and luteal phases of their menstrual cycle

Design: Prospective and targeted for a particular group of HIV sero-positive women in a tertiary institution in Midwestern Nigeria.

Setting: University of Benin Teaching Hospital, Edo State, Nigeria

Subjects and Methods: A target population of 100 HIV seropositive women of reproductive age (range 18 – 40 years, mean = 29 years) and 50 seronegative women of same age group (mean = 32 years) as control were recruited before the commencement of HAART therapy.

Intervention: All subjects and controls were monitored at three-monthly intervals for a period of nine months

Main Outcome Measures: The parameters that were examined included body mass index (BMI), CD4+ T cell count, packed cell volume (PCV) and albumin in both follicular and luteal phases of their menstrual cycles.

Results: HAART significantly (p < 0.05) raised BMI, CD4+ T cell count, PCV and albumin in both phases of the study. These parameters were initially significantly decreased by HIV infection.

Conclusion: HAART has demonstrated great promise in the management of HIV seropositive women. More studies are encouraged to determine how HAART can maintain its current high level of efficiency in these women.

KEY WORDS: albumin, BMI, CD4+ T cell count, HAART, HIV, PCV

INTRODUCTION

Human Immunodeficiency Virus (HIV) is a retrovirus which primarily attacks vital organs of the immune system, such as the CD4+ T cell and dendritic cells which process antigens and present them to the β-cells for antibody production. These cells are required for the proper functioning of the immune system. HIV directly or indirectly destroys CD4+ T cells[1]. When the virus has destroyed CD4+ T cells to below 200 cells/µl of blood, cellular immunity is significantly impaired[2]. HIV seeks out and destroys CCR5 co-receptor expressing CD4+ cells during acute infections. This is a major cause of CD4+ T cell loss. Another prominent effect of HIV is its suppression and lyses of T-helper cells.

Anemia has been reported several times in HIV / AIDS infection[3-5] and recovery from anemia has been shown to be associated with progressive increase in CD4+ T cells[6]. In recent times, the use of highly active antiretroviral therapy (HAART) for the treatment of HIV infected patients has generated some research findings. HIV infection decreases body mass index (BMI), but HAART has been shown to increase BMI[7,8]. Packed cell volume (PCV) and albumin levels related positively and significantly with HAART administration[4, 5] including CD4+ T cell count[9,10].

The pathophysiology as well as the clinical manifestation, including stigmatization of the disease has been exhaustively discussed[11].

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There are numerous reports in the literature on the effectiveness of HAART on HIV patients\cite{12}. However, none of the literature cited above studied the effect of HAART on a target population of women in the reproductive age at short intervals in their menstrual cycle. This study targeted the effect of HAART on these patients during the follicular and luteal phases of their menstrual cycle. The parameters investigated are BMI, CD4+ T cell count, PCV and albumin. The usefulness of this investigation to the epidemiology of the disease cannot be overemphasized. The findings on these parameters will be a yardstick in assessing the efficacy of HAART on these patients.

SUBJECTS AND METHODS

This study was done at the University of Benin Teaching Hospital (UBTH), a tertiary health-care institution in Midwestern part of Nigeria. This teaching hospital (UBTH) has a complement of over 600 beds and serves as a referral center for Edo state and the rest of the country.

Subjects

These were female patients seen at the hospital clinics, diagnosed and confirmed as HIV positive. Their status was not originally known to them and as such, they were not on any medication for HIV. One hundred (100) HIV positive women of reproductive age (range 18 to 40 years, mean = 29 years) and matched with fifty (50) HIV seronegative women (mean age = 32 years) were recruited into the study.

Ethical standards permission was obtained from the hospital management committee before commencement of the study. Only willing patients were recruited into the study. Only adult females who were confirmed HIV seropositive and referred to the infectious diseases clinic for treatment and monitoring were recruited. The subjects selected were not above 40-years of age. Pregnant and menopausal women were excluded. Only women whose CD4+ T cell count were below 350 cells/µl of blood were recruited into the study as this is the World Health Organization (WHO) treatment threshold.

Blood specimen separation was done with a centrifuge, registered and stored at – 70 °C. Specimen for CD4+ T cell count was taken immediately to the laboratory where analysis was done within six hours of collection of the specimen.

The packed cell volume (PCV) estimation was done using Sysinex KX-21. This is an automatic multiparameter blood cell counter for in-vitro diagnostic use in clinical laboratories.

CD4+ T cell count was done using Cyflow SL-3. Specimens were collected in EDTA-K$_2$ anticoagulant vacutainers and assayed within six hours of collection. Twenty microliters of well mixed whole blood collected within six hours was mixed in Rohren test tube and incubated in the dark for 15 min at room temperature. CD4+ buffer was subsequently added, mixed and read on the Cyflow. Calibration is based on the use of the count check beads to verify counting cycle, signal position on the scale and peak or signal characteristics (fine signal peak).

Albumin was assayed using the Randox method\cite{13}. The measurement of serum albumin is based on its quantitative binding to the indicator 3, 3’ 5, 5’-tetrabromo-m-cresol sulphonephthalein (BCG). The albumin-BCG-complex absorbs maximally at 630 nm, the absorbance being directly proportional to the concentration of albumin in the sample.

Body Mass Index (BMI)

BMI was derived by dividing the body weight (kg) by the square of the height in meters (m$^2$). The unit of BMI is kg/m$^2$. Using the data on weight and height obtained at each visit to the clinic. The following can be deduced from BMI:

- **Under nutrition:** BMI < 18.5 kg/m$^2$
- **Normal:** 18.5 $^2$ BMI < 25.0 kg/m$^2$
- **Over weight:** BMI > 25.0 kg/m$^2$

RESULTS

BMI responses

BMI was obtained for apparently healthy non-menopausal women who were HIV-negative (n = 50) and matched with the BMI of HIV-positive women who had not embarked on therapy and recorded as baseline data (n = 100) using their obtained weight and height values. The results obtained showed significant reduction (p < 0.05) in BMI for the infected women (Fig. 1a). The negative impact on BMI was felt equally in the follicular and luteal phases. The Mean ± SEM (standard error of mean) for the baseline data were further grouped into the different phases (Fig. 1b). The menstrual phase does not appear to be a factor for the alteration of weight since the changes obtained were not statistically significant (p < 0.05). With commencement of therapy (HAART), a significant weight increase was observed in the follicular phase.
up to the end of study (i.e., nine months after HAART) (Fig. 1c). In the luteal phase, there was significant increase in the BMI up to sixth months of HAART followed by a drop by the ninth month (Fig. 1c). The value obtained by the ninth month was still statistically higher than the baseline. There were also significant elevations in the amenorrhea phase up to the end of study (Fig. 1c). A comparison of all the phases as therapy progressed shows that statistically significant progressive increases were obtained in all the phases until the end of study (Fig. 1c).

CD4+ Cell count responses

The differences in CD4+ cell count at various phases before commencement of HAART (Fig. 2a) were not statistically significant indicating that it was not phase dependent. In the follicular phase during HAART administration, this study recorded continuous significant increases (p < 0.05) throughout the study period (Fig. 2b). The luteal phase recorded similar progressive significant increases as therapy progressed (Fig. 2b). The amenorrhea phase was not left out as progressive significant increases were also recorded throughout the study period (Fig. 2b). The statistically significant increases obtained in all the phases in this study showed over 100% increase from the baseline by the end of study which was nine months after HAART (Fig. 2b). The amenorrhea phase recorded the highest elevation (Fig. 2b).

Packed cell volume (PCV) responses

In this study, no statistically significant differences were recorded in the PCV values at the various

Fig. 1(a): BMI statistical analysis of HIV-negative and positive controls in the follicular and luteal phases

HIV infection significantly reduced BMI at both phases.

Fig. 1(b): Baseline BMI statistical comparative analysis

There were no statistically significant differences between the various phases. the menstrual phase does not appear to be a factor for alteration of weight before HAART.

NB: p - value < 0.05

BBMI = Total baseline BMI (n = 100)

FBMI = Follicular baseline BMI (n = 53)

LBMI = Luteal baseline BMI (n = 38)

ABMI = Amenorrhea baseline BMI (n = 9)

1st - Monitoring at 3 months

2nd - Monitoring at 6 months

3rd - Monitoring at 9 months

Fig. 1(c): BMI statistical analysis of all phases

There were statistically significant changes observed at the various phases and stages of management. Even though the patterns of changes were different at the various monitoring points, the end results were statistically significant increases at all phases by the end of the monitoring period.

Fig. 2(a): Baseline CD4+ statistical comparative analysis

There were no statistically significant differences between the follicular and Luteal phases. Amenorrhea seems to impact negatively on CD4+ T Cell count.

BCD4 = Total baseline CD4+ (n = 100)

FCD4 = Follicular Baseline CD4+ (n= 53)

LCD4 = Luteal baseline CD4+ (n - 38)

ACD4 = Amenorrhea baseline CD4+ (n = 9)
Phases before commencement of drugs (Fig. 3a). HIV-infection obviously led to anemic situations in all the phases with PCV values of less than 30%. In the follicular phase, HAART led to significant increases up to the end of study (Fig. 3b). The luteal phase recorded similar increases up to the end of study (Fig. 3b). The amenorrhea phase was not left out as significant increases were also recorded at the end of study (Fig. 3b). A comparison of the different phases showed that the elevations obtained were not dependent on the type of phase but distributed evenly (Fig. 3b).

**Albumin responses**

In this study, HIV-infection was confirmed to lead to reductions in albumin levels in all the phases (Fig. 4a). The reductions obtained were not preferentially tied to any phase (Fig. 4b). Statistically significant changes in the mean values of albumin were obtained, especially in the first three months of HAART administration. In the follicular phase, HAART led to significant increases (p < 0.05) in albumin when compared to the baseline level (Fig. 4c). In the luteal phase, the first three months did not record any significant change, but by the 6th and 9th month of HAART administration significant changes were recorded (Fig. 4c). The pattern of change in the amenorrhea phase was exactly the same as in the follicular phase (Fig. 4c). In these phases, reductions were observed at the 6th month of HAART with subsequent elevations thereafter. Changes at the same monitoring levels, though within normal reference range of albumin, were significant in different phases. HAART led to significant elevations in albumin with increased duration of treatment (Fig 4c) in all phases.
DISCUSSION

HAART has greatly reduced the morbidity and mortality of patients with acquired immune deficiency syndrome (AIDS). In this study, baseline subjects (non-HAART treated subjects) presented significant weight loss in the follicular and luteal phases when compared with negative controls. This is in consonance with the postulation that the disease course is a contributing factor to weight loss and wasting syndrome as seen in some subjects of certain age groups. With HAART, there was a general increase in BMI in all phases to the end of the monitoring period. Adipose tissue alterations (ATA) are common with persons on HAART and can have substantial psychological repercussions with a subsequent negative impact on the patients’ quality of life and HAART adherence. Adipose tissue remodeling and metabolic abnormalities observed with HAART during HIV infection may be related to increased pro-inflammatory cytokine activity. Increased cytokine secretion from adipose tissue and increased systemic pro-inflammatory cytokine activity may play a significant role in the adipose tissue remodeling and/or the metabolic abnormalities associated with HIV-LDS in these patients. Intrinsic host factors and disease status, as well as treatment duration and type, probably play key roles in the etiology. Several metabolic abnormalities such as dyslipidemia and insulin resistance have been commonly reported in these patients. Social stigmatization is a consequence of body fat changes that may lead to poorer adherence and the failure of HAART, having observed significant changes in BMI in both the follicular and luteal phases of their menstrual cycle. Drug dosage must therefore account for the weight of the patient, since weight plays a role in the distribution of drugs in the body tissues.

Antiretroviral therapy is designed to reduce morbidity rate and consequently mortality rate. It therefore follows, that ensuring a BMI normal rate is advisable that development of further studies on BMI-HAART relationship is explored using anthropometric measurements as well as computed tomography to detect fat redistribution. BMI will serve as an overt index in the monitoring and evaluation of people living with HIV/AIDS (PLWHA) among other diagnostic indices in developing countries especially in terms of cost.

Overall treatment efficacy showed an increase of CD4+ cell count by at least 50% of the baseline value within the study period and in agreement with some earlier workers. It is a well-documented fact that CD4+ cell count and viral load typically reciprocate each other. This distribution was not tied to the menstrual phase, indicating a lack of influence of the sex hormone levels. For better management results, it is suggested that HAART be initiated at CD4+ cell counts of 500 cells/µl and below in order to decrease the risk of developing treatment-limiting antiretroviral resistance. A higher baseline CD4+ T cell count predicted a greater post-HAART CD4+ T cell count and absolute CD4+ T cell count attained post-HAART is highly dependent on the baseline count.
Anemia has been frequently reported in HIV/AIDS infection\cite{4,5}. Recovery from anemia has been linked to improved survival outcomes\cite{6}. Anemia is the most commonly occurring hematological abnormality in HIV positive patients\cite{22} and may be as a result of the direct attack on the reticuloendothelial cells by the virus\cite{23}.

In this study, significantly increased PCV from their baseline values was observed at all levels (p < 0.05) which increased with therapy up to the end of the study period. Thus it has been established that treatment improves the condition and is sustained as treatment progresses. This correlates with progressive increase in CD4$^+$ cell count and progressive decrease in viral load and opportunistic infections leading to increase in hemoglobin concentration and a decrease in prevalence of anemia. This study has therefore reiterated, that PCV concentrations are significantly increased as HAART treatment progresses and CD4$^+$ cell count increases in both the follicular and luteal phases.

Serum albumin level was observed to increase significantly in response to therapy in the follicular and luteal phases. The changes observed were however, within the normal reference limits of albumin within the study period but increased as HAART progressed. There was a significant decrease in the baseline albumin level as compared with the negative control. HIV/AIDS have been shown to have a negative impact on the value of albumin\cite{24}. The positive significant change with HAART observed in this study is in agreement with some earlier workers\cite{25,26}. It would be difficult to use albumin in this group of patients as a marker for monitoring response to therapy and as good index for severity of disease, as suggested by earlier workers\cite{26,27}.

Though consistent with some previous studies in industrialized countries\cite{28}, increase in albumin correlated positively with duration of treatment. Some workers have suggested that monitoring of albumin can be used in therapy monitoring against CD4$^+$ cell count\cite{24,28}.

It has been observed that declining albumin correlates positively in the prediction of mortality and that low albumin is associated with low CD4$^+$ cell count \cite{29}. When therapy is well monitored, it increases serum albumin levels\cite{28}. Serum albumin reflects the level of nutrition as well as improvements in metabolism and liver function. It has been suggested that serum albumin would be a very useful surrogate test for predicting the severity of HIV infection and also for the clinical monitoring of response to therapy especially, in developing countries where majority of the populace live below poverty line. Even though serum albumin is not a marker of HIV-1 infection, it is one of the strongest independent predictors of mortality\cite{28}. A fall in albumin over time could indicate that a patient already taking HAART should change therapy and lastly, because serum albumin is an inexpensive and widely available measurement, it may be particularly useful in developing countries. These women, however, did not exhibit enough alterations in albumin levels making it a limited tool.

The investigation of HAART effect on women in both the follicular and luteal phases of the menstrual cycle has therefore, revealed significant increases in these measured parameters that were not menstrual phase dependent. The different phases, with their different hormonal milieu, appear not to influence these parameters. The observed changes in BMI can suggest poor adherence to HAART and indicates that drug dosage be weight dependent. Albumin changes have therefore been shown to be an improper tool for measurement of the severity of disease in this group of women in their reproductive ages.

**CONCLUSION**

HAART has been shown to lead to marked increases in BMI, PCV, CD4$^+$ T cell counts and serum albumin. These parameters were hitherto reduced by HIV infection. The significant increases in these parameters show efficacy of HAART and is not tied to the menstrual phases with their different hormonal milieu. It is therefore, necessary to encourage HAART, since currently it is the only solution to HIV infection.

**ACKNOWLEDGEMENT**

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Original Article

Comparison of Glycosylated Hemoglobin (HbA1c) Levels in 2009 and 2012 among Diabetic Patients at a Primary Care Clinic: A Retrospective Cohort Study

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ABSTRACT

Objective: To update the existing knowledge on glycemic control measures in Saudi Arabia, by comparing the glycosylated hemoglobin (HbA1c) levels of diabetic patients attending a primary care clinic in 2009 and 2012

Design: Retrospective cohort study

Setting: Primary care clinic, King Khalid University Hospital, College of Medicine, King Saud University, Riyadh, Saudi Arabia

Subjects: Diabetic patients visiting a primary care clinic at a tertiary hospital

Intervention: Laboratory tests were reviewed for all diabetic patients attending a primary care clinic, by using the Hospital Information System (HIS).

Main Outcome Measures: Two laboratory tests of HbA1c were determined, one performed in 2009, and the other in 2012, for all diabetic patients visiting a primary care clinic at the King Khalid University Hospital. The HBA1c levels in 2009 and 2012 were compared. Data were analyzed using SPSS version 17 software.

Results: The results of this study showed that the percentage of diabetic patients with good blood glucose control (HbA1c < 7) was 39.1% during 2009, and 34.9% during 2012. In addition, the results showed that the percentage of diabetic patients with bad control (HbA1c ≥ 9) was 24.5% during 2009, and 23.9% during 2012.

Conclusion: Diabetic patients' blood glucose control at the primary care level did not improve from 2009 to 2012. Thus, there is urgent need to evaluate and monitor patients towards improving the quality of diabetic care and the prevention of diabetic complications. Further national cohort studies in different health sectors and regions of Saudi Arabia are recommended.

KEY WORDS: blood glucose control, diabetes, HbA1c, primary care

INTRODUCTION

Glycosylated hemoglobin (HbA1c) is used as an objective measurement for glycemic control of diabetes mellitus, reflecting a patient’s blood glucose control over the previous three months[10]. Among diabetic patients, blood glucose levels are not constant and vary throughout the day, being primarily elevated during postprandial periods. However, HbA1c is not influenced by acute perturbation or insufficient fasting, making HbA1c one of the precise indicators used to assess the control of blood glucose level among diabetic patients[23]. Further, one of the important aspects for diabetic patients is that HBA1c can be measured anytime, irrespective of fasting or feeding. An International Expert Committee was convened by the American Diabetes Association, the European Association for the Study of Diabetes, and the International Diabetes Federation to consider HbA1c in the diagnosis of diabetes mellitus[4-8]. Treating physicians should provide constructive feedback to diabetic patients about their HbA1c results, and explain their meaning as some patients may have insufficient knowledge of HbA1c, such as what is the best target level, and how it will help in their future management plan[9,10]. Monitoring of HbA1c has been recommended for the purpose of blood glucose control among patients diagnosed with diabetes mellitus[11].

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on the basis of the established association between HbA1c and microvascular disease[12,13]. There are limited available cohort studies for examining whether glycemic control has improved in recent years among diabetic patients in Saudi Arabia. This study aims to add to the existing knowledge by comparing the HbA1c levels of diabetic patients, attending a primary care clinic in 2009 and 2012.

**SUBJECTS AND METHODS**

A retrospective cohort study was performed at King Khalid University Hospital, College of Medicine, King Saud University, Riyadh, Saudi Arabia. The study protocol was reviewed and approved by the Institutional Review Board Ethical Committee of King Saud University College of Medicine (research project number E-12-851). The laboratory test results for all diabetic patients attending the primary care clinic were reviewed, by using the Hospital Information System (HIS). For all diabetic patients, two laboratory tests of HbA1c levels were selected, one performed in 2009, and the other in 2012. The study was performed to compare HbA1c levels in 2009 and 2012. Data were entered and analyzed by using the SPSS version 17 software.

**DISCUSSION**

Diabetic blood glucose control can be assessed by means of different laboratory tests, including fasting blood glucose, 2-hour postprandial, home glucometer, and HbA1c. Available evidence has demonstrated that the most accurate indicator of blood glucose control among diabetic patients is HbA1c, which reflects blood glucose control for the previous three months[14,15]. This study showed that during 2009, when blood glucose control assessment among diabetic patients was carried out using HbA1c, 39.1% of patients had good control (HbA1c < 7), whereas 24.5% had bad control (HbA1c ≥ 9). During 2012, the percentage of diabetic patients with good blood glucose control was 34.9% (HbA1c < 7), while that of those with bad control was 23.9% (HbA1c ≥ 9). These results indicate that there was no improvement in blood glucose control among diabetic patients visiting the primary care clinic; the reason for lack of improvement might be owing to a lack of implementation of updated evidence-based diabetes guidelines at the primary care level. Further, another possible factor that might contribute to the lack of improvement in blood glucose control among diabetic patients is that some treating physicians might only be concerned with the follow-up of fasting blood glucose and 2-hour postprandial glucose levels without monitoring the HbA1c level. In addition, some patients might not understand the role of HbA1c in monitoring diabetes. Accordingly, it is very important that diabetic patients are explained the importance of follow-up using HbA1c levels and that they are told to keep the level below 7%, as different studies show that lowering HbA1c to below 7% reduces microvascular and neuropathic complications of both type 1 and type 2 diabetes mellitus[16,17]. In Saudi Arabia, different studies have shown that the prevalence of diabetic complications was high, affecting patients, families, societies, economics, and productivity[18-21]. For these reasons, good glycemic control should be achieved to prevent complications among diabetic patients, and both family physicians and diabetic patients should collaborate to improve the quality of diabetic care at the primary care level. In addition, family

<table>
<thead>
<tr>
<th>Table 1: Age distribution of diabetic patients (year 2012)</th>
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<tbody>
<tr>
<td><strong>Age groups (years)</strong></td>
</tr>
<tr>
<td>12 - 29</td>
</tr>
<tr>
<td>30 - 44</td>
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<tr>
<td>45 - 59</td>
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<tr>
<td>≥ 60</td>
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<tr>
<td>Total</td>
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<table>
<thead>
<tr>
<th>Table 2: Glycosylated hemoglobin (HbA1c) levels among diabetic patients during 2009</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Glycosylated hemoglobin (HbA1c)</strong></td>
</tr>
<tr>
<td>&lt; 7</td>
</tr>
<tr>
<td>7 - 7.9</td>
</tr>
<tr>
<td>8 - 8.9</td>
</tr>
<tr>
<td>≥ 9</td>
</tr>
<tr>
<td>Total</td>
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</tbody>
</table>

**RESULTS**

The results of this study showed that the percentage of diabetic patients with good blood glucose control (HbA1c < 7) was 39.1% during 2009, which decreased to 34.9% during 2012. Additionally, the percentage of diabetic patients with bad control (HbA1c ≥ 9) was 24.5% during 2009, decreasing to 23.9% during 2012. Table 1 - 3 present the details of HbA1c among diabetic patients during 2009 and 2012, respectively.
physicians should educate diabetic patients about the importance of diet and lifestyle choices in the management of diabetes. Some diabetic patients might require insulin, but are reluctant or hesitant to use it because of fear and misconception. In such cases, counseling diabetic patients about insulin treatment while appreciating their fears may prove beneficial in convincing some patients to use insulin as evidence shows it will be of benefit[24,25]. Diabetic patients should be encouraged to monitor their blood glucose at home, because self monitoring of blood glucose has been shown to help in improving the quality of diabetic care[26-27]. Results of the current study are inconsistent with a previous study carried out in the USA, which showed that glycemic control improved between 1999 and 2004, indicating corresponding improvements over time (i.e., HbA1c < 7% increased from 37% in 1999 - 2000 to 49.7% in 2001 - 2002 and to 55.7% in 2003 - 2004)[28]. Another retrospective cohort study performed in the United Arab Emirates from 2008 to 2010 showed that there is encouraging progress in diabetes care as reflected by the overall improvement in HbA1c[29]. Another retrospective cohort study done in the UK between 2001 and 2007 showed that the introduction of the quality and outcomes framework did not lead to an improvement in the management of patients with type 1 diabetes or to a reduction in the number of patients with type 2 diabetes who had HbA1c levels greater than 10%[30]. Accordingly, it is very important to explore and discuss diabetic blood glucose control during quality improvement strategic planning in our health services in Saudi Arabia as most of the hospitals in our country are planning to be accredited by different internal and external audit agencies specializing in quality assurance.

CONCLUSION

Diabetic patients’ blood glucose control at the primary care level did not improve between 2009 and 2012. Hence, it should be urgently evaluated and monitored to improve the quality of diabetic care and prevent diabetic complications. Further, national cohort studies in different health sectors and regions of Saudi Arabia are recommended.

REFERENCES


Laparoscopic Adrenalectomy Compared with Open Resection for Pheochromocytoma: A Review of 43 Cases

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Department of Anesthesia and Critical Care, G. R Doshi and K. M. Mehta Institute of Kidney Diseases and Research Centre (IKDRC) & Dr. H. L. Trivedi Institute of Transplantation Sciences (ITS), Ahmedabad, Gujarat, India

ABSTRACT

Objective: To summarize the experience of perioperative hemodynamic changes and recovery profile during laparoscopic versus open adrenalectomy for pheochromocytoma.

Design: Retrospective study

Settings: Department of Anesthesia and Critical Care and Department of Urology, IKDRC and ITS, Ahmedabad, India

Subjects: Twenty-eight patients who underwent laparoscopic surgery were compared to fifteen patients who underwent open surgery under general anesthesia.

Interventions: Open or laparoscopic adrenalectomy

Main Outcome Measures: Preoperative medical history and therapy, intraoperative hemodynamic data, blood loss and postoperative outcome

Results: Preoperative therapy with alpha-adrenergic blockers was comparable in both the groups. There was conversion to the open procedure in three patients in the laparoscopic surgery group. A comparison between the open and laparoscopic procedures did not show any significant difference between the maximum intraoperative systolic blood pressure (p = 0.232) and heart rate (p = 0.729) values although intraoperative blood pressure peaks were seen more frequently during laparoscopic adrenalectomy (17 patients [60.7%]) as compared to six (40%) of the open group. The operative time, intraoperative blood transfusion and perioperative morbidity did not differ significantly between the two groups (p > 0.05). 10% of patients in the laparoscopic group required rescue analgesia. Length of postoperative hospital stay was shorter in the laparoscopic group as compared to open surgery and the difference was statistically significant (p = 0.0001).

Conclusion: The intraoperative hemodynamic stability was comparable in open as well as laparoscopic adrenalectomy for pheochromocytoma. Patients who underwent laparoscopic surgery required lesser postoperative analgesia and had a faster postoperative recovery. Therefore, the laparoscopic approach is better.

KEYWORDS: adrenalectomy, laparoscopy, pheochromocytoma

INTRODUCTION

Since the first laparoscopic cholecystectomy performed in 1987[1] laparoscopic surgery has emerged to become an excellent alternative to open procedure with significant advantages like shorter hospitalization time, decreased postoperative morbidity, improved cosmetics and quicker convalescence. Laparoscopic adrenalectomy is recognized as a feasible and preferred approach for surgical removal of pheochromocytoma. However, it has been suggested that catecholamine effects associated with pheochromocytoma render the laparoscopic approach to be more challenging and morbid as compared to the open approach[2]. This study aims to compare hemodynamic changes and the postoperative recovery profiles observed during laparoscopic surgery and open surgery for pheochromocytoma.

SUBJECTS AND METHODS

We retrospectively reviewed the records of 28 patients who underwent unilateral laparoscopic resection of pheochromocytoma between 1995 and 2011 at our institution. Comparisons were made with the records of 15 patients who underwent adrenalectomies using the traditional open transabdominal approach between 1992 and 1999. Patients with bilateral disease and malignant pheochromocytoma on postoperative histopathology report were excluded from the study.
Patient characteristics, preoperative medical status and medications used, intraoperative hemodynamic data and postoperative outcome in the terms of hospital stay and analgesic requirement were compared in both the groups. Preoperative blood pressure control was achieved primarily with the non-selective alpha blocker-phenoxbenzamine followed by ca++ channel blockers if necessary. Phenoxbenzamine was titrated to achieve symptomatic orthostatic hypotension, absence of paroxysms of hypertension and a fall in hematocrit of 5% from baseline. Tachycardia was controlled with beta blockers. On the day of surgery, the morning dose of phenoxybenzamine was given to all patients. All patients received balanced general anaesthesia and analgesic requirement were compared in both the groups.

Surgical Technique: In the laparoscopic group after placing the patient in kidney position (lateral decubitus with kidney bridge raised) all adrenalectomies were performed via a lateral transperitoneal laparoscopic approach using four or five ports. The pneumoperitoneum was produced using carbon dioxide and the intraabdominal pressure was maintained around 12 mmHg.

Open surgery was performed through the transabdominal approach by transverse incision just below the costal margin. Patients were placed in supine position. In most cases the adrenal vein was localized and secured before mobilizing the tumor.

Intraoperative hypertension was defined as a systolic blood pressure (SBP) over 180 mmHg and was treated with nitroglycerine infusion. Hypotension was defined as a SBP less than 90 mmHg and was treated by reducing the concentration of the inhalational anesthetic agent, volume expansion and titrated doses of dopamine or noradrenaline. A heart rate in excess of 110 beats per minute was treated with esmolol 25 mg boluses.

We analyzed the following hemodynamic data: The number of hypertensive or hypotensive episodes, highest and lowest heart rate and use of vasopressors and antihypertensives. The mean tumor size, intraoperative fluid administered, blood loss and duration of surgery (time of intial skin incision to completion of skin closure), were also recorded. Following reversal of neuromuscular blockade, all patients were extubated in the operation room.

Postoperative analgesia was provided in the form of intravenous (IV) dicleofenac sodium (1.5 mg/kg) and IV tramadol (1 – 2 mg/kg) to all patients. Intravenous pentazocine 0.5 mg/kg was used as a rescue analgesic. The duration of the hospital stay (number of days in the hospital after operative procedure) were also recorded.

Statistical analysis
Statistical analysis was performed using SPSS (12.0). Continuous variables were presented as mean ± SD or median (range) as appropriate and were compared using the independent t-test. If the data were not normally distributed, the Mann-Whitney U-test was used. Categorical variables were represented as number (%) and compared using chi-square test. A p-value < 0.05 was considered to be statistically significant.

RESULTS
In both groups, all tumors were successfully removed. However, three patients in the laparoscopic group required conversion to open procedure in view of persistent bleeding. Table 1 summarizes the patients’ demographic information, preoperative co-morbidities and medications. For most variables, there were no differences at baseline between the groups except that a larger number of male patients underwent laparoscopic surgery. Preoperative co-morbidities were comparable between the two groups.

Table 1: Demographics, preoperative comorbidities and medications

<table>
<thead>
<tr>
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<th>Open (N = 15)</th>
<th>Laparoscopic (N = 28)</th>
<th>p-value</th>
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<tr>
<td>Patient Characteristics</td>
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<tr>
<td>Male</td>
<td>7 (46.6)</td>
<td>19 (67.8)</td>
<td>0.176</td>
</tr>
<tr>
<td>Female</td>
<td>8 (53.3)</td>
<td>9 (32.1)</td>
<td>0.176</td>
</tr>
<tr>
<td>Mean age ± SD (Yrs)</td>
<td>33.68 ± 16.45</td>
<td>34.75 ± 14.71</td>
<td>0.858</td>
</tr>
<tr>
<td>Mean weight (kgs)</td>
<td>51.26 ± 13.11</td>
<td>50.21 ± 16.19</td>
<td>0.378</td>
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<tr>
<td>Medical History</td>
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<tr>
<td>Hypertension</td>
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<td>Diabetes mellitus</td>
<td>1 (6.6)</td>
<td>3 (10.7)</td>
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<td>Coronary Artery Disease</td>
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<td>5 (17.8)</td>
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<td>Preoperative medications</td>
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<tr>
<td>Alpha blockers</td>
<td>9 (60)</td>
<td>19 (67.8)</td>
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<tr>
<td>Beta-blocker</td>
<td>5 (33.3)</td>
<td>10 (35.7)</td>
<td>0.876</td>
</tr>
<tr>
<td>Calcium channel</td>
<td>1 (6.6)</td>
<td>4 (14.2)</td>
<td>0.458</td>
</tr>
<tr>
<td>Not treated</td>
<td>5 (33.3)</td>
<td>5 (17.8)</td>
<td>0.252</td>
</tr>
</tbody>
</table>

*p < 0.05

Nine patients from the open group (60%) and 19 patients from the laparoscopic group (68%) received preoperative therapy with alpha-adrenergic blockers. A total of 15 patients required beta blockers and five patients required Ca++channel blockers preoperatively. Five patients in each (open and laparoscopic) group who had a mild form of intermittent hypertension preoperatively did not receive any preoperative treatment. The tumor size and surgical time were similar between the groups. The preoperative baseline systolic and diastolic BP were comparable in the open and laparoscopic groups (p = 0.2). Both groups achieved satisfactory preoperative BP control. As shown in Table 2, hemodynamic parameters did not
More patients in the laparoscopic group received intraoperative antihypertensive treatment than in the open group (60.7% Vs 40% respectively). The severity as well as the number of hypertensive episodes was similar in both the groups. Similarly the intraoperatively in the extremes of high and low heart rates between the two groups. Table 3 shows, there was no significant difference in mean blood pressure at different time intervals during surgery in both the groups. The amount of fluids or blood administered intraoperatively and the duration of surgery were not significantly different between the two groups. Three patients in the laparoscopy group had persistent bleeding and the surgery was converted to open adrenalectomy (Table 4).

To control postoperative pain nine out of 15 patients in the open group required rescue analgesia, but only three patients in the laparoscopic group required rescue analgesia. The difference was statistically significant (p < 0.05). None of the patients in both the groups had any postoperative complications. The mean postoperative hospital stay was shorter (3.5 days) in laparoscopic group than in the open group (7.2 days) (p < 0.05). Three patients in the laparoscopy group and one patient in the open surgery group required antihypertensive treatment postoperatively but in all these patients blood pressure was well controlled with antihypertensive drugs (Table 4).

**DISCUSSION**

Laparoscopic adrenalectomy (LA) has become the gold standard for surgical removal of benign adrenal pathology since it was first described by Gagner and colleagues in 1992[3]. However, adrenal pheochromocytomas were considered a relative contraindication to laparoscopy due to increased risk of cardiovascular complications related to intraoperative catecholamine surges and preoperative uncertainty about malignancy. But now there is

<table>
<thead>
<tr>
<th>Table 2: Preoperative hemodynamic variables</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hemodynamic parameters</strong></td>
</tr>
<tr>
<td>Mean preoperative blood pressure (mmHg)</td>
</tr>
<tr>
<td>Highest blood pressure (mmHg)</td>
</tr>
<tr>
<td>Hypertensive episodes† SBP ≥ 180 mmHg</td>
</tr>
<tr>
<td>Lowest blood pressure (mmHg)</td>
</tr>
<tr>
<td>Highest Heart rate (bpm)</td>
</tr>
<tr>
<td>Tachycardic episodes† Heart rate ≥ 110 bpm</td>
</tr>
<tr>
<td>Lowest heart rate (bpm)</td>
</tr>
</tbody>
</table>

* p < 0.05; SBP = systolic blood pressure; † Median number of episodes in one patient with the range in parentheses; p-value based on the Mann-Whitney U test.

<table>
<thead>
<tr>
<th>Table 3: Mean blood pressure</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Time intervals</strong></td>
</tr>
<tr>
<td>Before induction</td>
</tr>
<tr>
<td>After intubation</td>
</tr>
<tr>
<td>During pneumoperitoneum</td>
</tr>
<tr>
<td>Tumor manipulation</td>
</tr>
<tr>
<td>Tumor removal</td>
</tr>
</tbody>
</table>

* Systolic and diastolic blood pressure presented as the mean ± standard deviation; p-value based on the t test.

<table>
<thead>
<tr>
<th>Table 4: Intraoperative and postoperative data</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Variables</strong></td>
</tr>
<tr>
<td>Tumor size (cm)</td>
</tr>
<tr>
<td>Intraoperative fluids (liters)</td>
</tr>
<tr>
<td>Blood transfusion (ml)</td>
</tr>
<tr>
<td>Conversion to open. n (%)</td>
</tr>
<tr>
<td>Surgical time (minutes)</td>
</tr>
<tr>
<td>Requirement of rescue analgesia. n (%)</td>
</tr>
<tr>
<td>Hospital stay (days)</td>
</tr>
<tr>
<td>Perioperative complications. n (%)</td>
</tr>
<tr>
<td>Requirement of postoperative antihypertensives. n (%)</td>
</tr>
</tbody>
</table>

* p < 0.0001 = highly significant
emerging evidence that LA for pheochromocytoma is safe and can achieve the same benefits as open for benign adrenal pathology\cite{10, 11, 12, 13, 14}.

The major concern in surgery for pheochromocytoma is the possibility of hypertensive crisis due to sudden and massive release of catecholamines from the tumor. It could be triggered either by induction of anesthesia or subsequent manipulation and retraction of the adrenal gland. Laparoscopy could aggravate this situation further as intra-abdominal insufflation alone can cause an increase in serum catecholamines\cite{7}. Also, pneumoperitoneum with CO$_2$ may lead to hypercapnia and acidosis which are known stimuli for catecholamine secretion and hypertension. In addition, laparoscopic surgery exposes the adrenal gland to constant pressure from the pneumoperitoneum during surgical retraction and dissection without physically handling the adrenal gland. During an open surgery there is no external pressure from the pneumoperitoneum and tumor handling is intermittent. On this basis, it might be expected that laparoscopic adrenalectomy would be associated with severe and persistent intraoperative hypertension and tachycardia, whereas open adrenalectomy would present a more stable hemodynamics, with brisk episodic hypertensive responses coincident with tumor manipulation.

In the current study, we were unable to demonstrate a statistically significant difference in the intraoperative hemodynamic profiles between laparoscopic and open approach for pheochromocytoma resection. The number of intraoperative hypertensive and hypotensive episodes was comparable in both groups. Although mean BP and the need for intraoperative antihypertensive agent was more in laparoscopic group prior to tumor removal. We did not observe long-lasting hypotension after tumor removal requiring vasopressor support. However, there was no difference in surgical outcome\cite{13}. In our study, all patients were treated preoperatively with phenoxybenzamine which may be one of the reasons for intraoperative hemodynamic stability but in contrast to above study we did not observe long-lasting hypotension after tumor removal.

Does this mean that all properly selected and pharmacologically well-prepared patients can undergo laparoscopic removal of pheochromocytoma safely? Sprung reported 34 patients (20 open, 14 laparoscopic) in which one patient who was to have a laparoscopic procedure and preoperatively medicated with Ca$^{++}$...
channel blocker, developed severe hypertension (320/220 mmHg) and tachycardia (140 bpm) with the attempted creation of the pneumoperitoneum, which was then abandoned. An open procedure was subsequently performed without problems.\textsuperscript{8} Tautzin-Fin \textit{et al}. also reported a patient with pheochromocytoma who has been prepared preoperatively with an α-blocker who developed severe hypertension and pulmonary edema following peritoneal insufflation.\textsuperscript{14} Subsequent open surgical adrenalectomy was carried out uneventfully. We did not require conversion to open surgery for severe hemodynamic changes but three cases required open surgery for surgical bleeding. This suggests that both anesthesia and surgical team should be prepared for conversion to open surgery, if there are any hemodynamic changes with the laparoscopic approach or any surgical complications.

Operative time and blood loss during laparoscopic surgery depend on surgeon’s experience. In most published series, operative time is longer for laparoscopic approach compared to open approach, mainly because of the initial learning curve which tends to decrease with time. We did not observe difference in our series probably because all our tumors were unilateral, < 8 cm in size and the procedures were performed by the surgeons who were well experienced in laparoscopic urosurgery. Similar results were observed in other reports.\textsuperscript{15-17}

Regarding postoperative recovery profile, our data demonstrate that patients required a shorter hospital stay and lesser analgesics with the laparoscopic approach as compared to the open approach. This is an important clinical result. The median hospital stay was 3 - 5 days in laparoscopic group compared to 6 - 8 days in open group which is identical to other studies.\textsuperscript{8,18} Similarly, postoperative rescue analgesic requirement was significantly less in the laparoscopic group.

**CONCLUSION**

From our study, we can conclude that laparoscopic removal of pheochromocytoma is not associated with enhanced risk of hemodynamic instability and offers all benefits of minimally invasive surgery in terms of faster recovery and less analgesic requirement. The limitation of our study is the small number of subjects included. A large case series is needed to show the clear benefits of laparoscopic approach for adrenalectomy.

**REFERENCES**

Original Article

Infant Formula in Saudi Arabia: A Cross Sectional Survey

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ABSTRACT

Objectives: To measure formula milk utilization and practices among mothers in Saudi Arabia including reasons for formula or mixed milk feeding, reasons for choosing a specific brand and number of formula brand changes and reasons for change

Design: Cross sectional survey

Setting: Shopping centers in Riyadh

Subjects: Women with children below three years of age

Main Outcome Measures: Rate and reason for mixed feeding, type of formula brand chosen, number and reasons for formula brand change, maternal attitude toward open market and maternal belief of pediatrician’s knowledge of formula brands

Results: Majority (80%) of mothers interviewed utilized either a mixed or exclusive formula feeding. Thirty-one percent attributed formula milk feeding due to lactation insufficiency. The most common factor behind choosing specific formula milk was doctor’s advice (40.7%). Forty percent had at least tried two different formula brands in the first year of life. The major reasons for changing a specific brand of formula were colic and gas (32%), constipation (23.6%) and gastroesophageal reflux (20.4%).

Conclusion: A huge diversity of formula brand utilization, change and confusion among Saudi mothers was observed. Major efforts are urgently required to rectify a national crisis in Saudi markets.

KEYWORDS: formula milk, practice, GI intolerance

INTRODUCTION

Breastfeeding is an unequalled method of providing ideal food for healthy growth and development in infants; evidence suggests a decreased incidence of gastrointestinal illnesses in infants who were exclusively breastfed for six months compared to those who had mixed feeding[1]. As a result, the World Health Organization (WHO) recommends exclusive breastfeeding in the first six months of life to achieve optimal growth, development and health. WHO recognized declining rates of exclusive breast feeding after four months of age and prioritized to identify constraints to exclusive breastfeeding in different geographical and cultural settings, and develop appropriate and effective interventions to deal with these barriers and their consequences[2].

Variables that may influence breastfeeding include race, maternal age, maternal employment, level of education of parents, socio-economic status, insufficient milk supply, infant health problems, maternal obesity, smoking, parity, method of delivery, maternal interest and other related factors[3,4].

Commercially available infant formulas serve, as best alternatives to human milk when breast-feeding is not possible. At present, a broad range of artificial formulas have been developed for feeding infants. The WHO published the international code of marketing of infant formula and other products used as breast-milk substitutes to promote exclusive breast feeding and ensure the proper use of breast milk substitutes[5]. WHO recommends in-country monitoring and auditing for its international code of marketing breast milk substitutes, as there are many examples of non-compliance including in Saudi Arabia[6,7].

In Saudi Arabia, published regional and national studies have shown that prevalence of exclusive breastfeeding is extremely low. Less than 10% of Saudi mothers exclusively breast feed their infants up to six months of age. Partial breastfeeding or exclusive formula feeding are the trend for feeding in the first six months of life[8-19].

These low rates for exclusive breast feeding in addition to the lack of strict regulations for registration and marketing from the Saudi Food and
Drug Agency (SFDA) resulted in more than 20 brands of milk formula being available in stores for newborn infants. This is in contrast to the current situation in well-industrialized countries offering less than five brands per country. The wide range of available formulas can be confusing and overwhelming for parents and physicians and it makes it difficult to ensure quality and safety of available products. This study was conducted to describe formula milk practices among mothers in Saudi Arabia including reasons for formula or mixed feeding, reasons for choosing a specific brand and number of formula brands changes and reasons for change.

MATERIAL AND METHODS

A cross-sectional survey was conducted in shopping centers in Riyadh from October 2011 up to February 2012 among mothers in Saudi Arabia. The target study population was women with children less than three years of age. Data was collected utilizing a structured questionnaire in a face to face interview. A clear explanation of the study’s purpose and verbal consent to participate in the study was taken from all participants prior to filling questionnaires.

Baseline characteristics such as age, nationality, educational level, job, infant’s age were collected. Questions regarding targeted measured outcomes such as rates of mixed feeding, reasons for mixed feeding, formula brand chosen, number and reason of any change of formula brand during the first two years of life, maternal attitude / opinion toward the open formula market, and maternal belief of pediatricians’ knowledge of formula brands were obtained.

Mothers were provided with multiple choices for targeted outcome measures. A direct question as to whether the participants believed that the open infant formula market status in Saudi Arabia was a positive factor for them or not, was administered.

As pediatricians are frequently asked as to what they consider the “best” formula brand” choice for infants participants were asked to express whether they believed pediatricians are well aware of the “best” formula for their babies.

Data were presented as mean and standard deviation for normally distributed continuous data and median and its inter-quartile range (IQR). Categorical data were presented as numbers and percentages. We chose a convenient sample size for our study.

RESULTS

We interviewed 436 mothers during the study period. Majority of interviewed participants were above 20 years of age, resided in Riyadh and were Saudi citizens. More than 50% of them had a university level education and only 30% were working mothers. Majority (80%) of mothers interviewed utilized either a mixed or exclusive formula feeding (Table 1).

<table>
<thead>
<tr>
<th>Variables</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years</td>
<td></td>
</tr>
<tr>
<td>&lt; 20</td>
<td>20 (4.6)</td>
</tr>
<tr>
<td>20-35</td>
<td>325 (74.5)</td>
</tr>
<tr>
<td>&gt; 35</td>
<td>20 (4.6)</td>
</tr>
<tr>
<td>Nationality</td>
<td></td>
</tr>
<tr>
<td>Saudi</td>
<td>358 (82.1)</td>
</tr>
<tr>
<td>Non-Saudi</td>
<td>76 (17.4)</td>
</tr>
<tr>
<td>Residency</td>
<td></td>
</tr>
<tr>
<td>Riyadh</td>
<td>378 (88.8)</td>
</tr>
<tr>
<td>Other cities</td>
<td>24 (5.5)</td>
</tr>
<tr>
<td>Level of education</td>
<td></td>
</tr>
<tr>
<td>Less than high school</td>
<td>38 (8.7)</td>
</tr>
<tr>
<td>High school</td>
<td>84 (19.3)</td>
</tr>
<tr>
<td>Academic</td>
<td>219 (50.2)</td>
</tr>
<tr>
<td>Job</td>
<td></td>
</tr>
<tr>
<td>Housewife</td>
<td>302 (69.3)</td>
</tr>
<tr>
<td>Working</td>
<td>125 (28.7)</td>
</tr>
<tr>
<td>Infant age</td>
<td></td>
</tr>
<tr>
<td>&lt; 6 months</td>
<td>83 (19)</td>
</tr>
<tr>
<td>6 months – 1 year</td>
<td>140 (32.1)</td>
</tr>
<tr>
<td>1 year – 2 years</td>
<td>83 (19)</td>
</tr>
<tr>
<td>&gt; 2 years</td>
<td>42 (10.3)</td>
</tr>
</tbody>
</table>

About one third of interviewed mothers expressed lactation insufficiency as the major reason for choosing to formula feed. Other reasons such as maternal health condition, having to go back to work or study, infant’s inability to latch were expressed as barriers to exclusive breast feeding (Fig. 1).

![Fig 1: Reported reasons for formula feeding](image)

Doctor’s advice (40%), formula available free of charge at post-natal ward (22%), previous experience with another child (13.6%) and friend’s advice (12.5%) were the most important factors influencing maternal choice of a specific formula brand (Fig. 2).
is a positive feature in their country; on the other hand a similar proportion believed it was negative and confusing in the care of their infants. Majority of interviewed mothers believed that a pediatrician does have the knowledge of the best formula to choose for their offspring. Only 20% believed that they don’t (Table 2).

**DISCUSSION**

Human milk is the ideal nutrition and is sufficient to support growth and development for most growing infants during the first six months and it is impossible to imitate. As a result, human milk should be the standard and exclusive infant feeding during the first months of life[16]. The low rates of exclusive breast feeding in Saudi Arabia has led to a chaos in the Saudi formula market and as a result great maternal confusion regarding the best way to feed infants if they chose not to breast feed. Our study showed that a significant number of mothers change the brand of their chosen formula more than two times. Most mothers attribute gastrointestinal symptoms of their infant to the formula and therefore tend to change it as an attempt to rectify those symptoms without a solid scientific ground.

The rates of exclusive breast feeding in Saudi Arabia are still at alarming low rates compared to international standards[15]. In a previous unpublished study of our team, the easy and widespread availability of formula was indicated as a limiting factor to breast feeding by almost half of our interviewed participants. Saudi mothers are bombarded with the availability of more than 20 brands of formula in the market. This open market policy could have given a false impression to our mothers that formula feeding is an acceptable alternative to breast feeding.

Our study has scientifically addressed methods of choosing a specific formula brand for the first time. We have observed that most mothers chose their formula milk brand based on doctor’s advice or formula brand availability in the postnatal ward. Although this shows the degree of trust our mothers have in their pediatricians, this method is not supported scientifically. The medical literature lacks prospective studies that investigate different formula brands in a head to head comparison with a solid outcome such as gastrointestinal intolerance, growth parameters, and future cognitive function. Two randomized controlled trials comparing the three most widely available infant formulas in United States with regard to gastrointestinal tolerance were conducted. Studies conducted in South America and Taiwan found that one brand was superior to the others. The small number of infant formula brands tested and fund by industry (same company
manufacturing the endorsed brand) hampered their results\cite{17,18}. We do believe that such an investigation is required in communities with very low rates of exclusive breast-feeding to guide maternal choice and to assess whether different formula brands are tolerated differently.

The latest nationwide nutritional survey performed as part of the Health Profile for Saudi Children and Adolescents Projects to evaluate trends in infant nutrition in Saudi Arabia and the degree of compliance with WHO recommendations showed that 51.4\% of infants were introduced to formula milk by the age of one month and 90\% of them by the age of six months, which is very far with even the most conservative WHO recommendations of exclusive breastfeeding for 4 - 6 months\cite{19}. Other reports from other Gulf Cooperation Council (GCC) countries reported similar rates\cite{20,21}.

Regardless of the reason that lead parents to start formula feeding, physicians should help them choose the best formula for their baby, if breast feeding is not applicable, and help them to change formula, if needed according to the nature and severity of symptoms the infants might have\cite{21}. More data addressing the role of different formula brands or specialized formula such as soy or partially hydrolyzed ones is needed to address the value of these types of milk in the treatment or prevention of infantile colic and constipation.

Our study is the first in the region to address such a debatable issue in infant's nutrition. Our results highlight the importance of a nationwide campaign to enhance women education with regard to the benefits of breast feeding starting in school and prenatal classes. It is also quite important for legislative bodies to apply strict registration requirements for infant formulas and implement strategies to ensure compliance of available formula with international standards and safety of these products regarding bacterial and chemical contamination.

We do recognize that our data were collected in Riyadh in a limited sample of mothers and that our results may not reflect the status nationwide.

CONCLUSION
A huge diversity of formula brand utilization, change and confusion among Saudi mothers was observed. Major efforts are urgently required to rectify a national crisis in the Saudi market.

ACKNOWLEDGEMENT
We extend our sincere appreciation to the Deanship of Scientific Research at King Saud University for funding this project through Research Group project # RGB-VPP-248.

REFERENCES


Is there a Benefit of Adding Conservative Treatment Modalities on Trospium Chloride Treatment in Overactive Bladder Syndrome

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Kuwait Medical Journal 2014; 46 (4): 333 - 336

ABSTRACT

Objective: To evaluate whether conservative treatment modalities of overactive bladder syndrome combined with trospium chloride increases the success rate when compared with trospium chloride alone

Design: Retrospective study

Setting: Department of Obstetrics and Gynecology, Istanbul Faculty of Medicine, Istanbul University, Istanbul, Turkey

Subjects: The data of 3200 patients, who were admitted with complaint of urinary incontinence, were analyzed and 270 patients treated with trospium chloride were included. Thirty-five patients were treated only with trospium chloride; 14 who continued medical treatment for at least six months were classified as Group 1. 235 patients were treated with trospium chloride in combination with other modalities; 126 who continued medical treatment for at least six months were classified as Group 2.

Intervention: Treatment with trospium chloride alone or with other modalities.

Main Outcome Measures: The 3-day bladder diaries of the two groups were compared before treatment and three and six months after treatment.

Results: There was a statistically significant decrease in the mean number of diurnal micturition and incontinence episodes in Group 1 before and after treatment (p = 0.017 and 0.02 respectively). In Group 2, there was a statistically significant decrease in the mean number of urgency, urinary incontinence episodes, diurnal, and nocturnal micturition (p < 0.001, < 0.001, < 0.001 and 0.002 respectively). We found no statistically significant difference between the two groups after the treatment.

Conclusions: Addition of conservative treatment modalities to trospium chloride in overactive bladder did not lead to a significant difference in results.

INTRODUCTION

Overactive bladder (OAB) is defined as a symptom complex of urgency, frequency, and nocturia with or without urinary incontinence[1-2]. The initial treatment of OAB includes lifestyle interventions, bladder training, anticholinergic treatment, and electrical stimulation modalities[3]. Anticholinergic drugs are the mainstay of treatment of OAB with grade A recommendation by the International Continence Society[1-3]. Trospium chloride, a quaternary amine, is an anticholinergic agent with predominantly peripheral non-selective antimuscarinic activity which does not have any central nervous system effects[4]. It antagonizes the effect of acetylcholine on cholinergic nerves and exhibits parasympatholytic action by decreasing detrusor muscle tone and uncontrolled detrusor muscle contractions that can cause urgency, frequency, and urinary incontinence.

The aim of this study was to evaluate whether the addition of conservative treatment to trospium chloride treatment increased the success rate when compared with trospium chloride treatment alone.

MATERIAL AND METHODS

The records of all patients admitted to the Department of Urogynecology with the complaint of urinary incontinence were analyzed retrospectively. The study was approved by the local ethics committee.
Among 3200 patients whose data were analyzed, 270 OAB patients who were treated with trospium chloride and did not undergo anti-incontinence surgery were included in the study. Patients who discontinued their medication before duration of six months were excluded from the study.

Among these 270 patients, 35 were treated only with trospium chloride and 235 with trospium chloride combined with at least one of the conservative treatment modalities including bladder training, pelvic floor muscle exercises, and biofeedback. Thirty-five patients were treated only with trospium chloride. Fourteen patients out of these selected patients who continued medical treatment for at least six months were classified as Group 1. Two hundred thirty-five patients were treated with trospium chloride in combination with other modalities. One hundred twenty-six out of these who continued medical treatment at least for six months were classified as Group 2. The two groups are presented in Fig. 1.

The 3-day bladder diaries of Group 1 patients were compared with Group 2 before treatment, and three months and six months after treatment. As a matter of fact, the mean number of diurnal micturition was found to be significantly higher in Group 2; thus Group 1 and 2 were not homogenous, which was due to our tendency to add conservative modalities to patients with more severe symptoms. This is a limitation of our study.

Statistical analysis was performed with Statistical Package for the Social Sciences (SPSS) 11.0 software (SPSS Inc. Chicago, Illinois) for Windows. Data were expressed as mean ± standard deviation. For normally distributed data, all univariate comparisons were performed using paired samples t test. Mann Whitney U test was used for data which didn't show normal distribution after the assumption of normality was tested. A p-value less than 0.05 was considered to be statistically significant.

RESULTS

The mean age of the patients was 47.29 ± 11.96 (range 28 - 72) for Group 1 and 50.10 ± 8.63 (range 28 - 73) for Group 2.

The results of the 3-day bladder diary before and after treatment are summarized in Table 1. Before treatment, the mean number of diurnal micturition

<table>
<thead>
<tr>
<th>Bladder diary variables</th>
<th>Group 1 (n = 14)</th>
<th>Group 2 (n = 126)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urgency episodes</td>
<td>19 ± 2.5</td>
<td>2.8 ± 3.9</td>
<td>0.628</td>
</tr>
<tr>
<td>Incontinence episodes</td>
<td>1.2 ± 1.5</td>
<td>1.7 ± 2.4</td>
<td>0.558</td>
</tr>
<tr>
<td>Diurnal micturition</td>
<td>7.2 ± 2.4</td>
<td>9.5 ± 3.5</td>
<td>0.006</td>
</tr>
<tr>
<td>Nocturia</td>
<td>0.3 ± 0.4</td>
<td>0.9 ± 1.0</td>
<td>0.072</td>
</tr>
<tr>
<td>3 months after treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urgency episodes</td>
<td>1.0 ± 1.7</td>
<td>0.7 ± 1.6</td>
<td>0.916</td>
</tr>
<tr>
<td>Incontinence episodes</td>
<td>0.5 ± 0.9</td>
<td>0.3 ± 0.6</td>
<td>0.345</td>
</tr>
<tr>
<td>Diurnal micturition</td>
<td>5.5 ± 2.1</td>
<td>6.5 ± 2.1</td>
<td>0.414</td>
</tr>
<tr>
<td>Nocturia</td>
<td>0.6 ± 0.9</td>
<td>0.6 ± 0.8</td>
<td>0.779</td>
</tr>
<tr>
<td>6 months after treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urgency episodes</td>
<td>0.7 ± 1.9</td>
<td>0.8 ± 1.7</td>
<td>0.419</td>
</tr>
<tr>
<td>Incontinence episodes</td>
<td>0.2 ± 0.2</td>
<td>0.3 ± 0.8</td>
<td>0.375</td>
</tr>
<tr>
<td>Diurnal micturition</td>
<td>5.7 ± 1.6</td>
<td>6.2 ± 1.3</td>
<td>0.169</td>
</tr>
<tr>
<td>Nocturia</td>
<td>0.1 ± 0.2</td>
<td>0.5 ± 0.6</td>
<td>0.646</td>
</tr>
</tbody>
</table>
medications are the initial treatment of choice for muscle training, bladder training, and anticholinergic drugs.

The bladder may be dysfunctional and/or deformation of bladder wall may be damaged, nerve supply of the syndrome is not clear but there are several theories; drugs often use concomitant medications which can limit the success of OAB increases with age[2-6]. The incidence pathway complete symptomatic relief is not usually achieved with only one intervention. The incidence of OAB syndrome does not seem to have only one cause[7-8]. In our department, each case is evaluated and appropriate antimuscarinic agent is chosen when indicated. This study includes the patients treated with trospium chloride.

SOLAR Study Group[9] compared the efficacy of solifenacin alone and solifenacin with bladder training. They found that the decrease in the number of micturition was statistically significantly higher in the group which received combined therapy. They did not find any statistically significant difference between the groups for urgency and urge incontinence episodes. They concluded that patients with high micturition frequency may benefit from using bladder training in addition to medical treatment.

Song et al[10] treated their OAB patients with tolterodine, bladder training or with the combination of both. They found that the group which received combination therapy showed greater improvements in frequency and urgency symptoms than did the patients in bladder training group. They also found that the patients who received tolterodine with or without bladder training showed significantly more improvement in urgency symptoms than did the patients in bladder training only group. They concluded that for the treatment of OAB, tolterodine may be added to the bladder training if the main symptom is frequency and urgency.

Schneider et al[10] investigated whether gender, age or lifestyle factors affect responses to darifenacin in OAB. They proposed in their report that an optimal therapeutic approach to OAB involves both medical treatment and lifestyle advice.

Our study was conducted to see whether combination of trospium chloride and conservative treatment modalities increase the success rate of the treatment. Our results showed that trospium chloride, alone, decreased the number of incontinence episodes and urinary frequency in OAB patients. The mean number of urgency episodes and nocturnal micturition decreased in both groups; however, the difference was not statistically significant between both groups after treatment.

DISCUSSION
OAB is characterized by urgency, frequency, nocturia with or without incontinence episodes. 12-17% of adults experience OAB[9]. The cause of this syndrome is not clear but there are several theories; bladder wall may be damaged, nerve supply of the bladder may be dysfunctional and/or deformation of pelvic floor may cause lower urinary tract symptoms. Conservative treatment modalities such as pelvic floor muscle training, bladder training, and anticholinergic medications are the initial treatment of choice for women suffering from OAB[11]. As the pathophysiology of OAB syndrome does not seem to have only one pathway complete symptomatic relief is not usually achieved with only one intervention. The incidence of OAB increases with age[3-4] and affected subjects often use concomitant medications which can limit the use and modify the effects of the anticholinergic drugs[3]. This is another reason why medical therapy does not cure every patient. Due to the complexity of the syndrome, anticholinergic agents may work synergistically with conservative treatment modalities. A combination of both is a safe and effective treatment for OAB and can permit discontinuation of the drug therapy in the follow-up.

Trospium chloride is one of the antimuscarinic agents and has benefits with regard to efficacy and tolerability because it is minimally metabolized by hepatic cytochrome P450 and is actively excreted in the urine[3-8]. In our department, each case is evaluated and appropriate antimuscarinic agent is chosen when indicated. This study includes the patients treated with trospium chloride.
A second limitation of our study is the difference in the number of patients between two groups. Our study is a retrospective research and our data reveal that among our patients, 14 met the inclusion criteria for Group 1 and 126 patients met the inclusion criteria for Group 2.

The last limitation is the fact that considering Group 2 patients, we did not state the number of patients who received each conservative treatment modality individually, nor did we specify the patients who received a combination of these conservative treatment modalities. The reason was that creating subgroups within Group 2, which included 126 patients, would result in multiple small groups and lead to insignificant statistical analysis.

CONCLUSION

Our research did not show any benefit of adding conservative treatment modalities to medical treatment, but as Group 1 and Group 2 were not homogenous we cannot conclude that combined therapy is unnecessary. The literature shows that combined therapy is efficacious in selected patients.

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The authors have no conflict of interests.

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Case Report

Moyamoya Syndrome in Monozygotic Twins with Down Syndrome

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ABSTRACT

We report a case of a pair of monozygotic twins with Down syndrome (DS) who developed Moyamoya syndrome (MS). The 1st twin presented at 15 months of age with focal seizure and hemiparesis. She was found to have bilateral attenuation of the supraclinoid internal carotid arteries (ICAs) and both middle cerebral arteries (MCAs) on magnetic resonant angiography (MRA). She had a bilateral revascularization procedure (encephaloduroarteriosynangiosis “EDAS”) and she is doing well, although the hemiparesis persists. The 2nd twin was neurologically normal but she had a screening MRA which showed stenosis of both MCAs. She too had a bilateral EDAS operation and is doing well.

We believe this to be the first reported case of monozygotic twins with DS and MS.

KEY WORDS: Down syndrome, monozygotic twins, Moyamoya syndrome

INTRODUCTION

The moyamoya arteriopathy was first described in a case report from Japan by Takeuchi and Shimizu in 1957. Moyamoya disease is a chronic, occlusive, cerebrovascular disorder of unknown pathogenesis that is characterized by progressive stenosis of both supraclinoid internal cerebral arteries (ICAs), with concomitant formation of tortuous arterial collateral vessels at the base of the brain, which reconstitute distal branches of the cerebral circulation [1]. The term moyamoya “puff of smoke” is a description of these collaterals as they are seen on angiography.

The age at onset of symptoms of Moyamoya disease shows a bimodal distribution with a peak in the first decade at age five years which is associated with ischemic stroke, and a peak in the 4th decade at age 34 years which is associated with hemorrhagic strokes. Hemiparesis is the most common symptom of presentation in both groups [1]. The term Moyamoya “syndrome” (MS) rather than disease is used when the arterial changes are associated with other disorders like neurofibromatosis, tuberous sclerosis, sickle cell disease or down syndrome (DS).

There have been 47 previous cases of MS in association with DS reported in the world literature (26 cases in the English literature) to date, but none in monozygotic twins with DS [1].

CASE REPORTS

Case 1

FMM is the 1st identical twin with a birth weight 1.9 kilogram, born pre-term (35 weeks of gestation) to 1st degree cousin parents. The mother was 23 years old. Genetic study of both twins showed trisomy 21 (karyotype 47, XX, +21) and the parents were normal. Histocompatibility antigen locus (HLA) typing was not done.

She was doing well till the age of 15 months, when she had status epilepticus for one hour with right sided hemiparesis but other systemic examination was normal including her blood pressure.

Full blood count, thyroid function tests, sickling test, Hb electrophoresis, electrocardiogram and echocardiogram were all normal. Magnetic resonance imaging (MRI) brain revealed subacute left fronto-cortical infarct with laminar necrosis and right chronic parietal infarct (Fig. 1). MRA showed bilateral attenuation of the supraclinoid ICAs and both MCAs.
with multiple collateral cerebral vessels in the base of the brain (Fig. 2). Full investigations to rule out possible associated medical conditions were negative.

Encephaloduroarteriosynangiosis (EDAS) revascularization procedures of the left MCA and five months later of the right MCA territories were done. On follow-up, one year later, there was no marked neurological improvement but she did not have further fits.

Case 2

AMM was the 2nd identical twin whose birth weight was 1.59 kilogram. Antenatal ultrasound showed suspected duodenal atresia. After birth, laparotomy revealed annular pancreas which was managed with ducto-duodenostomy operation. She was also found to have congenital hypothyroidism and she was kept on thyroxin therapy. On follow-up, she was doing well and neurologically free. At the age of 15 months her twin sister was diagnosed to have MS. She was screened with MRI brain and MRA. MRI brain revealed partial agenesis of the corpus callosum (Fig. 3) and MRA showed stenosis of the right MCA at its origin and narrowing of the left middle cerebral artery (MCA) but no collaterals (Fig. 4). A repeat MRA a year later revealed complete occlusion of the right MCA and its peripheral branches, complete occlusion of the proximal left MCA with identification of its peripheral branches and the development of multiple collaterals (Fig. 5). Full investigations to rule out possible associated medical conditions were negative.

Left-sided EDAS surgery and eight months later right-sided EDAS operations were done. She was followed up for one year and she continued to be neurologically free.
The exact etiology of Moyamoya disease is unknown. It is not clear whether it is congenital or acquired. Some genetic predisposition is apparent because it is familial 10% of the time. The disease may be hereditary and multifactorial. A recent Japanese study demonstrated that familial Moyamoya disease is autosomal dominant with reduced penetrance\[^2\].

A genetic component for the etiology of such cases is suggested by the occasional familial occurrence and the presence of DS with MS is still not understood. The fact that so many children with DS have cardiac structural anomalies suggests that the genetic defect in DS may also lead to disturbance in the formation or growth of vascular structures elsewhere in the body. Patients with DS have been noted to have an increased number of retinal vessels, compared with gender and age-matched normal control subjects. These vessels are said to have a “smoke-like” pattern, with frequent early branching, and this observation tends to support the postulation that there is a general vascular dysplasia in DS\[^4\].

The association of DS with MS is still not understood. The fact that so many children with DS have cardiac structural anomalies suggests that the genetic defect in DS may also lead to disturbance in the formation or growth of vascular structures elsewhere in the body. Patients with DS have been noted to have an increased number of retinal vessels, compared with gender and age-matched normal control subjects. These vessels are said to have a “smoke-like” pattern, with frequent early branching, and this observation tends to support the postulation that there is a general vascular dysplasia in DS\[^4\].

MS is a progressive disease with cumulative morbidity and this progression can be arrested with surgical treatment. The patients do require long-term aspirin therapy postoperatively\[^3\]. The most widely used procedure for surgical treatment of MS among children is probably EDAS. A branch of the superficial temporal artery is dissected intact from the scalp, and this healthy vessel is then sutured to the pial surface of the brain after a craniotomy is performed. The vessel is left intact; once the bone is replaced, the vessel passes under the skull proximally to contact the brain and then comes back out of the scalp distally. Subsequent ingrowth of blood vessels from the donor vessel and dural margins occurs over several months after the operation and results in collateral blood flow to the ischemic brain tissue. After surgery, additional strokes do not occur, and good functional outcomes can be anticipated for > 50% of surgically treated patients\[^1\].

The prognosis of patients with MS seems to depend on neurologic status at the time of diagnosis and surgical therapy\[^5\]. It seems that untreated children experience continued, progressive, neurologic decline secondary to increasing stroke burden. Children with large unilateral or bilateral infarctions involving the dominant hemisphere, that have occurred at an early age, frequently are severely developmentally delayed and may have chronic seizure disorders. In contrast, patients with multiple small infarctions or a single large infarction in the non-dominant hemisphere may have a satisfactory long-term prognosis if additional strokes can be prevented. So, it is recommended that revascularization surgery be performed early in the course of the disease before the development of multiple infarctions\[^5\].

**CONCLUSIONS**

The structural defects associated with DS might create a vulnerability for the development of ischemic cerebrovascular disease and, secondarily, MS. The presence of MS should be considered in the evaluation of patients with DS who present with transient ischemic attack-like symptoms. We support the prophylactic screening of patients with DS for MS with MRI / MRA.

**REFERENCES**

Case Report

Kikuchi-Fujimoto Disease

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ABSTRACT

Kikuchi-Fujimoto disease (KFD) manifests in most cases as unilateral cervical lymphadenopathy, with or without accompanying fever. The disease mainly affects young women and has a self-limited course. It should be included in the differential diagnosis in suspected cases of viral infections, tuberculosis, reactive lymphadenitis, systemic lupus erythematosus and metastatic diseases. It can be histologically confused with lymphoma. The disease is benign and self-limiting and an excisional biopsy of an affected lymph node is necessary for diagnosis. There is no specific therapy.

KEY WORDS: cervical lymphadenopathy, fever, histiocytic lymphadenitis, necrotizing

INTRODUCTION

Kikuchi-Fujimoto disease (KFD) is an extremely rare disease having worldwide distribution with higher prevalence amongst Japanese and other Asiatic individuals. It is mainly a disease of the young adult (mean age 20-30 years) and the female to male ratio of occurrence is 4:1[1,2]. KFD should be included in the differential diagnosis of suspected cases of viral infections, tuberculosis (TB), reactive lymphadenitis, systemic lupus erythematosus (SLE) and metastatic diseases. It can be histologically confused with lymphoma. An excisional biopsy from an affected lymph node is necessary for diagnosis[3]. The disease is benign and self-limited[4,5]. However, recurrent and even fatal cases have been reported in the literature[6,7].

Rheumatological diseases such as SLE and Sjogren’s syndrome may be associated with KFD, and therefore, investigation of the presence of these diseases and patient follow-up are necessary[8].

CASE REPORT

A 29-year-old female, was admitted to the infectious disease hospital with complaints of fever, painful and tender swelling in both sides of her neck, rigors, fatigue, malaise, myalgias, arthralgias, and a five-kg weight loss over previous three weeks. She had received various courses of antibiotics without improvement. Her temperature rose progressively to as high as 40 °C at night and was associated with night sweats and chills. She did not smoke or use illicit drugs, and did not consume alcohol. There was no recent history of insect bites, exposure to cat or other animals, cough, abdominal or back pain, and she took no medication.

Upon examination, the patient appeared ill; oral temperature was 39 °C. Physical examination revealed a supple neck with a chain of prominent, tender lymph nodes, 0.5 - 3 cm in diameter that extended from just below the right ear to the supraclavicular region, with a single node, 2.5 cm in diameter, in the right cervical region, and shotty left cervical nodes. There was no sign of splenomegaly or hepatomegaly.

Abnormal laboratory studies were a Westergren erythrocyte sedimentation rate (ESR) 90 mm/hr, CRP 10 mg/dl, Hb 11.1 g/dl; Hct 30%, WBC 3.3x 10^9/l, (46% segmented neutrophils, 40% lymphocytes, 12% band forms, 2% monocytes), AST 200 U/l, ALT 199 U/l, GGT 120 U/l, LDH 900 U/l. Blood, Throat, urine cultures were negative. PPD test was negative. Tests for ANA, ANCA, anti-ds-DNA, and RF were all negative. C3 and C4 complement levels were normal. Serologic tests for hepatitis A, B, and C, HIV, EBV, CMV, Parvovirus B19, brucellosis, syphilis, and toxoplasmosis were negative. An X-ray of the chest and ultrasonography of the abdomen were normal. A bone marrow biopsy revealed a normocellular marrow with no tumor cells or granuloma.

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A course of broad spectrum antibiotic was given over 14 days with no clinical response. Spiking fever and constitutional symptoms persisted. Biopsy of right cervical lymph node showed histiocytic necrotizing lymphadenitis typical of KFD. Prednisone therapy was started at 1 mg/kg/day x 3 weeks. Tapered steroid therapy was discontinued at eight weeks. At follow-up visits the patient was symptom free with no clinical or laboratory evidence of KFD or other concomitant diseases.

**DISCUSSION**

KFD, also known as apoptotic lymphadenitis or histiocytic necrotizing lymphadenitis is an uncommon, idiopathic, generally self-limited disease. Kikuchi first described this disease in 1972 in Japan. Fujimoto and colleagues independently described this disease in the same year. Although the first descriptions were in people of Asian origin, the disease has now been reported in individuals of all races. Its true incidence is unknown. There is an increased incidence in females and the age range is wide (between 11 - 80 years), but the majority of the patients are under 30 years of age.

The most common manifestation of KFD is cervical lymphadenopathy with or without systemic signs and symptoms in 70 to 98% of the patients. Fever is the primary symptom in 30 - 50% cases. Less common manifestations include weight loss, chills, skin rash, gastrointestinal symptoms and night sweats. Diagnosis is confirmed via histopathological findings of lymph node biopsy. Nevertheless, diagnosis of KFD should differentiate from other disease such as lymphoma, TB, sarcoidosis, cat scratch fever, SLE and toxoplasmosis all of which have different treatments and prognosis.

KFD symptoms generally resolve spontaneously over several months with a favorable outcome in most patients. In some cases, the course of the disorder appears to be unpredictable with respect to severity, complication, response to therapy and probability of development of other diseases. We used steroid therapy to control the disease in a patient with a prolonged course of severe systemic and constitutional symptoms which showed no response to broad spectrum antibiotic therapy. Steroid therapy is also recommended in patients with SLE, rheumatic disorders and in those who are unresponsive to antibiotic therapy or have severe symptoms. After initiation of steroid treatment we observed a reduction in lymph node size as well as fever and other constitutional symptoms.

**CONCLUSION**

We conclude that the workup for a differential diagnosis of prolonged fever and lymphadenopathy resistant to antibiotic treatment should include biopsy for KFD. Early recognition of KFD will minimize potentially harmful and unnecessary evaluation and will prevent misdiagnosis and inappropriate treatment.

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Case Report

Post-Transarterial Chemoembolization (TACE)
Biloma Mimicking Liver Abscess: The Role of Different Imaging Modalities

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ABSTRACT

Transarterial chemoembolization (TACE) is a recognized mode of treatment for patients with hepatocellular carcinoma. Complications related to the procedure such as liver failure, liver abscess, bile duct infection or even pulmonary embolism are known to cause morbidity and mortality in these patients. Biloma is a rare complication of TACE. Its incidence has been reported as between 0.9 – 2.1%. It is caused by injury to the arterial supply of bile duct, which then forms a bile-contained cavity either intra-hepatic or extra-hepatic in location. We report the case of a patient with recurrent hepatocellular carcinoma who was treated with TACE. He developed an infected biloma post-procedure. He had different imaging modalities that pointed to the diagnosis of biloma. He underwent appropriate management that led to resolution of the biloma.

KEYWORDS: biloma, complication, post-chemoembolization, TACE

INTRODUCTION

Transarterial chemoembolization (TACE) is an effective treatment for unresectable or recurrent hepatocellular carcinoma as well as for the management of resectable small hepatocellular carcinoma or hepatic metastases[1-3]. TACE uses an emulsion of an oil-soluble anti-cancer agent and lipiodol that aims to occlude the hepatic arterial supplies of the liver tumor[2]. Various complications related to TACE include hepatic failure, hepatic infarction, liver abscess, bilomas, cholecystitis and multiple intrahepatic aneurysms[2-4]. It is important to understand the complications related to this procedure in order to minimize the risk associated with TACE[2].

Biloma is defined as a localized cystic collection of bile extravasated after bile duct injury or necrosis[3,4]. The incidence of biloma formation following TACE has been reported to be between 0.9 - 2.1%[1,4].

We highlight this rare complication of biloma formation following TACE and discuss the patient’s risk factor for developing it as well as various imaging modalities used in the diagnosis and management of this condition.

CASE REPORT

A 40-year-old man had been diagnosed to have a multicenteric hepatocellular carcinoma (HCC) with background Hepatitis B. He had undergone an extended left heptectomy two years prior to his current presentation. Currently, he presented with recurrent multicenteric HCC complicated with portal venous thrombosis. Decision of TACE was made in view of his recurrent tumor status with background of clinical Child C class of the liver disease.

He underwent TACE using 50 mg doxorubicin and 10 ml lipiodol via selective cannulation of the right hepatic artery. There was no immediate complication after the procedure and he was discharged home two days later.

He presented one week later with persistent fever associated with right upper abdominal pain. His physical examination revealed a normal blood pressure
and pulse rate but was febrile with a temperature of 38.5 °C. He had mild jaundice and his abdomen was tender especially in the right upper quadrant. His liver function revealed a raised alkaline phosphatase and bilirubin, which indicated an obstructive feature.

An abdominal ultrasound was performed which showed an echoic lesion in segment VII (Fig. 1). Initial diagnosis of a liver abscess was made after complementary MRI abdomen, which was carried out in order to exclude residual solid lesion of the liver tumor. There were dilated intrahepatic ducts proximally secondary to common bile duct (CBD) stenosis (Fig. 2). The patient then underwent percutaneous transhepatic drainage of the presumed liver abscess under ultrasound guidance. Bilious fluid was drained via the pigtail catheter. Thereafter, he was subjected to fluoroscopic / CT-tubogram in order to exclude a biloma. The tubogram showed an intrahepatic liver cavity, which communicated with the dilated proximal right intrahepatic duct (Fig. 3). He underwent an endoscopic retrograde cholangiopancreatography (ERCP) for re-insertion of a common bile duct stent in order to release the biliary obstruction. His liver function test improved after stenting and the fever subsided after antibiotics.

A follow-up ultrasound performed one month later demonstrated no residual biloma (Fig. 4). Later, he underwent a second TACE one month after the biloma presentation and is doing well until now.

Fig. 1: Ultrasound abdomen showing an anechoic cystic lesion in segment VII with thick and irregular walls. Minimal debris noted floating within it (arrow).

Fig. 2: MRI abdomen a: coronal T2WI, b: axial T1WI and c: axial T2WI showing cystic lesion in segment VII which is hypointense on T1WI and hyperintense on T2WI (star). It has echogenic hypointense debris within. There is an adjacent proximal intrahepatic ducts dilatation (arrow).

Fig. 3: a: Tubogram with complementary b: CT tubogram, showing contrast-filled cavity which communicates with adjacent intrahepatic ducts (arrows).
TACE is the mainstay for treatment of primary and secondary malignancies and a well-known keystone in interventional oncology\(^1\). TACE limits the systemic toxic complications of chemotherapeutic drugs by delivering the drugs directly to the tumor, especially in selective TACE\(^3\). Despite that, TACE is known to cause local complications, especially into the adjacent non-tumorous liver parenchyma, bile duct and the vessel itself since it is delivered via hepatic artery. The complication of TACE can be divided into technical complications, hepatic injury, extra-hepatic complications or even systemic complications\(^2,4\). Carin et al listed major complications of TACE. They are in (descending order); liver abscess, post-embolization syndrome and liver failure with reported rate of 25%, 4.6% and 2.3% respectively. The lowest complication rate of 1% was for surgical cholecystitis, biloma, pulmonary arterial oil embolism, gastrointestinal hemorrhage, iatrogenic vascular dissection and even death\(^3\).

Bile duct injury is a serious and rare complication of TACE. The incidence of bile duct injury post-TACE was reported to be 0.9% to 2.1%\(^4,3\). An incidence of 12.5% was reported from post-mortem studies\(^6\). Kobayashi et al also concluded that microscopically, the biloma is due to microinjury to the peribiliary capillary plexus (PBP)\(^6\).

Biloma should be considered in the differential diagnosis of cystic, intra-hepatic or peri-hepatic fluid collections especially when seen on ultrasound\(^7\). Magnetic resonance imaging (MRI) will show a heterogeneously intense picture on T1-weighted images, and homogeneously hyperintense picture on T2-weighted images. This can be sometimes mistaken as a liver abscess (as in this patient)\(^8\). In our case, the provisional diagnosis of liver abscess was made based on the clinical presentation and the cystic lesion with debris within the lesion seen on imaging. The concomitant intra-hepatic ducts dilatation could represent associated intra-hepatic ducts inflammation but is not always associated with liver abscess.

Perhaps, another differential diagnosis for biloma would be a subacute hematoma. Shigemura et al described two post-traumatic bilomas where the biloma was differentiated from a hematoma by an MRI showing hyperintensity in both T1 and T2 weighted images\(^9\). A CT scan without contrast study is not confirmatory for biloma. Indeed, it is useful in localizing the biloma by its regional anatomy\(^9,10\). The fluid density of pure biloma is less than 20 HU but it is not specific for confirming a biloma.

A biloma can be confirmed by needle aspiration\(^10,11\). We have benefited from contrast study through the percutaneous tube drainage with complementary CT tubogram, which confirmed the presence of communication between the cystic cavity and the rest of the biliary duct. This is specific for biloma and in fact, we believe this is the confirmatory imaging modality for biloma besides pre-drainage ultrasound guided needle aspiration\(^10,12\). We recommend that confirmatory diagnosis by needle aspiration of suspicious biloma is only needed for collection that does not need to be drained, i.e. a small collection or in a patient without sign of infection. On the other hand, the contrast study tubogram should be done following percutaneous drainage of intrabdominal collection, in a suspected biloma patient. Percutaenous treatment would be a subacute hematoma. Shigemura et al described two post-traumatic bilomas where the biloma was differentiated from a hematoma by an MRI showing hyperintensity in both T1 and T2 weighted images\(^9\). A CT scan without contrast study is not confirmatory for biloma. Indeed, it is useful in localizing the biloma by its regional anatomy\(^9,10\). The fluid density of pure biloma is less than 20 HU but it is not specific for confirming a biloma.

CONCLUSION
Biloma is a rare but treatable complication of TACE. In a correct clinical setting, the physician should suspect this diagnosis whenever patient has a history of TACE with support of background of risk factor(s) that have been discussed above. Definitely, with the help of imaging, this diagnosis can be confirmed and appropriate intervention can be carried out to reduce morbidity.

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Cholesterol Embolization Syndrome Following Thrombolytic Therapy

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ABSTRACT

Cholesterol embolization syndrome (CES) is a rare and serious complication of thrombolytic therapy. Awareness of this complication would lead to earlier diagnosis and better management. We report a case of a 70-year-old man who presented with acute myocardial infarction and was thrombolysed with tenecteplase. His hospital stay was complicated by acute renal failure, blue toe syndrome and livedo reticularis. Skin biopsy revealed cholesterol crystals. He eventually became dialysis dependent.

KEY WORDS: cholesterol embolization syndrome, thrombolytic therapy

INTRODUCTION

Cholesterol embolization syndrome (CES) is a multisystem disease caused by showers of cholesterol crystals released from an atherosclerotic plaque. In the majority of cases CES is iatrogenic following angiographic procedures and aortic surgery, and less often following anticoagulant or thrombolytic therapy (TT)¹. Despite the widespread use of TT in the treatment of ST segment elevation myocardial infarction (STEMI), relatively few cases have been reported in the literature². Furthermore, CES was not tracked, and consequently not reported, as a complication of TT in large thrombolytic trials³.

We describe a patient who developed CES after receiving tenecteplase for acute inferior STEMI.

CASE REPORT

A 70-year-old male, smoker and hypertensive on captopril treatment, presented with acute inferior STEMI and was treated with tenecteplase, unfractionated heparin, aspirin, clopidogrel, nitrates and statin, with good response to thrombolytic therapy. He was not known to have dyslipidemia but on admission his cholesterol was 6.3 mmol/l, low-density lipoprotein (LDL) was 4 mmol/l and triglyceride (TG) was 3.5 mmol/l.

On the day after his TT, his creatinine, which was 96 umol/l on admission, increased to 180 umol/l. The patient had a blood pressure of 140/90 mmHg, a normal urine output and a normal fundus examination. Urine analysis showed proteinuria, and renal ultrasound showed normal sized kidneys. A week after admission, the patient suddenly developed a blue right toe and livedo reticularis (Fig. 1). His peripheral pulses remained palpable bilaterally. On the ninth day of hospital stay, his erythrocyte sedimentation rate (ESR) was raised at 108 mm/hour, C -reactive protein was raised at 26 mg /dl and complete blood count showed hypereosinophilia (600 cells/mm³). This hypereosinophilia progressively increased to 2000 cells/mm³ (total white cell count 19,700 cells/mm³) over the next three weeks. C3 and C4 were done on the second week of admission and were within normal values. He was treated with enoxaparin and prostacyclin analog for 10 days. He was then started on high dose methyl prednisolone for suspected interstitial nephritis, using 500 mg daily for 3 days, then 60 mg daily for 5 days. The dose was then tapered gradually and was maintained at 5 mg daily. Two weeks after admission there was no response to treatment; therefore, it was decided to obtain a skin biopsy to help with the diagnosis. Skin biopsy was...
Atheroembolic renal disease, the renal manifestation of CES, is caused by showers of cholesterol crystals that occlude small renal arteries [1]. A renal biopsy was chosen over renal biopsy because it is less invasive and has a high diagnostic yield of about 92% [4]. Skin biopsy from the vasculitic patch revealed multiple cholesterol crystal clefts in the lumen of the arterioles (Fig. 2).

After three weeks creatinine reached 600 umol/l, and the patient was started on hemodialysis. He was later discharged on warfarin, corticosteroid and antithrombotic treatment including aspirin, clopidogrel, statin, beta-blocker and nitrates. In addition, the patient was referred to an outpatient hemodialysis program and started on a schedule of three sessions per week. Coronary angiography was not done as he had no further chest pain and because of his renal failure.

DISCUSSION
We are reporting a case of CES following TT with histopathological confirmation of the diagnosis by skin biopsy. Our patient, an elderly man with history of hypertension, smoking and arterial disease, fitted the demographics of CES patients [1]. He also had the common clinical and laboratory findings including acute renal failure (ARF), blue toe syndrome, livedo reticularis and hypereosinophilia.

A new treatment approach for CES is needed. A large prospective study showed that statin therapy started after diagnosis [7]. There are limited studies with inconsistent results using high dose corticosteroids and only few case reports showing benefit from iloprost [9]. Our patient was already on statins as part of management of myocardial infarction and received high dose corticosteroids during hospital stay. The prognosis of CES is poor with high morbidity and mortality. Our patient eventually became dialysis dependent.

CONCLUSION
New onset renal failure with other clinical signs including peripheral ischemia, vasculitis-like skin lesions and eosinophilia should alert the clinician to the possibility of CES.
REFERENCES

Case Report

Thyroid Tuberculosis Presenting with Thyrotoxicosis

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ABSTRACT

Tuberculosis of the thyroid gland is rare. The true incidence is unknown. We describe the case of a 33-year-old woman who presented with a thyroid mass and cervical lymphadenopathy. She was thyrotoxic, an extremely rare presentation of thyroid tuberculosis. The diagnosis was established with fine needle aspiration cytology (FNAC) of the thyroid and histopathology of a lymph node. The patient was treated with anti-tuberculous therapy with complete resolution of her disease. Although thyroid tuberculosis is rare, it should be considered in the differential diagnosis of nodular thyroid enlargement and granulomatous thyroid lesions.

KEYWORDS: fine needle aspiration cytology, thyroid nodule, tuberculosis

INTRODUCTION

Thyroid tuberculosis is rare. Only 186 cases were reported in the English literature[1]. Involvement of the thyroid with tuberculosis manifests in many ways. Patients may present with localized swelling, cold abscess or thyroid nodule[1]. Thyroid function is preserved in most patients with thyroid tuberculosis[2]. Hypothyroidism or hyperthyroidism is a rare presentation of the diseases. Diagnosis of thyroid tuberculosis may be challenging. The disease is rare and the clinical and biochemical features are non-specific.

We report the case of a patient who presented with a neck swelling and symptoms of thyrotoxicosis. After confirmation of the diagnosis the patient was commenced on anti-tuberculous therapy which resulted in complete resolution of the neck mass and thyroid dysfunction.

The aim of presenting this case is to increase physicians’ awareness of this rare form of tuberculosis and present ways to its diagnosis and treatment.

CASE REPORT

A 33-year-old Filipino woman presented with a one-year history of neck swelling. She denied a history of dysphagia or difficulty in breathing. She denied a history of fever or weight loss. Two months prior to this presentation, she started to have intermittent fever, associated with sweating. She complained of anorexia and weight loss. Three weeks prior to presentation, she noted tremors of her hands. She had lost a total of nine kilograms of her weight. Her past medical history was not significant. She was not taking any medications. On examination, she was febrile. Her pulse rate was 90 beats per minute. She had multiple enlarged cervical lymph nodes in the posterior and anterior compartments. She had a hard right thyroid swelling measuring 4 X 3 cm. No other lymph nodes were palpable. Her chest, heart and abdominal examination were normal. Her free thyroxine level was 31.7 pmol/l (normal range: 7.8 – 16 pmol/l), thyroid stimulating hormone (TSH) was < 0.015 pmol/l (normal range: 0.27 - 4.2 pmol/l). She had normocytic, normochromic anemia with an erythrocyte sedimentation rate (ESR) of 120 mm/hr (normal range: 0 - 20 mm/hr). She had normal electrolytes and kidney function. Alkaline phosphatase was 210 IU/l (normal range: 26 - 88 IU/l), gamma glutamyl transferase (GGT) was 179 IU/l (normal range: 7 - 64 IU/l), aspartate transaminase (AST) was 44 IU/l (normal range: 10-42 IU/l), alanine transaminase was normal and albumin was 25 g/l (normal range: 35 - 47 g/l). Corrected calcium was 2.64 mmol/l (normal range: 2.2-2.6 mmol/l). Computerized tomography showed a diffuse enlargement of the thyroid gland, more on the
right side, with no focal masses. There were bilateral enlarged upper and lower deep cervical, and right supravacular lymph nodes. There was no evidence of lymphadenopathy in the chest and abdomen. The tuberculin skin test was positive. A fine needle aspiration cytology (FNAC) of the thyroid gland showed numerous large multinucleated giant cells and epithelioid granuloma (Fig. 1). FNAC of a cervical lymph node showed granulomatous lymphadenitis. An excisional biopsy of a lymph node was done and its histopathology showed caseating granulomas (Fig. 2). A diagnosis of tuberculous lymphadenitis associated with tuberculous thyroiditis was made. The patient was started on anti-tubercular therapy consisting of isoniazid, rifampicin, pyrazinamide and ethambutol. After two months of therapy, the patient became euthyroid, her neck mass disappeared, her ESR as well as her liver enzymes normalized. She continued isoniazid and rifampicin for another four months. The patient remained well after completing the anti-tuberculous therapy.

**DISCUSSION**

Tuberculosis of the thyroid gland is rare. The true incidence of thyroid tuberculosis is unknown. Thyroid tuberculosis can mimic other thyroid diseases, and the diagnosis may be overlooked. At least 186 cases were reported in the English literature\[^{[1,2]}\]. The rare involvement of the thyroid could be explained by the bactericidal effect of the colloid and the increased blood supply to the gland\[^{[3]}\]. Tuberculosis of the thyroid gland can occur via the hematogenous or lymphatic route, or by direct invasion of the thyroid from adjacent structures. Involvement of the thyroid with focal caseous tuberculosis presents as localized swelling, cold abscess or thyroid nodule with or without cystic component. Miliary spread to the thyroid results in formation of multiple tubercles within the gland\[^{[4]}\].

Middle-aged women are most commonly affected\[^{[2]}\]. The most common presentation is a solitary thyroid nodule with or without cystic component. It can also present as a cold abscess, a multinodular swelling, as thyroid swelling mimicking carcinoma or show signs of thyroiditis\[^{[4]}\]. Localized pain is a presenting symptom, which can resemble De Quervain’s thyroiditis. Patients sometimes might be asymptomatic. The thyroid function is preserved in the majority of patients\[^{[2,4]}\]. Our patient presented with thyrotoxicosis, which is an extremely rare presentation. Thyrotoxicosis occurs at the beginning of the gland involvement due to its destruction\[^{[4]}\]. Hypothyroidism occurs because of complete destruction of the gland by caseous necrosis. Only three cases of hypothyroidism due to thyroid tuberculosis have been reported in the literature\[^{[4]}\].

The diagnosis can be missed, if it is not suspected as thyroid tuberculosis is rare and it can mimic other thyroid diseases. The presence of high ESR and positive tuberculin skin test may suggest the diagnosis. Our patient had a very high ESR and positive skin test. High ESR and a painful thyroid can also be seen in patients with De Quervain’s thyroiditis. Radiological tests are not helpful in establishing the diagnosis. Thyroid ultrasound may show a heterogeneous, hypoechoic mass with or without cystic degeneration\[^{[5]}\]. FNAC of the thyroid, preferably under ultrasound guidance can help establish the diagnosis. The presence of granulomatous lesions may suggest the diagnosis. Granulomas however, are not specific for tuberculosis. They may be seen in patients with De Quervain’s thyroiditis, sarcoidosis and fungal infection of the thyroid\[^{[2]}\]. Caseating granuloma, if present, is specific for tuberculosis. Our patient had epithelioid granuloma of the thyroid and caseating granuloma in the excised lymph node. Granulomas may not be present in FNAC of patients with thyroid tuberculosis.
The diagnosis is then made with histopathology of the excised thyroid gland[3]. The presence of granulomas in FNAC aspirate should alert the physician for the possibility of thyroid tuberculosis. Smears should be stained with Ziehl-Neilsen stain to demonstrate acid-fast bacilli (AFB), and sent for microbiological culture. Demonstration of AFB is diagnostic of tuberculosis but is rarely seen[2]. Recently, the polymerase chain reaction (PCR) has been used to diagnose thyroid tuberculosis. In granulomatous thyroid lesions, PCR detected mycobacterium infection in 56% of thyroid aspirates compared to 6% with Ziehl-Neilsen stain[6]. The PCR might offer a chance for diagnosis of thyroid tuberculosis when AFB is negative.

Treatment of thyroid tuberculosis can be achieved with medical therapy alone[4]. Surgical resection or drainage of an abscess might be indicated in some cases. The duration of anti-tuberculous therapy ranges between 6 - 9 months in the literature[2,4]. Our patient received six months of therapy with complete resolution of her disease.

CONCLUSION
Thyroid tuberculosis is rare, but should be considered in the differential diagnosis of thyroid nodule, and granulomatous lesions of the thyroid. Early treatment is necessary to avoid unnecessary surgery and destruction of the gland.

REFERENCES
Case Report

Unusual Presentation of Extensive Urinary Tuberculosis: A Case Report

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ABSTRACT

Tuberculosis (TB) has been one of the great imitators of old time, and only a few years ago, was thought to be a disease of the past. TB is a deadly infectious disease with a rising incidence worldwide. The urologists awareness of the clinical features of genitourinary TB is necessary to effectively treat patients with this disease. We report a case of unusual genitourinary TB in a patient who had extensive urinary bladder TB without any pulmonary manifestations. He presented with severe gross hematuria associated with blood clots without general constitutional symptoms. The current concepts regarding the management of genitourinary TB are discussed and the relevant literature is reviewed.

KEYWORDS: genitourinary, hematuria, tuberculosis

INTRODUCTION

Genitourinary tuberculosis (TB) remains an important, but uncommon form of TB. It is caused by metastatic spread of the organism through the bloodstream during the initial infection[1]. The kidney is usually the primary organ infected in urinary disease, and other parts of the urinary tract become involved by direct extension[2]. The kidney, epididymis in men, and fallopian tubes in women are the primary landing sites for hematogenous spread of TB[3]. The prostate is also considered one of the sites for hematogenous spread, though its involvement with TB bacilli in urine is more common. TB of the ureter usually affects the uretero-vesical junction[4]. Bladder lesions were always secondary to renal TB[5].

CASE REPORT

A 37-years-old unmarried Asian male, a non-smoker, with no previously significant medical or surgical history presented with gross hematuria and clot retention for one day. The patient reported similar but milder attack one year ago for which he did not seek any medical advice. He had a history of a painless left scrotal swelling since three months. There were no other symptoms. Clinical examination revealed clot urine retention and two discharging left anterior and posterior scrotal sinuses connected to a non-tender epididymal mass (Fig. 1). Per rectal digital examination was normal. All preliminary investigations were ordered which revealed the following information:

- Hemogram was within normal limits;
- serum creatinine and liver function tests were unremarkable.
- Urine examination revealed abundant red blood cells only.
- Chest X-ray did not reveal any abnormality.
- Ultrasonography exhibited mild left hydrenephrosis and left postero-lateral urinary bladder wall mass measuring 4.2 x 2.3 cm, possibly an organized hematoma. Scrotal ultrasound showed a heterogeneous mass lesion (2 x 1 cm) at the lower aspect of left epididymis and connected to the scrotal wall with mild hydrocele and normal right testis and epididymis. The patient was initially managed by insertion of a three-way Foley catheter with extraction of blood clots and urinary bladder irrigation. However, hematuria persisted with recurrent severe blood clot formation. Multi-detector computerized tomography of the abdomen and pelvis with contrast was performed which revealed moderate left hydro-uretero-nephrosis. There was periureteral minimal stranding and thickening of the wall extending up to the renal pelvis. Right kidney and right ureter were unremarkable. Urinary bladder exhibited circumferential diffuse thickening of the wall (Fig. 2).

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A clinical suspicion of genitourinary TB led us to undertake investigation using tuberculin test, urine analysis, urinary polymerase chain reaction (PCR) for TB and sputum examination for TB bacilli. However, due to extensive gross hematuria and drop of hemoglobin we could not wait for result; the patient underwent urethro-cystoscopy which revealed a severely hyperemic edematous and dirty urinary bladder mucosa (pan cystitis) without ulcer or erythema. The right one was normal. Left retrograde uretero-renography study showed multiple ureteric strictures throughout its whole length from intramural part upto renal pelvis with evidence of moderate hydronephrosis of the left kidney. A left double-J stent (DJS) (6 / 26 Fr) was inserted and multiple urinary bladder biopsies were taken from all areas with good hemostasis. Excision of scrotal sinus and the underlying mass were also performed.

**Pathological Findings**

In the pathology department, multiple biopsies from the bladder wall (anterior, posterior, left and right lateral), scrotal sinus and periepididymal tissue were received. Microscopic examination revealed ulcerated bladder mucosa with chronic inflammatory infiltrate comprising of plasma cells, lymphocytes and eosinophils in the lamina propria. A few epithelioid cell granulomas with giant cell formation were also noted (Fig. 3). A special stain revealed an occasional acid fast bacillus (AFB). The biopsy from the scrotal sinus revealed a similar picture of chronic granulomatous inflammation; no AFBs could be seen. Sections from the periepididymal soft tissue mass showed hyalinated fibro-collagenous tissue with thick walled blood vessels. No epithelioid cell granuloma was identified. Thus a diagnosis of tubercular cystitis and chronic granulomatous inflammation of the scrotum was entertained.

A tuberculin test was positive and bladder biopsy revealed epithelioid cell granulomas with AFBs confirming the diagnosis of urinary bladder tuberculosis. Culture from sinus discharge showed E. coli. The patient was put on a six-month regimen of rifampicin, INH, pyrazinamide, and ethambutol. The patient is now on close follow-up.

**DISCUSSION**

Tuberculosis can often mimic a wide range of non-specific urologic symptoms. It is thus, that many cases of genitourinary TB are easily overlooked. A high index of clinical suspicion of TB is required to further investigate cases of unexplained symptoms in the urinary tract. This is especially important when there is a failure to respond to initial treatments given for lower urinary tract symptoms or when urinalysis and routine culture reveal sterile pyuria. The most common physical finding is an abnormal scrotal finding in about half of the patients. It remains a fact that up to 25% of patients will present only with sterile pyuria and 13% might have gross or microscopic hematuria.
as their only presentation. In clinically suspected cases, IVU may be suggestive of the diagnosis, but it is not specific. Specific modalities include bacteriologic culture, biopsy, and urinary PCR for detection of *Mycobacterium tuberculosis* (MTb)\[^6\,^7\].

The most common findings on contrast-enhanced CT include renal parenchymal masses and scarring, thick urinary tract (ureter and bladder) walls and extrarenal tubercular manifestations particularly in miliary TB\[^8\]. Most CT findings are in themselves nonspecific, and the collective interpretation of multiple findings in conjunction with the clinical picture is the best option in decision making\[^9\].

Here in this case, the patient had extensive urinary bladder and left ureteral tuberculosis with no apparent renal TB. Although endoscopy plays a limited role in the diagnosis of TB, because we were suspecting malignancy, we did cystoscopy and urinary bladder biopsy. Although posterior scrotal fistulae in endemic areas, is suggestive of TB, in our case it proved to be from non-specific infection. The patient received a four drug combination of rifampicin, INH, pyrazinamide, and ethambutol for two months, and then rifampicin and INH for four more months; this is in accordance with EAU guidelines for the management of genitourinary tuberculosis\[^10\]. The recent renal function and liver function test were within normal range, the pelvicalyceal system dilatation decreased and the kidney was not obstructed on repeated diuretic renography. The patient is still under our follow-up in the outpatient clinic.

**CONCLUSION**

In conclusion, TB can affect any organ of the body and urologists should be aware of its clinical manifestation and treatment. Severe ureteral and urinary bladder affection can occur without apparent renal tubercular lesion. Any surgical intervention should be postponed until proper coverage with anti-tuberculous drugs has been done unless we are facing an emergency situation.

**REFERENCES**

Case Report

X-Linked Adrenoleukodystrophy: A Novel Mutation of ABCD1 Gene in a Bahraini Boy

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ABSTRACT

Adrenoleukodystrophy (ALD) is an X-Linked recessive neurodegenerative disease that affects the brain and the adrenal glands. It presents with a wide spectrum of clinical variants. The severe childhood cerebral form of ALD is a known cause of severe disability in children that leads to early death. ABCD1 is the only gene associated with X-linked ALD. More than 1400 different mutations have been identified in the ABCD1 gene. We present a case of X-linked ALD with novel mutation. Our patient was a boy who presented with intermittent right eye exotropia, poor attention span and subsequent deterioration in hearing, vision, speech and swallowing. He had dramatic worsening of his neurological symptoms over few months.

His investigations showed high serum very long chain fatty acids (VLCFA) with extensive demyelination involving bilateral parieto-occipital regions on brain MRI. His mother had an extended family history of ALD in five of her brothers with variable phenotypes ranging from the severe childhood cerebral form to the milder variant of ALD. Genetic testing revealed novel missense mutation in exon 6 of the ABCD1 gene with hemizygous ABCD1:c.1585G>T variant. The same mutation was detected in his younger asymptomatic brother. The aim of this case report is to present a familial case of childhood onset cerebral X-linked ALD with novel gene mutation in exon 6 of the ABCD1 gene.

KEY WORDS: adrenoleukodystrophy (ALD), novel mutation, very long chain fatty acid (VLCFA)

INTRODUCTION

Adrenoleukodystrophy (ALD) is one of the X-Linked recessive neurodegenerative group of disorders with a wide clinical spectrum (X-ALD; OMIM 300100) that affects the peroxisomal β-oxidation pathway. These disorders are characterized by progressive white matter demyelination and adrenocortical insufficiency. Simmerling and Creutzfeldt described the first clinical cases in 1923[1]. The clinical variants of ALD include the childhood cerebral form, adolescent, adult, ALD with Addison’s disease only, asymptomatic patients with biochemical defects only and the adult form of ALD adrenomyeloneuropathy[2].

In ALD, more than 1400 mutations in ABCD1 gene have been reported from all over the world. Here, we report the first case of childhood ALD with a novel missense mutation in exon 6 of ABCD1 gene in the Arab population.

CASE HISTORY

Our patient was a Bahraini boy born by lower segment cesarean section (LSCS) for oligohydramnios, with a birth weight of 2400 grams after an uneventful pregnancy. He presented at the age of four and half years with six months history of intermittent right eye squint (exotropia). Over the following six months, parents noted poor attention span with suspicion of poor vision as he described a black spot in his visual field and lost visual tracking. They also noted poor hearing and unclear speech. This was followed by a weak grip, poor limb coordination and unsteady gait. His condition deteriorated over the following four to five months with worsening of his neurologic symptoms and loss of vision and hearing, frequent choking and he was rendered bedridden.

Parents are a non-consanguineous healthy couple. He has three younger siblings. Two are fraternal twins,
a boy and a girl, now two years of age and a younger sister who is four-month-old. Five of his maternal uncles are affected with X-linked ALD, three of whom died at the age of 43, 12 and 10 years respectively because of the cerebral form of the disease. The other two are alive; one is 45-years-old with severe cerebral form of disease in a vegetative state with grand mal epilepsy, while the other is 39-years-old with normal cognition, vision and hearing but has severe motor dysfunction in his lower limbs. All five maternal uncles had high serum very long chain fatty acid (VLCFA) levels but no genetic studies were done. Screening of the mother for VLCFA was normal.

On initial presentation, at the age of four and half years, the patient was a thin built child with a weight 11 kg (3rd percentile), height 95 cm (3rd percentile) and head circumference 53 cm (85th percentile). He had normal vital signs with blood pressure 116/71 mmHg. He was conscious, alert, oriented to time, place and person with delayed verbal responses. His speech was coherent with normal tune. His pupils were round, regular and reactive in response to light stimulus, with full extra ocular movements, no nystagmus and normal fundi. He had no facial asymmetry. His tongue was in the midline. He had a normal gag reflex. His motor examination showed normal tone, power and deep tendon reflexes. There were no signs of ataxia and his gait was normal.

Examination during follow-ups, over a period of twelve months, showed that his overall condition was deteriorating rapidly as he lost hearing and vision. He developed bilateral optic nerve atrophy. Initially he had dysarthric speech and later on he became mute. He developed hypertonia with increased deep tendon reflexes and positive Babinski test with contractures in both ankles with mild scoliosis. His gait was initially wide and unsteady. Later on, he was bed ridden. There was no skin or mucus membrane hyperpigmentation.

He was investigated extensively where in brain stem auditory evoked potentials showed delayed conduction time in the central sensory pathways in both ears, probably due to demyelination. VLCFA testing showed high concentration of lig诺eric acid (24:0), 108.6 µmol/l (reference range 24.9 - 90), cerotic acid (26:0) 3.5 µmol/l (reference range 0.2 - 1.6), ratio of ligoneric / behenic acid (C24:C22) 1.468 (reference range < 0.95) and ratio of cerotic / behenic acid (C26:C22) 0.047 (reference range < 0.02). Synaehen test was done and it confirmed adrenal insufficiency.

Brain MRI in fluid attenuated inversion recovery (FLAIR) images showed hyper-intensities in parieto-occipital white matter bilaterally, splenium of corpus callosum and bilateral cortico-spinal tracts with very significant IV gadolinium contrast enhancement in T1 weighted images. (Fig. 1, 2, 3). Molecular genetic testing was done by sequencing of the entire coding region (exons 1 - 10) and all intron-exon boundaries of the ABCD1 gene. The reference sequence and exon numbering on the genomic level is according to Genbank accession number NG_009022.1 and on the cDNA level according to NM_000033.2, with the ‘A’ of the ATG start codon at position 1. It showed a hemizygous ABCD1:c.1585G > T identified in exon-6 of the ABCD1 gene. This substitution is a missense variant predicted to lead to the substitution of a glycine by a cysteine on amino acid position 529 of the resulting protein (ABCD1:p. Gly529Cys).

Our patient was started on low fat diet, Lorenzo’s oil, Baclofen, vitamin E and hydrocortisone. He was on gastrostomy tube for feeding and on regular
physiotherapy. Bone marrow transplant (BMT) was not feasible due to the late stage of the disease. However, his parents took him to the Ukraine where fetal stem cell transplant was done. His condition though continued to be the same.

His siblings were screened and VLCFA (C26) was found to be high in his brother, who is currently asymptomatic and has a normal brain MRI for age. He was tested and found to be affected with the same gene mutation. Accordingly, he was started on low fat diet and Lorenzo’s oil. BMT was discussed with the family as a favorable option for him once he shows early signs of the disease to halt disease progression. He is being worked up with regular brain MRI every 6 - 9 months. His two other siblings are normal.

DISCUSSION

ALD is an X-linked neurometabolic disorder, characterized by accumulation of saturated VLCFA primarily in the adrenal cortex and the myelin of the central nervous system.

Childhood cerebral forms represent around 35% of affected individuals and are usually present between the ages of four and eight years, with a peak at age seven years. It virtually never occurs before age three years. ALD has a wide phenotypic presentation but generally boys often present with symptoms of attention deficit disorder, which may respond initially to stimulant therapy but soon will deteriorate with signs of dementia, progressive behavioral disturbance, vision loss, difficulty in understanding spoken language, worsening handwriting, incoordination, or other neurologic disturbances. Seizures may be the first manifestation.

Impaired adrenocortical function is usually detected at the time that neurologic disturbances are diagnosed. Once the neurological manifestations appear, progression of the illness is rapid and the child is often in a vegetative state within one to two years.

Older age group can present with progressive spastic paraparesis or only signs of adrenocortical insufficiency. Differential diagnosis of childhood onset ALD includes other types of leukodystrophies including arylsulfatase deficiency (metachromatic leukodystrophy) and galactocerebrosidase deficiency (Krabbe disease also known as globoid cell leukodystrophy). Various phenotypes have been recognized to occur within the same pedigree. The cause of the phenotypic variability is unknown. It is not due to the nature of the mutation or the severity of the defect in VLFFA oxidation. A Chinese study of 89 patients concluded that the clinical phenotype had no definite relationship with the nature of gene mutation. A single mutation may result in different phenotypes, missense mutation being the most common.

Brain MRI is always abnormal in neurologically symptomatic males with cerebral disease and is at times the first diagnostic tool. In approximately 85% of affected cases, MRI shows a characteristic pattern of symmetrically increased T2 signal in the parieto-occipital region with contrast enhancement at the advancing margin, as was seen in our patient.

The principal biochemical abnormality is the accumulation of saturated VLCFA, particularly hexacosanoic (C26:0) and tetracosanoic (C24:0) fatty acids, as a result of the impaired capacity to degrade these substances, a function that normally takes place in the peroxisome. Plasma concentration of very long chain fatty acids (VLCFA) is abnormal in 99% of males with X-ALD, irrespective of age.

Increased concentration of VLCFA in plasma and/or cultured skin fibroblasts is present in approximately 85% of affected females. It is known that the VLCFA testing can result in a negative profile in around 20% of female carriers, as was the case in our patients’ mother. Female carriers at age above or equal to 35 years can manifest signs and symptoms that resemble a mild form of adrenomyeloneuropathy. The majority of heterozygous females will develop symptoms by the age of 60 years.

Molecular genetic testing for ABCD1, the only gene known to be associated with X-ALD is now widely available. About 93% of index cases have inherited the ABCD1 mutation from one parent and around 7% of individuals with X-ALD have a de novo mutation. Evidence of germline or somatic / germline mosaicism is present in less than 1% of parents.

X-ALD database has listed 1413 non-recurrent disease-causing mutations. The non-recurrent mutations account for around half of the disease-causing mutations, which include missense mutations.
and patients recommended treatment predictions to Variant is pharmacologic (~Lorenzo a radical hydroxy reductase inhibitor is another drug that was reported to reduce cholesterol and saturated VLCFA levels in adult ALD patients but also with limited evidence of clinical improvement[17]. Corticosteroid replacement therapy is very essential for patients with adrenal insufficiency. General supportive measures, including physical therapy, psychological therapy and educational support should be provided to both patients and parents when needed.

CONCLUSION
ALD is a neurodegenerative disorder with no proven cure yet. Molecular genetic testing of ABCD1, the only gene known to be associated with X-ALD, is widely available. Early identification of asymptomatic or at-risk males permits timely treatment of adrenal insufficiency and offers opportunities for hematopoietic stem cell transplantation hoping to reverse some neurological symptoms and lead to disease stabilization. Each new disease mutation may provide us with additional information to better understand this rare disorder.

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(62%), frameshift mutations (~22%), nonsense mutations (~10%), amino acid deletion / insertions (3%), and one or more exon deletion (3%). Missense mutations are most common in the membrane domain or the ATP-binding domain. In our patient, the ABCD1:c.1585G > T variant is a novel variant not previously described in other patients nor in controls. Other variants in the same codon have been reported before in other patients: p.Gly529Ser: (Wichers et al. Hum Genet 1999; 105:116, and p.Gly529Asp: ALD Locus specific database, unpublished). In silico predictions showed that it was probably damaging according to Polyphen-2. As for SIFT it was not tolerated and it was disease causing in Mutation Taster. It is not listed in the NHLBI Exome Variant database (~13000 alleles). It is classified as a variant with unknown significance (VUS) according to the MutaDATABASE criteria, although in silico predictions suggest pathogenicity.

Three therapeutic approaches have been recommended for ALD and these include hematopoietic bone marrow transplantation, dietary treatment and adrenal hormone replacement. BMT has most favorable effects when performed early in the course of cerebral involvement[11-13]. It was shown to reverse early neurologic involvement[11] and in some cases to lead to disease course stabilization[12]. Dietary therapy includes the administration of a low fat diet that restricts the intake of VLCFA[14] combined with the oral intake of Lorenzo’s oil[15]. Lorenzo’s oil had a great promise. However, studies have shown that VLCFA plasma levels of ALD patients treated with Lorenzo’s oil were lowered within four weeks of initiating treatment but there was no improvement of the neurological symptoms[8,16]. New pharmacologic approaches included the use of the free-radical scavenger, Edaravone, that was studied on a patient with ALD and that showed the drug to be somehow effective in improving symptoms of ALD but still needs more formal evaluation[16]. Lovastatin, a 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitor is another drug that was reported to reduce cholesterol and saturated VLCFA levels in adult ALD patients but also with limited evidence of clinical improvement[17]. Corticosteroid replacement therapy is very essential for patients with adrenal insufficiency. General supportive measures, including physical therapy, psychological therapy and educational support should be provided to both patients and parents when needed.


Clinicopathological Features and Prognosis of Triple Negative Breast Cancer in Kuwait: A Comparative/Perspective Analysis

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Aim: The aim of this study was to determine the incidence of TNBC in Kuwait, to analyze the clinicopathologic features and prognosis of this type of breast cancer, and compare it with reports from other regions of the world.

Background: Triple negative breast cancer (TNBC) is defined as a subtype that is negative for estrogen receptor, progesterone receptor, and human epidermal growth factor receptor 2 (HER2). There is a growing evidence of the heterogeneity of such entity on the molecular level that may cause discrete outcomes.

Methods: We analyzed the clinicopathologic features of 363 TNBC cases which were diagnosed in Kuwait from July 1999 to June 2009. The disease-free survival (DFS) and overall survival (OS) were analyzed by Kaplan-Meier method. Comparison was done with reports from USA, Europe, Middle and Far East.

Results: Among 2986 patients diagnosed with breast cancer in Kuwait, 363 patients (12.2%) were TNBC. The median age was 48 years, 57.2% had lymph nodes (LN) metastasis, 56.9% were of grade III tumor and 41.9% had stage II disease. 81% developed recurrences and 75% of deaths occurred by 2.5 years after treatment. There is marked variation of clinicopathologic features according to country of patients’ cohort.

Conclusion: The incidence of TNBC in our study is similar to other studies. TNBC patients showed an early major recurrence surge peaking at approximately year 2.5. Regional variation of clinicopathologic features indicates a need for molecular studies to define underlying molecular features and its impact on survival.

Evaluation of Leptin, Interleukin-1 Beta and Tumor Necrosis Factor Alpha in Serum of Malaria Patients as Prognostic Markers of Treatment Outcome

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Objective: To analyze serum leptin levels in patients with malaria falciparum and compare them with healthy controls and correlate with development and outcome of malaria infection.

Methods: Sixty cases of malaria falciparum were included in this study as patients. Thirty healthy individuals of comparable age, racial and body mass index were taken as controls. All patients were diagnosed by clinical picture and the presence of malaria parasites in blood film. Estimation of liver function test, kidney function test, complete blood count, fasting blood sugar, fasting serum insulin, pro-inflammatory cytokine tumor necrosis factor alpha (TNFα) and interleukin 1 (IL1), estimation of morning serum leptin and calculation of body mass index (kg/m(2)) were done in both groups on the day of admission, on discharge and 7 d after discharge.
Results: At admission, leptin levels were significantly higher in patients group than in control while fasting serum insulin levels were not significantly different between the two groups. There were significant increases as regard to TNFα and IL1 in malaria patients. Significant differences were observed between the control and the patient group for leptin, TNFα and IL1 at the time of admission and discharge. After discharge for 7 d, a significant decline in serum leptin levels, TNFα and IL1 in the patients group was observed as compared with time of admission and time of discharge, a positive correlation between serum leptin levels and TNFα and IL1.

Conclusions: Leptin hormone level might play an important role in development and outcome of malaria infection.

Analysis of the Effect of the Active Compound of Green Tea (EGCG) on the Proliferation of Peripheral Blood Mononuclear Cells

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Background: Cancer immunotherapy requires proper manipulation of the immune system, lymphocytes in particular, in order to identify and destroy the cancer cells as non-self. In this study we investigated the effect of the flavonoid present in green tea, namely epigallocatechin-3-gallate (EGCG), on the proliferation of, and IFN-γ production by, peripheral blood mononuclear cells (PBMC) from breast cancer patients stimulated with a mitogen, anti-CD3 and the common breast cancer peptides Her-2/neu, and p53.

Methods: Blood samples were collected from 25 patients with breast cancer at the Kuwait Cancer Control Centre (KCCC). The patients were newly diagnosed, and had not undergone any treatment or surgery at the time of sample collection. The control group consisted of 25 healthy women age-matched (±5 years) to the patients. PBMC were isolated from the patients and controls, and were cultured separately with the mitogen PHA, anti-CD3 antibodies, and Her-2/neu and p53 in the presence or absence of standardized doses of EGCG. The degree of proliferation and interferon-γ [IFN-γ] release were then analyzed.

Results: EGCG significantly suppressed the proliferation of PBMC in response to stimulation separately with (i) the mitogen, (ii) anti-CD3, and (iii) the cancer antigen peptides. IFN-γ production was also significantly suppressed by EGCG in vitro.

Conclusions: EGCG appears to have an immunosuppressive effect on the proliferation of PBMC, indicating that EGCG is worth exploring for immunomodulatory effects in autoimmune diseases and tissue transplantation.

Non-Parametric Analysis of Seasonality in Birth and Multiple Sclerosis Risk in Second Generation of Migrants in Kuwait

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Background: There are inconsistent reports about multiple sclerosis (MS) risk among migrants from low to high MS risk geographical regions. This study assessed the overall MS incidence and evaluated seasonality in birth and subsequent MS risk later in the life in second generation of migrants born and lived in Kuwait.
Month of Birth and Risk of Multiple Sclerosis in Kuwait:
A Population-Based Registry Study

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Mult Scler 2014 Aug 4. pii: 1352458514541578

Background: Multiple sclerosis (MS) is a complex immune-mediated disorder of central nervous system with undefined etiology. This study examined the month of birth effect on subsequent MS risk later in the life in Kuwait.

Methods: The month of birth of MS patients enrolled in Kuwait MS Registry between 1 January 1950-30 April 2013 was compared with the month of births in the general population during the comparable period. Multivariable log-linear Poisson regression model was used to analyze the data.

Results: Data on 1035 confirmed MS patients were collected, of which 65.2% were female and 77.1% were Kuwaiti. The overall risk of MS births (per 105 births in general population) was 28.5 (95% confidence interval (CI): 26.8-30.3). Multivariable log-linear Poisson regression model showed a significant (p = 0.004) peak in the number of MS births during December (80 = 340). During this month, the risk of MS birth was 1.3 times the risk of MS birth in the trough month after adjusting for the effects of gender and nationality (adjusted relative risk = 1.3; 95% CI: 1.1-1.6). The amplitude (±standard deviation: 0.13 ± 0.014) of sinusoidal curve showed a significant (p = 0.004) difference of 13% from the mean to maximum MS births during peak month.

Conclusions: This study showed a statistically significant month of birth effect on MS risk with 13% excess MS births during December in Kuwait. Future studies may contemplate ascertaining the seasonal factors eliciting the observed association. The insight gained by unraveling such factors may help curtail MS risk in this and other similar settings in the region.
Forthcoming Conferences and Meetings

Compiled and edited by Babichan K Chandy

Kuwait Medical Journal 2014; 46 (4): 363 - 373

2015 Interventional Cardiology: 30th Annual International Symposium
Mar 1 - 6, 2015
United States / Colorado / Snowmass
Contact: Rebecca Law, Symposium Manager, Promedica International CME
Phone: 760-720-2263, Fax: 760-720-6263
Email: rlaw@promedicacme.com

Infectious Diseases Far East Discovery Cruise
Mar 2 - 16, 2015
China / Hong Kong
Contact: Continuing Education, Inc, Continuing Education, Inc
Phone: 800-422-0711
Email: registrar@continuingeducation.net

Mental Health Care in the Community: Psychosis
Mar 2, 2015
United Kingdom
Contact: Amy Partleton, Centre For Professional Development, University of Birmingham
Phone: 011-44-12-1414-2677
Email: a.partleton@bham.ac.uk

20th Annual Vermont Perspectives in Anesthesia
Mar 4 - 8, 2015
United States / Vermont / Stowe
Contact: Continuing Medical Education, University of Vermont College Of Medicine
Phone: 802-656-2292, Fax: 802-656-1925
Email: uvmcme@med.uvm.edu

Essential Medical Dermatology
Mar 4 - 6, 2015
United Kingdom / London
Contact: Conference & Event Services, British Association of Dermatologists
Phone: 011-44-20-7383-0266, Fax: 011-44-20-7388-5263
Email: conference@bad.org.uk

12th International Workshop of Lower Genital Tract Pathology
Mar 5 - 7, 2015
Italy / Rome
Contact: Organizing Secretariat, Triumph C&C Srl
Phone: 011-39-6-3553-0382, Fax: 011-39-6-3553-0362
Email: hpv2015rome@thetriumph.com

4th Annual American Society for Nutrition Middle East
Mar 5 - 7, 2015
United Arab Emirates / Ajman
Contact: Mohamed Magdy, Mr., Pure Spot
Phone: 011-20-10-9002-1262
Email: mohamed.magdy@egypure.org

Heart Failure Day for Revalidation & Training
Mar 5, 2015
United Kingdom / London
Contact: British Society for Heart Failure
Phone: 011-44-186-539-1836
Email: info@bsh.org.uk

PET 1 (Paediatric Epilepsy Training)
Mar 6, 2015
United Kingdom / Leicester
Contact: Sara Rowan, Course Co-Ordinator, British Paediatric Neurology Association
Phone: 011-44-120-469-5958, Fax: 011-44-120-446-8539
Email: sara@bpna.org.uk

22nd Annual Echocardiographic Workshop On 2-D & Doppler Echocardiography at Vail
Mar 9 - 12, 2015
United States / Colorado / Vail
Contact: Sheila Fick, Education Specialist, Mayo Clinic
Phone: 507-266-6703, Fax: 507-266-7403
Email: cvcme@mayo.edu

British Association of Plastic Reconstructive & Aesthetic Surgeons (BAPRAS) Advanced Educational Course: Series 3, Course 4 - Burns
Mar 9 - 10, 2015
United Kingdom / Manchester
Contact: Bapras
Phone: 011-44-20-7831-5161, Fax: 011-44-20-7831-4041

2015 British Association for Surgery of The Knee (BASK) Annual Spring Meeting
Mar 10 - 11, 2015
United Kingdom / Telford
Contact: Hazel Choules, Bask
Email: hazel.choules@virginmedia.com
Paediatric Palliative Care
Mar 10 - 10, 2015
United Kingdom / London
Contact: Education and Conference Centre, the Royal Marsden
Phone: 011-44-20-7808-2921
Email: conferencecentre@rmh.nhs.uk

2015 Gulf Thoracic
Mar 11 - 14, 2015
United Arab Emirates / Dubai
Contact: Mr. Hassan Alorainy, Executive Director, Saudi Thoracic Society
Phone: 011-966-50-199-4114, Fax: 011-966-11-248-7431
Email: mсалhajjaj@gmail.com

Neoheart: Cardiovascular Management of the Neonate
Mar 11 - 14, 2015
United States / California / Huntington Beach
Contact: Susan Schwamb, Registrar, Children’s Hospital of Orange County
Phone: 714-509-4363, Fax: 714-509-8785
Email: sschwamb@choc.org

2015 International Convention of Psychological Science
Mar 12 - 14, 2015
Netherlands / Amsterdam
Contact: Association for Psychological Science
Email: icps@psychologicalscience.org

3rd International Congress on Controversies in Rheumatology & Autoimmunity
Mar 12 - 14, 2015
Italy / Sorrento
Contact: Anna Varsanyi, APM, Kenes International
Phone: 011-41-22-908-0488, Fax: 011-41-22-906-9140
Email: cora@kenes.com

Advanced Prostate Cancer Consensus Conference
Mar 12 - 14, 2015
Switzerland / St. Gallen
Contact: Conference Secretariat, Kantonsspital St.Gallen
Phone: 011-41-71-494-2922
Email: prostatecancerconsensus@kssg.ch

Cardiovascular Health & Disease: Occupational & Environmental Factors & Updates in Occupational Health & Environmental Medicine
Mar 12 - 14, 2015
United States / California / San Francisco
Contact: Office of Continuing Medical Education, UCSF
Phone: 415-476-4251, Fax: 415-476-0318
Email: info@ocme.ucsf.edu

Medical CBT for Depression: Ultra-Brief Techniques For Real Doctors (Cognitive Behavior Therapy)
Mar 12 - 14, 2015
United States / Hawaii / Kauai
Contact: Greg Dubord, MD, Cme Director, CBT Canada
Phone: 877-466-8228
Email: registrar@cbt.ca

1st Annual MSK Clinical Pearls Upper Extremities: Shoulder & Elbow
Mar 13, 2015
Canada / Alberta / Calgary
Contact: Ruth-Anne Marley, Cumming School of Medicine, University of Calgary
Phone: 403-210-6272
Email: ramarley@ucalgary.ca

International Society of Nephrology (ISN) World Congress of Nephrology
Mar 13 - 17, 2015
South Africa / Cape Town
Contact: Wessel Nieuwenweg, ISN
Phone: 011-32-2-808-0420, Fax: 011-32-2-808-4454
Email: wnieuwenweg@theisn.org

2015 Updates In Primary Care & Current Topics in Ophthalmology for Primary Care Providers Western Caribbean Cruise
Mar 14 - 21, 2015
United States / Florida / Fort Lauderdale
Contact: Continuing Education, Continuing Education, Continuing Education, Continuing Education, Continuing Education, Inc
Phone: 800-422-0711
Email: registrar@continuingeducation.net

6th Association of South-East Asian Pain Societies Congress
Mar 15 - 17, 2015
Philippines / Manila
Contact: Natalene Ng, APM, Kenes Asia-Singapore
Phone: 011-65-6393-0234, Fax: 011-65-6292-4721
Email: info@aseaps2015.org

19th International Society for Psychological & Social Approaches to Psychosis International Congress
Mar 18 - 22, 2015
United States / New York
Contact: Natalie Shear, Natalie Shear
Email: Isps2015nyc@NatalieShear.Com

2015 Australasian Society for Infectious Diseases (ASID) Annual Scientific Meeting
Mar 18 - 21, 2015
New Zealand / Auckland
Contact: ASID
Phone: 011-61-2-9222-6204, Fax: 011-61-2-9231-2907
Email: admin@asid.net.au
2015 St. Gallen Breast Cancer Conference: Primary Therapy of Early Breast Cancer
Mar 18 - 21, 2015
Austria / Vienna
Contact: St. Gallen Oncology Conferences
Phone: 011-41-71-243-0032, Fax: 011-41-71-245-6805
Email: info@oncoconferences.ch

5th Biennial Congress of the Asian-Pacific Hepato-Pancreato-Biliary Association
Mar 18 - 21, 2015
Singapore / Singapore
Contact: Congress Secretariat, Congress Secretariat, Kenes Mp Asia
Email: info@aphpba2015.com

10th International Workshop on Interventional Pediatric & Adult Congenital Cardiology
Mar 19 - 21, 2015
Italy / Milan
Contact: Organizing Secretariat, Aim Group International Milan
Email: ipcworkshop@aimgroup.eu

2015 Central States Occupational & Environmental Medicine Association (CSOEMA) Annual Spring Seminar
Mar 19 - 21, 2015
United States / Illinois / Chicago
Contact: Marlyce Nutt, Executive Director, CSOEMA
Phone: 630-497-0286
Email: marlyce@csoema.org

4th Global Congress for Consensus in Pediatrics & Child Health
Mar 19 - 22, 2015
Morocco / Marrakesh
Contact: Karen Davidson, Conference Secretariat, Paragon Group
Phone: 011-41-22-533-0948
Email: cip@cipediatrics.org

Management of Non Muscle Invasive & Muscle Invasive Bladder Cancer
Mar 19, 2015
United Kingdom / Coventry
Contact: Amy Stratton, Urology Section, Royal Society of Medicine
Phone: 011-44-20-7290-2987
email: urology@rsm.ac.uk

Menopause Special Skills Module
Mar 19 - 20, 2015
United Kingdom / Kenilworth
Contact: Kate Ellis, British Menopause Society
Phone: 011-44-16-2899-0199, Fax: 011-44-16-2847-4042
Email: kate@thebms.org.uk

6th International Meeting on Indigenous Child Health
Mar 20 - 22, 2015
Canada / Ontario / Ottawa
Contact: Education Department, Canadian Paediatric Society
Phone: 613-526-9397 Ext. 264
Email: Education@Cps.Ca

73rd American Academy of Dermatology (AAD) Annual Meeting
Mar 20 - 24, 2015
United States / California / San Francisco
Contact: AAD
Phone: 866-503-7546 (Us) Or 847-240-1280, Fax: 847-240-1859

2nd International Neonatology Association Conference
Mar 21 - 23, 2015
Morocco / Marrakesh
Contact: Janine Koeries, Conference Secretariat, Paragon Group
Phone: 011-41-22-53-3094
Email: secretariat@worldneonatology.com

6th World Congress on Sleep Medicine
Mar 21 - 25, 2015
South Korea / Seoul
Contact: World Association of Sleep Medicine
Phone: 507-316-0084
Email: info@wasmonline.org

Sports Medicine Hawaiian Cruise
Mar 21 - 28, 2015
United States / Hawaii / Honolulu
Contact: Continuing Education, Continuing Education, Inc
Phone: 800-422-0711
Email: contactus@continuingeducation.net

6th World Congress on Women’s Mental Health
Mar 22 - 25, 2015
Japan / Tokyo
Contact: Debra Tucker, Executive Director, International Association for Women’s Mental Health
Phone: 301-983-6282, Fax: 301-983-6288
Email: iawmh2015@congre.co.jp

83rd European Atherosclerosis Society Congress
Mar 22 - 25, 2015
United Kingdom / Glasgow
Contact: Raquel Lewis, APM, Kenes International
Phone: 011-41-22-908-0488, Fax: 011-41-22-906-9140
Email: eas@kenes.com
4th Intensive Interactive Brain & Spine Conference
Mar 23 - 27, 2015
United States / Utah / Salt Lake City
Contact: Stephanie James, University of Utah
Phone: 801-587-7957
Email: stephanie.james@hsc.utah.edu

9th International Conference on Managing Fatigue
Mar 23 - 26, 2015
Australia / Perth
Contact: Conference Secretariat, EECW Pty Ltd
Phone: 011-61-3-9863-7606
Email: eecw@eecw.com.au

Infectious Diseases: Adult Issues in the Outpatient & Inpatient Settings
Mar 23 - 27, 2015
United States / Florida / Sarasota
Contact: Tara Esteves, Live Cme Manager, American Medical Seminars, Inc.
Phone: 866-267-4263 (Toll Free) Or 941-388-1766, Fax: 941-365-7073
Email: testeves@ams4cme.com

Medical CBT for Anxiety: Ultra-Brief Techniques for Real Doctors (Cognitive Behavior Therapy)
Mar 23 - 25, 2015
United States / Hawaii / Maui
Contact: Greg Dubord, MD, CME Director, CBT Canada
Phone: 877-466-8228
Email: registrar@cbt.ca

Targeted Treatments for Breast & Ovarian Cancers
Mar 24, 2015
United Kingdom / Manchester
Contact: Robyn, Education Events, Christie Nhs Foundation Trust
Phone: 011-44-16-1446-3403
Email: education.events@christie.nhs.uk

National Pain Management Study Day
Mar 25, 2015
United Kingdom / London
Contact: Education And Conference Centre, The Royal Marsden
Phone: 011-44-20-7808-2921
Email: conferencecentre@rmh.nhs.uk

2015 Rehabtech Asia (Alternative Medicine, Clinical Pharmacology, General Medicine, Genetics, Nutrition, Pediatrics, Physiatry, Sports Medicine)
Mar 26 - 28, 2015
Singapore / Singapore
Contact: Sia Chen Wei, Senior Executive (Events Marketing), Singex Exhibitions Pte Ltd
Phone: 011-65-6403-2520
Email: chenwei.sia@singex.com

2015 World Congress on Osteoporosis, Osteoarthritis & Musculoskeletal Diseases
Mar 26 - 29, 2015
Italy / Milan Other Specialties
Contact: Laurence Triouleyre, Meetings Manager & Committee Of National Societies Coordinator, International Osteoporosis Foundation
Phone: 011-41-22-994-0122
Email: ltriouleyre@iofbonehealth.org

6th International Conference on Fixed Combination In The Treatment of Hypertension, Dyslipidemia & Diabetes Mellitus
Mar 26 - 29, 2015
Germany / Berlin
Contact: Gail Tito, Conference Secretariat, Paragon Group
Phone: 011-41-22-533-0948, Fax: 011-41-22-580-2953
Email: fixed2015@fixedcombination.com

8th International Conference on Neonatal & Childhood Pulmonary Vascular Disease
Mar 26 - 28, 2015
United States / California / San Francisco
Contact: Office Of Continuing Medical Education, Ucsf
Phone: 415-476-4251, Fax: 415-476-0318
Email: info@ocme.ucsf.edu

12th Workshop on Costs & Assessment in Psychiatry: Mental Health Policy & Economics Research: Improving Access, Quality & Outcomes
Mar 27 - 29, 2015
Italy / Venice
Contact: International Center of Mental Health Policy & Economics
Fax: 011-39-02-5810-6901
Email: info@icmpe.org

2015 Female Pelvic Medicine & Reconstructive Surgery Comprehensive Review Course
Mar 27 - 28, 2015
United States / Texas / Dallas
Contact: American Urogynecologic Society
Phone: 202-367-1167, Fax: 202-367-2167
Email: info@augs.org

Ultrasound Guided Emergency Medicine Procedures Course
Mar 27, 2015
British Columbia / Vancouver
Contact: Continuing Professional Development, University Of British Columbia
Phone: 604-875-5101, Fax: 604-875-5078
Email: cpd.info@ubc.ca
23rd European Congress of Psychiatry
Mar 28 - 31, 2015
Austria / Vienna
Contact: Vanessa Fisher, Pm,Kenes International
Phone: 011-41-22-908-0488, Fax: 011-41-22-906-9140
Email: epa@kenes.com

Masterclass in Ophthalmic Oncology
Mar 28 - 29, 2015
India / Mumbai
Contact: Varuna Punjabi, Medical Education & Healthcare Institute
Phone: 011-91-22-2494-0518, Fax: 011-91-22-2494-0517
Email: support.ionco@mehi.in

Giant Strides in Anesthesia
Mar 29 - Apr 3, 2015
Mexico / Cozumel
Contact: Coleen Hilliard, Meeting Coordinator, Northwest Anesthesia Seminars
Phone: 509-547-7065, Fax: 509-547-1265
Email: coleen@nwas.com

Infectious Diseases for Primary Care
Mar 30 - Apr 1, 2015
United States / Florida / Lake Buena Vista
Contact: Leslie Burk, Mce Conferences, Mce Conferences Inc.
Phone: 888-533-9031, Fax: 858-777-5588
Email: Info@Mceconferences.Com

5th Asian Football Confederation Medical Conference
Apr 2 - 4, 2015
India / New Delhi
Contact: Conference Secretariat, All India Football Federation
Phone: 011-91-11-2804-1430
Email: aiff@the-aiff.com

Airway Interventions & Management in Emergencies
- Montreal
Apr 7, 2015
Canada / Quebec / Montreal
Contact: Janice Macisaac, CME Manager,Canadian Association of Emergency Physicians
Phone: 613-523-3343 Ext. 20, Fax: 613-523-0190
Email: jmacisaac@caep.ca

Airway Interventions & Management In Emergencies
- Montreal
Apr 8, 2015
Canada / Quebec / Montreal
Contact: Janice Macisaac, Cme Manager,Canadian Association of Emergency Physicians
Phone: 613-523-3343 Ext. 20, Fax: 613-523-0190
Email: jmacisaac@caep.ca

Diagnosis to Treatment: Recognizing Obesity as a Disease
Apr 8 - 12, 2015
United States / Colorado / Denver
Contact: Asbp
Phone: 303-770-2526, Fax: 303-779-4834
Email: info@asbp.org

2015 Anxiety & Depression Conference
Apr 9 - 12, 2015
United States / Florida / Miami
Contact: Anxiety & Depression Association of America
Phone: 240-485-1032

2015 Australain Psychological Society (APS) College of Health Psychologists Conference
Apr 10 - 11, 2015
Australia / Sydney
Contact: Aps
Phone: 011-61-3-8662-3300, Fax: 011-61-3-9663-6177
Email: events@psychology.org.au

94th American Association of Plastic Surgeons (AAPS) Annual Meeting
Apr 11 - 14, 2015
United States / Arizona / Scottsdale
Contact: Aaps
Phone: 978-927-8330, Fax: 978-524-8890

Football Medicine Strategies for Player Care
Apr 11 - 13, 2015
United Kingdom / London
Contact: Giulia Indelicato, Conference Manager, Isokinetic Medical Group
Phone: 011-39-5-1298-6878
Email: G.indelicato@isokinetic.com

2015 British Neuroscience Association (BNA) Festival of Neuroscience
Apr 12 - 15, 2015
United Kingdom / Edinburgh Neurology
Contact: Bna
Phone: 011-44-20-8166-8713
Email: office@bna.org.uk

Chronic Pain Management for the Family Physician
Apr 13, 2015
Canada / Alberta / Calgary
Contact: Sylvia Vespa, Cumming School of Medicine, University of Calgary
Phone: 403-909-9095
Email: sylvia-vespa@albertahealthservices.ca
Clinical Training Course: **Osteoporosis & Other Metabolic Bone Diseases**

Apr 13 - 15, 2015
*United Kingdom / Oxford*

Contact: Janet Crompton, Course Organiser, Bone Research Society
Phone: 011-44-14-5354-9929, Fax: 011-44-14-5354-8919
Email: janet@janet-crompton.com

Mental Health Care in the Community: **Dementia & Older Adult Mental Health**

Apr 13, 2015
*United Kingdom / Birmingham*

Contact: Amy Partleton, Centre For Professional Development, University of Birmingham
Phone: 011-44-12-1414-2677
Email: a.partleton@bham.ac.uk

2nd International Conference on Advances in Medical Science (ICAMS)

Apr 14 – 16, 2015
*Malaysia / Kuala Lumpur*

Contact: Organising Chairman, 2nd Icams 2015
Phone: 011-60-3-9145-8605, Fax: 011-60-3-9145-8607
Email: info@klconference.com

14th Asian Australasian Congress of Neurological Surgeons

Apr 15 - 18, 2015
*South Korea / Jeju*

Contact: Gabriel Heng, Apm,Kenes Asia
Phone: 011-65-295-6984, Fax: 011-65-292-4721
Email: info@aacns2015.com

2015 American Academy of Ophthalmology (AAO) Mid-Year Forum

Apr 15 - 18, 2015
*United States / District of Columbia / Washington*

Contact: Gabrielle Naughten, Aao
Phone: 415-561-8565
Email: gnaughten@aoao.org

2015 European Lung Cancer Conference

Apr 15 - 18, 2015
*Switzerland / Geneva*

Contact: European Society For Medical Oncology
Phone: 011-41-91-973-1900, Fax: 011-41-91-973-1902
Email: esmo@esmo.org

23rd Biennial Congress of the SA Arthroplasty Society

Apr 15 - 18, 2015
*South Africa / Port Edward*

Contact: C/O South African Orthopaedic Association
Phone: 011-27-51-430-3280, Fax: 011-27-51-430-3284
Email: info@saoa.org.za

# 7th International Congress on Psychopharmacology / 3rd International Symposium on Child & Adolescent Psychopharmacology

Apr 15 - 19, 2015
*Turkey / Antalya*

Contact: Gokcen Demirkaya, Project Coordinator, Valor Congress Organizations
Phone: 011-90-31-2491-8888, Fax: 011-90-31-2491-9989
Email: valor@valor.com.tr

# 7th World Cornea Congress

Apr 15, 2015
*United States / California / San Diego*

Contact: Gail Reggio, Executive Director,Cornea Society
Phone: 703-591-0196, Fax: 703-434-3000
Email: info@corneasociety.org

# 8th International Dip Symposium on Diabetes, Hypertension, Metabolic Syndrome & Pregnancy

Apr 15 - 18, 2015
*Germany / Berlin*

Contact: Dip Secretary,Comtecmed
Phone: 011-972-3-566-6166
Email: dip@comtecmed.com

2015 Canadian Association for Clinical Microbiology & Infectious Diseases (CACMID) Annual Conference

Apr 16 - 18, 2015
*Canada / Prince Edward Island / Charlottetown*

Contact: Dr. Matthew W. Gilmour, Secretary Treasurer, Cacmid
Phone: 204-787-4597, Fax: 204-787-4699
Email: matthew.gilmour@cacmid.ca


Apr 16 - 18, 2015
*France / Paris Orthopedics*

Contact: Sylke Anderson, Meeting Administrator,Icjr
Phone: 760-942-7859, Fax: 760-942-1140
Email: sanderson@icjr.net

# 2nd World Congress on Controversies in Pediatrics

Apr 16 - 19, 2015
*Hungary / Budapest*

Contact: Secretariat, Congressmed
Phone: 011-972-73-706-6950
Email: copedia@congressmed.com

# 36th Annual American College of Oral & Maxillofacial Surgeons (ACOMS) Scientific Conference & Exhibition

Apr 18 - 20, 2015
*United States / Florida / Fort Lauderdale*

Contact: ACOMS
Phone: 202-367-1182, Fax: 202-367-2182
Forthcoming Conferences and Meetings

December 2014

55th British Society for Haematology (BSH) Annual Scientific Meeting
Apr 20 - 22, 2015
United Kingdom / Edinburgh
Contact: Sharon Forster, BSH Conference Secretariat, BSH
Phone: 011-44-132-350-3019, Fax: 011-44-132-350-9753
Email: sharon.forster@bshconferences.co.uk

Management of Gynaecology in the Community
Apr 20 - 22, 2015
United Kingdom / Birmingham
Contact: Amy Partleton, Centre for Professional Development, University of Birmingham
Phone: 011-44-12-1414-2677
Email: a.partleton@bham.ac.uk

2015 Chronic Disease Management & Pain Management Update Panama Canal Cruise
Apr 21 - May 7, 2015
Peru / Lima
Contact: CMEATSEA
Phone: 888-523-3732 or 604-684-9283

Challenges in Pediatric Hematology & Oncology: 2nd International / 9th National Congress of Iranian Society of Pediatric Hematology & Oncology (IPHOS)
Apr 21 - 24, 2015
Iran / Tehran
Contact: Gholamreza Bahoush, Scientific Secretary of The Congress,IPHOS
Phone: 011-98-21-6691-2679, Fax: 011-98-21-6691-2679
Email: info@iphos.ir

2015 Association of Surgeons of Great Britain & Ireland (ASGBI) International Surgical Congress
Apr 22 - 24, 2015
United Kingdom / Manchester
Contact: Asgbi
Phone: 011-44-20-7973-0300, Fax: 011-44-20-7430-9235
Email: admin@asgbi.org.uk

2015 Canadian Society of Nephrology (CSN) Annual General Meeting
Apr 22 - 26, 2015
Canada / Ontario / Ottawa
Contact: Stacey Pacheco, Coordinator, Csn Administrative Office
Phone: 514-643-4985
Email: coordinator@csnsn.ca

2015 British Maternal & Fetal Medicine Society (BMFMS) Annual Conference
Apr 23 - 24, 2015
United Kingdom / London
Contact: Society Administrator,Bmfms
Email: bmfms@rcog.org.uk

2015 Canadian Respiratory Conference
Apr 23 - 25, 2015
Canada / Ontario / Ottawa
Contact: C/O Taylor & Associates
Phone: 613-747-0262, Fax: 613-745-1846
Email: crc@taylorandassociates.ca

3rd World Congress on Controversies, Debates & Consensus in Bone, Muscle & Joint Diseases under the auspices of The IOF & ESECO
Apr 23 - 26, 2015
Canada / Quebec / Montreal
Contact: Secretariat, Congressmed Ltd
Phone: 011-972-73-706-6953, Fax: 011-972-73-725-6266
Email: bmjd@congressmed.com

2015 International Congress of Korean Society of Otorhinolaryngology-Head & Neck Surgery
Apr 24 – 26, 2015
South Korea / Seoul
Contact: Danny D. Jung, Manager,lb Planning
Phone: 011-82-2-2273-7650, Fax: 011-82-2-2273-7651
Email: korl@ibmed.co.kr

Diagnosis & Management of Prolapse, Including Use of Pessaries & Follow-Up of the Pessary Patient
Apr 24, 2015
Canada / Alberta / Calgary
Contact: Laurie Simmonds, Cumming School of Medicine, University of Calgary
Phone: 403-210-6275
Email: lisimmond@ucalgary.ca

Imaging in Adult Congenital Heart Disease: Pearls for All Cardiac Providers
Apr 24 - 26, 2015
United States / Florida / Ponte Vedra Beach
Contact: Cvcme, Coordinator, Mayo Clinic
Phone: 800-283-6296 or 507-266-6703
Email: cvcme@mayo.edu

1st World Conference on Abdominal Wall Hernia Surgery
Apr 25 - 29, 2015
Italy / Milan
Contact: Organizing Secretariat, Aim Group International Milan
Email: hernia2015@aimgroup.eu

4th Joint Meeting of European Calcified Tissue Society & International Bone & Mineral Society
Apr 25 - 28, 2015
Netherlands / Rotterdam
Contact: Kate Timms, Congress Secretariat, Bioscientifica
Phone: 011-44-14-5464-2240, Fax: 011-44-14-5464-2222
Email: katie.timms@bioscientifica.com
5th Annual Bit World Congress of Molecular & Cell Biology
Apr 25 - 28, 2015
China / Nanjing
Contact: Judy, Bit Congress, Inc.
Phone: 011-86-411-8479-9609 Ext. 856, Fax: 011-86-411-8479-9629
Email: judy@cmcbcongress.com

67th Southwestern Surgical Congress (SWSC) Annual Meeting
Apr 26 - 29, 2015
United States / California / Monterey
Contact: SWSC
Phone: 913-402-7102, Fax: 913-273-9940
Email: events@lp-etc.com

2015 Transcatheter Cardiovascular Therapeutics Angioplasty Summit (TCTAP)
Apr 28 - May 1, 2015
South Korea / Seoul
Contact: Summit Md
Email: cvrf@summitmd.com

13th International Symposium on Myelodysplastic Syndrome
Apr 29 - May 2, 2015
United States / District of Columbia / Washington
Contact: Francesca Starr, Kenes International
Phone: 011-41-22-908-0488, Fax: 011-41-22-906-9140
Email: mds@kenes.com

2015 Asian Pacific Society of Cardiology Congress 2015
Apr 29 - May 2, 2015
United Arab Emirates / Abu Dhabi
Contact: MCI Middle East, Congress Secretariat, MCI Middle East
Phone: 011-97-14-311-6300, Fax: 011-97-14-311-6301
Email: apscc2015@mci-group.com

10th Annual International San Francisco Orthopaedic Trauma Course
Apr 30 - May 2, 2015
United States / California / San Francisco
Contact: Office of Continuing Medical Education, UCSF
Phone: 415-476-4251, Fax: 415-476-0318
Email: info@ocme.ucsf.edu

Clinical Endocrinology for Primary Care
Apr 30 - May 3, 2015
United Kingdom / Cayman Islands
Contact: Medical Education Resources, Inc.
Phone: 800-421-3756 or 303-798-9682, Fax: 303-798-5731
Email: info@mer.org

Diabetes Update & Advances in Endocrinology & Metabolism
Apr 30 - May 2, 2015
United States / California / San Francisco
Contact: Office of Continuing Medical Education, UCSF
Phone: 415-476-4251, Fax: 415-476-0318
Email: info@ocme.ucsf.edu

Geriatric Medicine for Primary Care
May 1 - 3, 2015
United States / Louisiana / New Orleans
Contact: Medical Education Resources, Inc.
Phone: 800-421-3756 or 303-798-9682, Fax: 303-798-5731
Email: info@mer.org

Geriatrics & Pain Management for Primary Care
May 1 - 3, 2015
United States / New Mexico / Santa Fe
Contact: Leslie Burk, MCE Conferences, MCE Conferences Inc.
Phone: 888-533-9031, Fax: 858-777-5588
Email: info@mceconferences.com

2015 American Transplant Congress
May 2 - 6, 2015
United States / Pennsylvania / Philadelphia
Contact: American Society of Transplant Surgeons
Phone: 703-414-7870, Fax: 703-414-7874
Email: asts@asts.org

2015 American Occupational Health Conference
May 3 - 6, 2015
United States / Maryland / Baltimore
Contact: Mary Lunn, Conference Coordinator, American College of Occupational & Environmental Medicine
Phone: 847-818-1800 Ext. 393, Fax: 847-818-9265
Email: mlunn@acoem.org

2015 Association for Research in Vision & Ophthalmology (ARVO) Annual Meeting
May 3 - 7, 2015
United States / Colorado / Denver
Contact: ARVO
Phone: 240-221-2900, Fax: 240-221-0370

2015 Annual International Conference on Public Health
May 4 – 7, 2015
Greece / Athens
Contact: Gregory Papanikos, Mr, Athens Institute For Education and Research (ATINER)
Phone: 011-30-210-363-4210
Email: info@atiner.gr
Forthcoming Conferences and Meetings

December 2014

2015 Annual International Conference on Internal Medicine
May 4 - 7, 2015
Greece / Athens
Contact: Gregory Papanikos, Internal Medicine Conference, Athens Institute For Education And Research (Atiner)
Phone: 011-30-210-363-4210
Email: info@atiner.gr

3rd Annual International Conference on Health & Medical Sciences
May 4 - 7, 2015
Greece / Athens
Contact: Gregory Papanikos, Mr, Athens Institute For Education And Research (Atiner)
Phone: 011-30-210-363-4210
Email: info@atiner.gr

7th International Pediatric Simulation Symposia & Workshops
May 4 - 6, 2015
Canada / British Columbia / Vancouver
Contact: Tanguy Roelens, IPSS Corporate Relations Manager, International Pediatric Simulation Society
Phone: 011-32-2-740-2254
Email: tanguy.roelens@associationhq.com

Anesthesia Update Mediterranean Cruise
May 4 - 16, 2015
Italy / Venice
Contact: Coleen Hilliard, Meeting Coordinator, Northwest Anesthesia Seminars
Phone: 509-547-7065, Fax: 509-547-1265
Email: coleen@nwas.com

11th International Symposium on Endovascular Therapeutics
May 6 - 9, 2015
Spain / Barcelona
Contact: Site Secretariat
Phone: 011-34-93-505-2503, Fax: 011-34-93-488-3703
Email: secretariat@sitesymposium.org

2015 Association of Professors of Human & Medical Genetics Annual Workshop & Special Interest Group Meetings
May 6 - 8, 2015
United States / Florida / Clearwater Beach
Contact: ACMG Meetings
Phone: 301-718-9603, Fax: 301-718-9604
Email: pfreire@acmg.net

48th Annual European Society for Paediatric Gastroenterology, Hepatology & Nutrition (ESPGHAN) Meeting
May 6 - 9, 2015
Netherlands / Amsterdam
Contact: Lucy Church, Project Assistant, MCI Uk Ltd
Phone: 011-44-845-180-0360
Email: annualmeeting2015@espghan.org

74th Annual Society for Investigative Dermatology (SID) Meeting
May 6 - 9, 2015
United States / Georgia / Atlanta
Contact: SID
Phone: 216-579-9300, Fax: 216-579-9333
Email: sid@sidnet.org

2015 Arteriosclerosis, Thrombosis & Vascular Biology Peripheral Vascular Disease Scientific Sessions
May 7 - 9, 2015
United States / California / San Francisco
Contact: American Heart Association
Phone: 888-242-2453 (Us) Or 214-570-5935
Email: scientificconferences@heart.org

21st World Congress on Controversies in Obstetrics, Gynecology & Infertility (COGI)
May 7 - 10, 2015
China / Guilin
Contact: Secretariat, Secretariat, Congressmed
Phone: 011-972-73-706-6950, Fax: 011-972-73-706-6959
Email: cogi@congressmed.com

14th European Association for Palliative Care World Congress
May 8 - 10, 2015
Denmark / Copenhagen
Contact: Interplan Congress, Meeting & Event Management Ag
Phone: 011-49-89-5482-3462, Fax: 011-49-89-5482-3444
Email: eapc2015@interplan.de

Rheumatology and Musculoskeletal Medicine for Primary Care
May 8 – 10, 2015
United States / California / San Diego
Contact: Medical Education Resources, Inc.
Phone: 800-421-3756 or 303-798-9682, Fax: 303-798-5731
Email: info@mer.org

2015 Canadian Blood & Marrow Transplant Group (CBMTG) Annual Conference
May 13 - 16, 2015
Canada / Quebec / Montreal
Contact: CBMTG Head Office
Phone: 604-874-4944, Fax: 604-874-4378
Email: cbmtg@malachite-mgmt.com

23rd Annual Symposium: New Developments in Prenatal Diagnosis & Medical Genetics
May 13, 2015
Canada / Ontario / Toronto
Contact: Elizabeth Gan, CME Administrative Course Director, Dept. of Ob/Gyn, University of Toronto / Mount Sinai Hospital
Phone: 416-586-4800 Ext. 2489, Fax: 416-586-5958
Email: egan@mtsinitai.on.ca
Medical CBT: Ten-Minute Cognitive Behaviour Therapy Techniques For Real Doctors
May 15 - 16, 2015
Canada / Ontario / Ottawa
Contact: Greg Dubord, MD, CME Director, CBT Canada
Phone: 877-466-8228
Email: registrar@cbt.ca

2015 Australasian College of Dermatologists (ACD) Annual Scientific Meeting
May 16 - 19, 2015
Australia / Adelaide
Contact: ACD
Phone: 1300 361 821 (Australia Only) or 011-61-2-8765-0242
Fax: 011-61-2-9736-2194
Email: admin@dermcoll.asn.au

10th Recent Advances in Neuropsychiatric, Psychological & Social Sciences
May 19 - 22, 2015
Greece / Athens Clinical
Contact: John Kouros, Dr., Association of Psychology & Psychiatry for Adults & Children
Phone: 011-30-210-684-2663, Fax: 011-30-210-684-2079
Email: congress@appac.gr

2015 Association of Psychology & Psychiatry for Adults & Children (APPAC) Annual International Conference
May 19 - 22, 2015
Greece / Athens
Contact: Secretariat, APPAC
Phone: 011-30-210-684-2663, Fax: 011-30-210-684-2079
Email: congress@appac.gr

10th European Congress on Menopause and Andropause
May 20 - 22, 2015
Spain / Madrid
Contact: Stephane Talboom, K.I.T. Group GMBH
Phone: 011-49-30-246-030, Fax: 011-49-30-2460-3310
Email: info@emas-online.org

2015 Obstetric Anaesthesia
May 20 - 22, 2015
United Kingdom / Torquay
Contact: Obstetric Anaesthetists' Association
Phone: 011-44-20-7631-8883, Fax: 011-44-20-7631-4352

63rd Canadian Association of Physical Medicine & Rehabilitation (CAPM&R) 63rd Annual Scientific Meeting
May 20 - 23, 2015
Canada / British Columbia / Vancouver
Contact: Lisa Baker, Membership/Conference Registrar, CAPM & R
Phone: 613-507-0480, Fax: 866-531-0626
Email: info@capmr.ca
Forthcoming Conferences and Meetings

December 2014

7th International Symposium on the Diabetic Foot
May 20 - 23, 2015
Netherlands / Den Hague
Contact: Symposium Secretariat, Congress by Design
Phone: 011-31-88-89-8101, Fax: 011-31-88-89-8109
Email: isdf@congressbydesign.com

2015 Canadian Society for Transfusion Medicine (CSTM) Annual Conference
May 21 - 24, 2015
Canada / Manitoba / Winnipeg
Phone: 905-415-3917, Fax: 905-415-0071
Email: conference@transfusion.ca

Advances in QPCR & DPCR
May 21 - 22, 2015
Singapore / Singapore
Contact: Paul Raggett, CEO, Select Biosciences South East Asia Pte. Ltd.
Phone: 011-65-9186-3246
Email: p.raggett@selectbio.com

2015 Canadian Centre for Applied Research in Cancer Control (ARCC) Conference
May 24 - 25, 2015
Canada / Quebec / Montreal
Contact: ARCC
Phone: 416-971-9800 Ext. 2326
Email: arcc@cancercare.on.ca

2015 Paris-Echo
May 27 - 29, 2015
France / Paris
Contact: Overcome
Phone: 011-33-1-4192-0120, Fax: 011-33-1-4641-0521
Email: paris-echo@overcome.fr

Advances in Brain Cancer Research
May 27 - 30, 2015
United States / District of Columbia / Washington
Contact: American Association for Cancer Research
Phone: 215-440-9300, Fax: 215-440-9313
Email: aacr@aacr.org

5th World Congress on ADHD: From Childhood To Adult Disorder
May 28 - 31, 2015
United Kingdom / Glasgow
Contact: Congress and Exhibition Office, CPO Hanser Service
Phone: 011-49-40-670-8820, Fax: 011-49-40-670-3283
Email: info@adh.org

Clinical Pearls in Medicine / Mediterranean Cruise
May 28 - Jun 9, 2015
Italy / Venice
Contact: Dr. Martin Gerretsen, Director of CME, Sea Courses Cruises
Phone: 888-647-7327, Fax: 888-547-7337
Email: cruises@seacourses.com

Virtual Colonoscopy Workshop
May 28 - 30, 2015
United States / California / San Francisco
Contact: Office of Continuing Medical Education, UCSF
Phone: 415-476-4251, Fax: 415-476-0318
Email: info@ocme.ucsf.edu

2015 American Society of Colon & Rectal Surgeons (ASCRS) Annual Scientific Meeting
May 30 - Jun 3, 2015
United States / Massachusetts / Boston
Contact: ASCRS
Phone: 847-290-9184, Fax: 847-290-9203
Email: ascrs@fascrs.org

10th International Symposium on Pediatric Pain
May 31 - Jun 4, 2015
United States / Washington / Seattle
Contact: Seattle Children's Hospital
Email: ispp2015@seattlechildrens.org

24th Asian & Oceanic Congress of Obstetrics & Gynaecology - AOCOG 2015
Jun 3 - 6, 2015
Malaysia / Kuching
Contact: Marcus, Console Communications
Email: info@aocog2015.com

Antepartum & Intrapartum Management
Jun 4 - 6, 2015
United States / California / San Francisco
Contact: Office of Continuing Medical Education, UCSF
Phone: 415-476-4251, Fax: 415-476-0318
Email: info@ocme.ucsf.edu

Practical Emergency Airway Management
Jun 4 - 5, 2015
United States / Maryland / Baltimore
Contact: Center for Emergency Medical Education
Phone: 800-651-2363
1. EBOLA VIRUS DISEASE

Overview

Ebola or Marburg virus disease outbreaks constitute a major public health issue in Sub-Saharan Africa. The Ebola virus is transmitted among humans through close and direct physical contact with infected bodily fluids, the most infectious being blood, faeces and vomit. The Ebola virus has also been detected in breast milk, urine and semen. In a convalescent male, the virus can persist in semen for at least 70 days; one study suggests persistence for more than 90 days.

Saliva and tears may also carry some risk. However, the studies implicating these additional bodily fluids were extremely limited in sample size and the science is inconclusive. In studies of saliva, the virus was found most frequently in patients at a severe stage of illness. The whole live virus has never been isolated from sweat.

The Ebola virus can also be transmitted indirectly, by contact with previously contaminated surfaces and objects.

KEY FACTS

- Ebola virus disease (EVD), formerly known as Ebola haemorrhagic fever, is a severe, often fatal illness in humans.
- The virus is transmitted to people from wild animals and spreads in the human population through human-to-human transmission.
- The average EVD case fatality rate is around 50%. Case fatality rates have varied from 25% to 90% in past outbreaks.
- The first EVD outbreaks occurred in remote villages in Central Africa, near tropical rainforests, but the most recent outbreak in west Africa has involved major urban as well as rural areas.
- Community engagement is key to successfully controlling outbreaks. Good outbreak control relies on applying a package of interventions, namely case management, surveillance and contact tracing, a good laboratory service, safe burials and social mobilisation.
- Early supportive care with rehydration, symptomatic treatment improves survival. There is as yet no licensed treatment proven to neutralise the virus but a range of blood, immunological and drug therapies are under development.
- There are currently no licensed Ebola vaccines but two potential candidates are undergoing evaluation.

Background

The Ebola virus causes an acute, serious illness which is often fatal if untreated. Ebola virus disease (EVD) first appeared in 1976 in two simultaneous outbreaks, one in Nzara, Sudan, and the other in Yambuku, Democratic Republic of Congo. The latter occurred in a village near the Ebola River, from which the disease takes its name.

The current outbreak in west Africa, (first cases notified in March 2014), is the largest and most complex Ebola outbreak since the Ebola virus was first discovered in 1976. There have been more cases and deaths in this outbreak than all others combined. It has also spread between countries starting in Guinea then spreading across land borders to Sierra Leone and Liberia, by air (1 traveller only) to Nigeria, and by land (1 traveller) to Senegal.

The virus family *Filoviridae* includes three genera: Cuevavirus, Marburgvirus, and Ebolavirus. There are five species that have been identified: Zaire, Bundibugyo, Sudan, Reston and Tai Forest. The first three, Bundibugyo ebolavirus, Zaire ebolavirus, and Sudan ebolavirus have been associated with large
outbreaks in Africa. The virus causing the 2014 west African outbreak belongs to the Zaire species.

Transmission

It is thought that fruit bats of the Pteropodidae family are natural Ebola virus hosts. Ebola is introduced into the human population through close contact with the blood, secretions, organs or other bodily fluids of infected animals such as chimpanzees, gorillas, fruit bats, monkeys, forest antelope and porcupines found ill or dead or in the rainforest.

Ebola then spreads through human-to-human transmission via direct contact (through broken skin or mucous membranes) with the blood, secretions, organs or other bodily fluids of infected people, and with surfaces and materials (e.g. bedding, clothing) contaminated with these fluids.

Health-care workers have frequently been infected while treating patients with suspected or confirmed EVD through close contact with patients without precautions.

Burial ceremonies in which mourners have direct contact with the body of the deceased person can also play a role in the transmission of Ebola.

People remain infectious as long as their blood and body fluids, including semen and breast milk, contain the virus. Men who have recovered from the disease can still transmit the virus through their semen for up to seven weeks after recovery from illness.

Not an airborne virus

Ebola virus disease is not an airborne infection. Airborne spread among humans implies inhalation of an infectious dose of virus from a suspended cloud of small dried droplets.

This mode of transmission has not been observed during extensive studies of the Ebola virus over several decades. Theoretically, wet and bigger droplets from a heavily infected individual, who has respiratory symptoms caused by other conditions or who vomits violently, could transmit the virus – over a short distance – to another nearby person. Good quality studies from previous Ebola outbreaks show that all cases were infected by direct close contact with symptomatic patients.

Symptoms of Ebola virus disease

The incubation period, that is, the time interval from infection with the virus to onset of symptoms is 2 - 21 days. Humans are not infectious until they develop symptoms. First symptoms are the sudden onset of fever fatigue, muscle pain, headache and sore throat. This is followed by vomiting, diarrhoea, rash, symptoms of impaired kidney and liver function, and in some cases, both internal and external bleeding (e.g., oozing from the gums, blood in the stools). Laboratory findings include low white blood cell and platelet counts and elevated liver enzymes.

Diagnosis

It can be difficult to distinguish EVD from other infectious diseases such as malaria, typhoid fever and meningitis. Confirmation that symptoms are caused by Ebola virus infection are made using the following investigations:

- antibody-capture enzyme-linked immunosorbent assay (ELISA)
- antigen-capture detection tests
- serum neutralization test
- reverse transcriptase polymerase chain reaction (RT-PCR) assay
- electron microscopy
- virus isolation by cell culture.

Samples from patients are an extreme biohazard risk; laboratory testing on non-inactivated samples should be conducted under maximum biological containment conditions.

Treatment and vaccines

Supportive care-rehydration with oral or intravenous fluids and treatment of specific symptoms, improves survival. There is as yet no proven treatment available for EVD. No licensed vaccines are available yet, but 2 potential vaccines are undergoing human safety testing.

Prevention and control

Good outbreak control relies on applying a package of interventions, namely case management, surveillance and contact tracing, a good laboratory service, safe burials and social mobilisation. Risk reduction messaging should focus on several factors such as:

- Reducing the risk of wildlife-to-human transmission from contact with infected fruit bats or monkeys/apes and the consumption of their raw meat. Animals should be handled with gloves. Animal products should be thoroughly cooked before consumption.
- Reducing the risk of human-to-human transmission from direct or close contact with people with Ebola symptoms, particularly with their bodily fluids. Gloves and appropriate personal protective equipment should be worn when taking care of ill patients at home.
- Outbreak containment measures including prompt and safe burial of the dead, identifying people who may have been in contact with someone infected with Ebola, monitoring the health of contacts for 21 days, the importance of separating the healthy
from the sick to prevent further spread, the importance of good hygiene and maintaining a clean environment.

**Controlling infection in health-care settings**

Health-care workers should always take standard precautions when caring for patients, regardless of their presumed diagnosis. These include basic hand hygiene, respiratory hygiene, use of personal protective equipment (to block splashes or other contact with infected materials), safe injection practices and safe burial practices.

Health-care workers caring for patients with suspected or confirmed Ebola virus should apply extra infection control measures to prevent contact with the patient’s blood and body fluids and contaminated surfaces or materials such as clothing and bedding. Health-care workers should wear face protection (a face shield or a medical mask and goggles), a clean, non-sterile long-sleeved gown, and gloves (sterile gloves for some procedures).

Laboratory workers are also at risk. Samples taken from humans and animals for investigation of Ebola infection control measures to prevent contact with the surfaces or materials such as clothing and bedding. Laboratory workers should wear face protection (a face shield or a medical mask and goggles), a clean, non-sterile long-sleeved gown, and gloves (sterile gloves for some procedures).

**No evidence that viral diseases change their mode of transmission**

Moreover, scientists are unaware of any virus that has dramatically changed its mode of transmission. For example, the H5N1 avian influenza virus, which has caused sporadic human cases since 1997, is now endemic in chickens and ducks in large parts of Asia.

That virus has probably circulated through many billions of birds for at least two decades. Its mode of transmission remains basically unchanged.

Speculation that Ebola virus disease might mutate into a form that could easily spread among humans through the air is just that: speculation, unsubstantiated by any evidence.

**WHO: EBOLA response roadmap update as on 10 October 2014**

A total of 8399 confirmed, probable, and suspected cases of Ebola virus disease (EVD) have been reported in seven affected countries (Guinea, Liberia, Nigeria, Senegal, Sierra Leone, Spain, and the United States of America) up to the end of 8 October. There have been 4033 deaths. Following the WHO Ebola Response Roadmap structure, country reports fall into two categories: 1) those with widespread and intense transmission (Guinea, Liberia, and Sierra Leone); and 2), those with an initial case or cases, or with localized transmission (Nigeria, Senegal, Spain, and the United States of America). An overview of the situation in the Democratic Republic of the Congo, where a separate, unrelated outbreak of EVD is occurring, is also provided.

**Countries with widespread and intense transmission**

Eight thousand three hundred and seventy-six (probable, confirmed and suspected cases and 4024 deaths from EVD have been reported up to the end of 7 October 2014 by the Ministries of Health of Guinea and Liberia, and up to the end of 8 October by the Ministry of Health of Sierra Leone.

Exposure of health-care workers (HCWs) to EVD continues to be an alarming feature of this outbreak. As of 8 October 2014, 416 HCWs are known to have developed EVD (74 in Guinea, 201 in Liberia, 11 in Nigeria and 129 in Sierra Leone, and one in Spain). Two hundred and thirty three HCWs have died as a result of EVD infection (38 in Guinea, 95 in Liberia, five in Nigeria, 95 in Sierra Leone) and investigations are ongoing.

**2. Countries with an initial case or cases, or with localized transmission**

Four countries, Nigeria, Senegal, Spain, and the United States of America have now reported a case or cases imported from a country with widespread and intense transmission. In Nigeria, there have been 20 cases and eight deaths. In Senegal, there has been one case, but as yet there have been no deaths or further suspected cases attributable to Ebola.

*For more information contact:*

WHO Media centre, Telephone: +41 22 791 2222,
E-mail: mediacompliances@who.int

**2. BLOOD SAFETY AND AVAILABILITY**

**KEY FACTS**

- Of the 108 million blood donations collected globally, approximately half of these are collected in the high-income countries, home to 18% of the world’s population. This shows an increase of almost 25% from 80 million donations collected in 2004.

- In low-income countries, up to 65% of blood transfusions are given to children under five years of age; whereas in high-income countries, the most frequently transfused patient group is over 65 years of age, accounting for up to 76% of all transfusions.

- Blood donation rate in high-income countries is 36.8 donations per 1000 population; 11.7 donations in middle-income and 3.9 donations in low-income countries.
• An increase of 8.6 million blood donations from voluntary unpaid donors has been reported from 2004 to 2012. In total, 73 countries collect over 90% of their blood supply from voluntary unpaid blood donors; however, 72 countries collect more than 50% of their blood supply from family/replacement or paid donors.
• Only 43 of 156 reporting countries produce plasma-derived medicinal products (PDMP) through the fractionation of plasma collected in the country, whereas the majority of the other 113 countries import PDMP from abroad.

National blood policy and organization
Blood transfusion saves lives and improves health, but many patients requiring transfusion do not have timely access to safe blood. Providing safe and adequate blood should be an integral part of every country’s national health care policy and infrastructure.

In 2012, 70% countries had a national blood policy, compared with 60% countries in 2004. Overall, 62% countries have specific legislation covering the safety and quality of blood transfusion:
• 81% high-income countries;
• 60% middle-income countries; and
• 44% low-income countries.

Blood supply
About 108 million blood donations are collected worldwide. More than half of these are collected in high-income countries, home to 18% of the world’s population. About 10,000 blood centres in 168 countries report collecting a total of 83 million donations. Collections at blood centres vary according to income group. The median annual donations per blood centre is 3100 in the low- and middle-income countries, as compared to 15,000 in the high-income countries.

There is a marked difference in the level of access to blood between low- and high-income countries. The whole blood donation rate is an indicator for the general availability of blood in a country. The median blood donation rate in high-income countries is 36.8 donations per 1000 population. This compares with 11.7 donations in middle-income countries and 3.9 donations in low-income countries.

Seventy-five countries report collecting fewer than 10 donations per 1000 population. Of these, 40 countries are in WHO’s African Region, eight in the Americas, seven in the Eastern Mediterranean Region, six in Europe, six in South-Eastern Asia and eight in the Western Pacific. All are low- or middle-income countries.

BLOOD DONORS
Age and gender of blood donors
Data about the gender profile of blood donors show that globally 30% of blood donations are given by women, although this ranges widely. In 20 of the

111 reporting countries, less than 10% donations are given by female donors.

The age profile of blood donors shows that more young people donate blood in low- and middle-income countries, proportionally than in high-income countries.

Types of blood donors
There are three types of blood donors:
• voluntary unpaid,
• family/replacement, and
• paid.

An adequate and reliable supply of safe blood can be assured by a stable base of regular, voluntary, unpaid blood donors. These donors are also the safest group of donors as the prevalence of bloodborne infections is lowest among this group. World Health Assembly resolution (WHA63.12) urges all Member States to develop national blood systems based on voluntary unpaid donation and work towards the goal of self-sufficiency. Data reported to WHO shows significant increases of voluntary unpaid blood donations in low- and middle-income countries:
• An increase of 8.6 million blood donations from voluntary unpaid donors from 2004 to 2012 has been reported by 162 countries. The highest increase of voluntary unpaid blood donations is in the South-East Asia (78%) and African (51%) Regions. The maximum increase in absolute numbers was reported in the Western Pacific Region.
• Seventy-three countries collect more than 90% of their blood supply from voluntary unpaid blood donations (38 high-income countries, 26 middle-income countries and nine low-income countries). This includes 60 countries with 100% (or more than 99%) of their blood supply from voluntary unpaid blood donors.
• In 72 countries, more than 50% of the blood supply is still dependent on family/replacement and paid blood donors (8 high-income countries, 48 middle-income countries and 16 low-income countries).
• 25 countries still report collecting paid donations in 2012, around 1 500 000 donations in total.

Blood screening
WHO recommends that screening should be mandatory for HIV, hepatitis B, hepatitis C and syphilis. Blood screening should be performed according to the quality system requirements.
• Twenty-five countries are not able to screen all donated blood for one or more of the above infections.
• Irregular supply of test kits is one of the most commonly reported barriers to screening.
• 97% blood screening laboratories in high-income countries are monitored through external quality assessment schemes, as compared to 33% in
middle-income countries and 16% in low-income countries.

- The prevalence of transfusion-transmissible infections (TTI) in blood donations in high-income countries is considerably lower than in low- and middle-income countries (Table 1).

These differences reflect the variation in prevalence among population who are eligible to donate blood, the type of donors and the effectiveness of the system of educating and selecting donors.

**Blood processing**

Blood collected in an anticoagulant can be stored and transfused to a patient in an unmodified state. This is known as ‘whole blood’ transfusion. However, blood can be used more effectively if it is processed into components, such as red cell concentrates, platelet concentrates, plasma and cryoprecipitate. In this way, it can meet the needs of more than one patient.

**Supply of plasma-derived medicinal products (PDMP)**

World Health Assembly resolution (WHA63.12) urges Member States to establish, implement and support nationally-coordinated, efficiently-managed and sustainable blood and plasma programmes according to the availability of resources, with the aim of achieving self-sufficiency. Individual governments should ensure sufficient and equitable supply of plasma-derived medicinal products namely immunoglobulins and coagulation factors, which are needed to prevent and treat a variety of serious conditions that occur worldwide.

Forty-three countries (23 high-income, 18 middle-income, 2 low-income) of the 156 reporting countries, reported producing all or part of the PDMP through the fractionation (e.g. domestic or/and contract fractionation) of plasma collected in the country.

- Thirty-five of the 43 countries report plasma fractionation carried out within the country.
- Eight of the 43 countries report plasma sent for contract fractionation in another country.

Ninety-five countries report that all PDMP are imported. Fifteen countries report that no PDMP were used during the reporting period; three countries report that plasma collected in the country was sold to the manufacturers of plasma-derived medicinal products and products purchased from PMDP suppliers in the market. Around 10 million litres

<table>
<thead>
<tr>
<th>Income group</th>
<th>HIV</th>
<th>HBV</th>
<th>HCV</th>
</tr>
</thead>
<tbody>
<tr>
<td>High-income countries</td>
<td>0.002% (0.0004% - 0.02%)</td>
<td>0.02% (0.008% - 0.24%)</td>
<td>0.02% (0.004% - 0.22%)</td>
</tr>
<tr>
<td>Middle-income countries</td>
<td>0.12% (0.03% - 0.2%)</td>
<td>0.64% (0.19% - 2.33%)</td>
<td>0.37% (0.13% - 0.71%)</td>
</tr>
<tr>
<td>Low-income countries</td>
<td>0.85% (0.48% - 2.0%)</td>
<td>3.59% (2.01% - 6.08%)</td>
<td>1.07% (0.63% - 1.96%)</td>
</tr>
</tbody>
</table>

Clinical use of blood

Unnecessary transfusions and unsafe transfusion practices expose patients to the risk of serious adverse transfusion reactions and TTI. Unnecessary transfusions also reduce the availability of blood products for patients who are in need. WHO recommends the development of systems to monitor and improve the safety of the transfusion process such as hospitals transfusion committees and hemovigilance.

- One hundred and eleven countries have national guidelines on the appropriate clinical use of blood.
- Transfusion committees are present in 70% of the hospitals performing transfusions in high-income countries and in about half of the hospitals in middle- and low-income countries.
- Clinical audits are conducted in 89% of hospitals performing transfusion in the high-income countries and in 52% of hospitals in the middle- and low-income countries.
- Systems for reporting adverse transfusion events are present in 93% of hospitals performing transfusion in high-income countries and 63% in middle- and low-income countries.
- 77% high-income countries have a national hemovigilance system, compared to only 30% of middle- and low-income countries.

**Blood transfusions**

There are great variations between countries in the age distribution of transfused patients. For example, in the high-income countries, the most frequently transfused patient group is over 65 years, which accounts for up to 76% of all transfusions. In the low-income countries, up to 65% of transfusions are for children under the age of five years.

In high-income countries, transfusion is most commonly used for supportive care in cardiovascular surgery, transplant surgery, massive trauma, and therapy for solid and hematological malignancies. In low- and middle-income countries it is used more often to manage pregnancy-related complications and severe childhood anemia.
WHO response
The risk of transmission of serious infections, including HIV and hepatitis, through unsafe blood and chronic blood shortages brought global attention to the importance of blood safety and availability. WHO recommends the following integrated strategy for blood safety and availability:
- Establishment of a national blood system with well-organized and coordinated blood transfusion services, effective evidence-based and ethical national blood policies with the goal of achieving self-sufficiency, and legislation and regulation, that can provide sufficient and timely supplies of safe blood and blood products to meet the transfusion needs of all patients.
- Collection of blood, plasma and other blood components from low-risk, regular, voluntary unpaid donors through the strengthening of donation systems, the phasing out of family/ replacement donation, the elimination of paid donation, and effective donor management, including care and counselling.
- Quality-assured screening of all donated blood for transfusion-transmissible infections (TTI), including HIV, hepatitis B, hepatitis C and syphilis, confirmatory testing of the results of all donors screen-reactive for infection markers, blood grouping and compatibility testing, and systems for processing blood into blood products (blood components for transfusion and plasma derived-medicinal products), as appropriate, to meet health care needs.
- Rational use of blood and blood products to reduce unnecessary transfusions and minimize the risks associated with transfusion, the use of alternatives to transfusion, where possible, and safe and good clinical transfusion practices, including patient blood management.
- Step-wise implementation of effective quality systems, including quality management, standards, good manufacturing practices, documentation, training of all staff and quality assessment.

Through its Blood and Transfusion Safety program, WHO supports countries in developing national blood systems to ensure timely access to safe and sufficient supplies of blood and blood products and good transfusion practices to meet the patients' needs.

Data source: This fact sheet is based on the data obtained through the WHO Global Database on Blood Safety (GDBS) for the year 2012 which were reported by 100 countries. To give a more complete overview of the global situation, data for the year 2011 have been used from 68 countries and data for the year 2010 have been used from 11 countries, where current data are not available. Overall, responses received from 179 countries cover 98.6% of the world’s population.

3. AMBIENT (OUTDOOR) AIR QUALITY AND HEALTH

Overview
Outdoor air pollution is a major environmental health problem affecting everyone in developed and developing countries alike. WHO estimates that some 80% of outdoor air pollution-related premature deaths were due to ischaemic heart disease and strokes, while 14% of deaths were due to chronic obstructive pulmonary disease or acute lower respiratory infections; and 6% of deaths were due to lung cancer. Some deaths may be attributed to more than one risk factor at the same time.

KEY FACTS
- Air pollution is a major environmental risk to health. By reducing air pollution levels, countries can reduce the burden of disease from stroke, heart disease, lung cancer, and both chronic and acute respiratory diseases, including asthma.
- The lower the levels of air pollution, the better the cardiovascular and respiratory health of the population will be, both long- and short-term.
- The “WHO Air quality guidelines” provide an assessment of health effects of air pollution and thresholds for health-harmful pollution levels.
- Ambient (outdoor air pollution) in both cities and rural areas was estimated to cause 3.7 million premature deaths worldwide in 2012.
- Some 88% of those premature deaths occurred in low- and middle-income countries, and the greatest number in the WHO Western Pacific and South-East Asia regions.
- Policies and investments supporting cleaner transport, energy-efficient housing, power generation, industry and better municipal waste management would reduce key sources of urban outdoor air pollution.
- Reducing outdoor emissions from household coal and biomass energy systems, agricultural waste incineration, forest fires and certain agro-forestry activities (e.g. charcoal production) would reduce key rural and peri-urban air pollution sources in developing regions.
- Reducing outdoor air pollution also reduces emissions of CO₂ and short-lived climate pollutants such as black carbon particles and methane, thus contributing to the near- and long-term mitigation of climate change.
- In addition to outdoor air pollution, indoor smoke is a serious health risk for some three billion people who cook and heat their homes with biomass fuels and coal.
Background
A 2013 assessment by WHO’s International Agency for Research on Cancer (IARC) concluded that outdoor air pollution is carcinogenic to humans, with the particulate matter component of air pollution most closely associated with increased cancer incidence, especially cancer of the lung. An association also has been observed between outdoor air pollution and increase in cancer of the urinary tract/bladder.

Ambient (outdoor air pollution) in both cities and rural areas was estimated to cause 3.7 million premature deaths worldwide per year in 2012; this mortality is due to exposure to small particulate matter of 10 microns or less in diameter (PM$_{10}$), which cause cardiovascular and respiratory disease, and cancers.

Most sources of outdoor air pollution are well beyond the control of individuals and demand action by cities, as well as national and international policymakers in sector like transport, energy waste management, buildings and agriculture.

There are many examples of successful policies in transport, urban planning, power generation and industry that reduce air pollution:

- **for industry:** clean technologies that reduce industrial smokestack emissions; improved management of urban and agricultural waste, including capture of methane gas emitted from waste sites as an alternative to incineration (for use as biogas);
- **for transport:** shifting to clean modes of power generation; prioritizing rapid urban transit, walking and cycling networks in cities as well as rail interurban freight and passenger travel; shifting to cleaner heavy duty diesel vehicles and low-emissions vehicles and fuels, including fuels with reduced sulfur content;
- **for urban planning:** improving the energy efficiency of buildings and making cities more compact, and thus energy efficient;
- **for power generation:** increased use of low-emissions fuels and renewable combustion-free power sources (like solar, wind or hydropower); co-generation of heat and power; and distributed energy generation (e.g. mini-grids and rooftop solar power generation);
- **for municipal and agricultural waste management:** strategies for waste reduction, waste separation, recycling and reuse or waste reprocessing; as well as improved methods of biological waste management such as anaerobic waste digestion to produce biogas, are feasible, low cost alternatives to the open incineration of solid waste. Where incineration is unavoidable, then combustion technologies with strict emission controls are critical.

In addition to outdoor air pollution, indoor smoke is a serious health risk for some three billion people who cook and heat their homes with biomass fuels and coal. Some 4.3 million premature deaths were attributable to household air pollution in 2012. Almost all of that burden was in low-middle-income countries as well.

The 2005 “WHO Air quality guidelines” apply worldwide and are based on expert evaluation of current scientific evidence for:

1. particulate matter (PM)
2. nitrogen dioxide (NO$_2$) and sulfur dioxide (SO$_2$), in all WHO regions.

### 1. Particulate matter (PM)

**Definition and principal sources:** PM affects more people than any other pollutant. The major components of PM are sulfate, nitrates, ammonia, sodium chloride, black carbon, mineral dust and water. It consists of a complex mixture of solid and liquid particles of organic and inorganic substances suspended in the air. The most health-damaging particles are those with a diameter of 10 microns or less, (≤ PM$_{10}$), which can penetrate and lodge deep inside the lungs. Chronic exposure to particles contributes to the risk of developing cardiovascular and respiratory diseases, as well as of lung cancer.

**Health effects:** There is a close, quantitative relationship between exposure to high concentrations of small particulates (PM$_{10}$ and PM$_{2.5}$) and increased mortality or morbidity, both daily and over time. Conversely, when concentrations of small and fine particulates are reduced, related mortality will also go down – presuming other factors remain the same. This allows policymakers to project the population health improvements that could be expected, if particulate air pollution is reduced. The WHO 2005 guideline limits aimed to achieve the lowest concentrations of PM possible.

**Guideline values**

PM$_{2.5}$ : 10 µg/m$^3$ annual mean; 25 µg/m$^3$ 24-hour mean
PM$_{10}$ : 20 µg/m$^3$ annual mean; 50 µg/m$^3$ 24-hour mean

In addition to guideline values, the Air Quality Guidelines provide interim targets for concentrations of PM$_{10}$ and PM$_{2.5}$ aimed at promoting a gradual shift from high to lower concentrations.

“WHO Air Quality Guidelines” estimate that reducing annual average particulate matter (PM$_{10}$) concentrations from levels of 70 µg/m$^3$, common in many developing cities, to the WHO guideline level of 20 µg/m$^3$, could reduce air pollution-related deaths by around 15%. However, even in the European Union, where PM concentrations in many cities do comply...
with Guideline levels, it is estimated that average life expectancy is 8.6 months lower than it would otherwise be, due to PM exposures from human sources.

In developing countries, indoor exposure to pollutants from the household combustion of solid fuels on open fires or traditional stoves increases the risk of acute lower respiratory infections and associated mortality among young children; indoor air pollution from solid fuel use is also a major risk factor for cardiovascular disease, chronic obstructive pulmonary disease and lung cancer among adults.

There are serious risks to health not only from exposure to PM, but also from exposure to ozone ($O_3$), nitrogen dioxide ($NO_2$) and sulfur dioxide ($SO_2$). Ozone is a major factor in asthma morbidity and mortality, while nitrogen dioxide and sulfur dioxide also can play a role in asthma, bronchial symptoms, lung inflammation and reduced lung function.

2. Ozone ($O_3$)

Guideline values: $O_3$ : 100 µg/m$^3$ 8-hour mean

The recommended limit in the 2005 Air Quality Guidelines was reduced from the previous level of 120 µg/m$^3$ in previous editions of the “WHO Air Quality Guidelines” based on recent conclusive associations between daily mortality and lower ozone concentrations.

Definition and principal sources: Ozone at ground level – not to be confused with the ozone layer in the upper atmosphere – is one of the major constituents of photochemical smog. It is formed by the reaction with sunlight (photochemical reaction) of pollutants such as nitrogen oxides ($NO_x$) from vehicle and industry emissions and volatile organic compounds (VOCs) emitted by vehicles, solvents and industry. As a result, the highest levels of ozone pollution occur during periods of sunny weather.

Health effects: Excessive ozone in the air can have a marked effect on human health. It can cause breathing problems, trigger asthma, reduce lung function and cause lung diseases. In Europe, it is currently one of the air pollutants of most concern. Several European studies have reported that the daily mortality rises by 0.3% and that for heart diseases by 0.4%, per 10 µg/m$^3$ increase in ozone exposure.

Nitrogen dioxide ($NO_2$)

Guideline values: $NO_2$ : 40 µg/m$^3$ annual mean; 200 µg/m$^3$ 1-hour mean

The current WHO guideline value of 40 µg/m$^3$ (annual mean) was set to protect the public from the health effects of gaseous.

Definition and principal sources: As an air pollutant, $NO_2$ has several correlated activities.

- At short-term concentrations exceeding 200 µg/m$^3$, it is a toxic gas which causes significant inflammation of the airways.
- $NO_2$ is the main source of nitrate aerosols, which form an important fraction of PM$_{10}$ and, in the presence of ultraviolet light, of ozone.

The major sources of anthropogenic emissions of $NO_2$ are combustion processes (heating, power generation, and engines in vehicles and ships).

Health effects: Epidemiological studies have shown that symptoms of bronchitis in asthmatic children increase in association with long-term exposure to $NO_2$.

Reduced lung function growth is also linked to $NO_2$ at concentrations currently measured (or observed) in cities of Europe and North America.

Sulfur dioxide ($SO_2$)

Guideline values: $SO_2$ 20 µg/m$^3$ 24-hour mean; 500 µg/m$^3$ 10-minute mean

A $SO_2$ concentration of 500 µg/m$^3$ should not be exceeded over average periods of 10 minutes duration. Studies indicate that a proportion of people with asthma experience changes in pulmonary function and respiratory symptoms after periods of exposure to $SO_2$ as short as 10 minutes. The (2005) revision of the 24-hour guideline for $SO_2$ concentrations from 125 to 20 µg/m$^3$ was based on the following considerations.

- Health effects are now known to be associated with much lower levels of $SO_2$ than previously believed.
- A greater degree of protection is needed.
- Although the causality of the effects of low concentrations of $SO_2$ is still uncertain, reducing $SO_2$ concentrations is likely to decrease exposure to co-pollutants.

Definition and principal sources: $SO_2$ is a colourless gas with a sharp odour. It is produced from the burning of fossil fuels (coal and oil) and the smelting of mineral ores that contain sulfur. The main anthropogenic source of $SO_2$ is the burning of sulfur-containing fossil fuels for domestic heating, power generation and motor vehicles.

Health effects: $SO_2$ can affect the respiratory system and the functions of the lungs, and causes irritation of the eyes. Inflammation of the respiratory tract causes coughing, mucus secretion, aggravation of asthma and chronic bronchitis and makes people more prone to infections of the respiratory tract. Hospital admissions for cardiac disease and mortality increase on days with higher $SO_2$ levels. When $SO_2$ combines with water, it forms sulfuric acid; this is the main component of acid rain which is a cause of deforestation.
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