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Original Article

Circulating Obestatin levels during Ramadan fasting in normal weight and obese subjects

Cavit Culha, Suheyla Gorar, Yalcin Aral
Department of Endocrinology and Metabolism, Ankara Training and Research Hospital, Ankara, Turkey

Kuwait Medical Journal 2019; 51 (4): 335 - 340

ABSTRACT

Objectives: To evaluate obestatin levels in both obese and normal subjects before and after Ramadan period. Also, the relationships between plasma obestatin levels and anthropometric and metabolic parameters were analysed.

Design: Prospective study

Setting: Ankara Training and Research Hospital, Ankara, Turkey

Subjects: Premenopausal women between the ages of 21 - 42 years, 30 obese and 35 normal weight, were recruited to the study.

Intervention: Blood samples were received and anthropometric measurements were made from all of the subjects two days before and two days after Ramadan.

Main Outcome Measures: Obestatin was measured by an enzyme immunoassay (EIA). Insulin resistance was calculated by homeostasis model assessment of insulin resistance (HOMA-IR).

Results: Obestatin levels were significantly lower in obese individuals compared with normal controls [0.65 (0.72) vs 1.10 (1.22) ng/ml; p<0.01]. While obestatin [1.45 (1.22) vs 0.65 (0.72) ng/ml; p=0.002] and HDL-C levels were higher after Ramadan in obese group; BMI, HOMA-IR and LDL-C levels were found to be lower. After Ramadan, BMI, HOMA-IR, fasting blood glucose and fasting insulin were negatively correlated with obestatin level.

Conclusions: The changes in pattern of sleep and fasting, and eating two times in a day during Ramadan may lead to increased obestatin in obese subjects, and this result may positively affect obesity, glucose and lipid metabolism. Thus, this peptide may be a therapeutic helper in pathological conditions such as insulin resistance and diabetes.

INTRODUCTION

Today, the prevalence of obesity is continuously increasing. Thus, the discovery of the molecular mechanisms regulating food intake and body weight also increases. Obestatin was found by Zhang et al in 2005[1]. It is produced in the gut and encoded by the ghrelin gene, with 23 amino acid peptide, a hormone. Obestatin is a contraction of the words “obese” and “statin” denoting suppression[2]. Pathophysiological significance in humans is still unknown.

A matter of debate is the biological role of obestatin. First, it has been proposed as an anorectic hormone and has opposite effect of ghrelin, but subsequent studies have not supported this view[2]. Obestatin levels are reported to be higher in women than men, does not correlate with age[3] and is higher in smokers non-significantly[4]. It has been suggested that plasma obestatin levels are lower in individuals with obesity[5,6], type 2 diabetes and impaired glucose tolerance than individuals with normal weight[7].

The month of Ramadan is holy in Islam and Ramadan fasting is one of the five pillars of Islam. Fasting during Ramadan is obligatory for all healthy Muslims. During Ramadan, Muslims abstain from food and drink from dawn until sunset. Traditionally the practise is to eat 2 meals, 1 before dawn (suhore) and 1 just after sunset (iftar)[8]. Eating and drinking is permitted only at night (between iftar and suhore). A large quantity is eaten in one evening meal instead of in several meals during the day in Ramadan. Ramadan teaches Muslims self-restraint and reminds them of the feelings of the impoverished. According to previous studies, a nutrient given to the body at an unusual time may lead to different metabolic effects[8-10].
Sahur, which is called the morning breakfast, is eaten between 03:00 and 05:00 in the Ramadan month. Also, Ramadan fasting is an opportunity to investigate the effect of reduced frequency of meals (at least two meals a day instead of three meals a day) on body metabolism.

Our hypothesis is that at the time of Ramadan, with changes in the number of meals and sleep times of the day, and changes in social habits, including obestatin changes of rhythmic oscillation pattern, the amount of hormone can cause many changes in the body. If any, these changes may differ between normal weight and obese people.

Very little is known about obestatin’s physiological role in humans. Thus, to examine the relationship of obestatin with biochemical, anthropometric parameters, and energy metabolism in the body may be interesting. Plasma levels of obestatin in humans, affecting factors, and its interaction with energy metabolism and about data is still limited and requires further investigation. Every bit of information to be obtained about obestatin may be important for this hormone to take place and applicability in the treatment of obesity in future.

To our knowledge, this is the first study done in relation to levels of obestatin during Ramadan fasting. We know that lipid profile is affected by dietary habits, and oxygen saturation, % of daily dietary fat, carbohydrates and exercise. There is limited and contradictory information in relation to lipid levels in Ramadan. In this study, lipid levels were also specially evaluated and its relationship with obestatin was examined.

SUBJECTS AND METHODS
This study was conducted in June-July period of 2015 during the month of Ramadan. Thirty fasting obese subjects (mean age: 35 years, age range: 21-42 years, BMI = 34.56 ± 4.0 kg/m²) and 35 fasting normal healthy premenopausal women (mean age: 34 years, age range: 20-40 years, BMI = 23.6 ± 1.4 kg/m²) (control group) were recruited to the study. Male sex, diabetes mellitus, hypertension, hyperlipidemia, heart failure, liver cirrhosis, cancer, chronic kidney disease, adrenal and thyroid gland disease, prolactinoma (hyperprolactinemia), acromegaly patients, smokers, pregnant and lactating ones, carbohydrate and lipid metabolism, and any drug users whose medication might affect the studied parameters were excluded from the study. Because of menstruation during this period, six women in the obese group and seven women in the control group were excluded from the study. Obese and control groups who were normally menstruating were tested in the follicular phase of their menstrual cycle (d 5-10 from menses).

The local ethics committee approved the study and subjects gave written informed consent before study participation.

Two days prior to the start of Ramadan and in the last 2 days of Ramadan, as two times, blood was received from the study participants and related measurements were made. Obestatin levels and anthropometric and biochemical parameters were evaluated. Blood sample analyses and anthropometric measurements were done in same center (Ankara Training and Research Hospital) and by the same staff. Anthropometric measurements were performed at the time of blood sampling and included the body weight and body mass index (BMI). Body weights (BW) of subjects were measured with TANITA-Feed Body Composition Analyzer (Model TBF-300, Tokyo, Japan) (BW, % fat and BMI were determined) in the morning. Blood samples were taken after a night fast at 08.00 hours before Ramadan and 12 hours after last meal (17.00 hours) on the 28-30th day of Ramadan in all subjects. Plasma was collected and kept at -80 °C until assayed. The concentration of plasma obestatin was determined with commercial radioimmunoassay kits (Phoenix Pharmaceuticals Inc, Belmont, CA, USA) using 125I-labelled obestatin as a tracer. The intra-assay coefficient of obestatin was 5%, and the interassay coefficient was 9%. The sensitivity of the assay was 50 ng/l. Fasting plasma glucose levels were measured by standard enzymatic methods (Roche Diagnostic GmbH, Manheim, Germany). Serum insulin levels were measured by immunoradiometric assay (IRMA) (sandwich-type assay) using an insulin IRMA kit (Immunotech, Prague, Czech Republic). Intra-assay and inter-assay coefficients of variation were 4.3% and 3.4%, respectively, and the minimum detectable insulin concentration was 0.5 µIU/ml. Insulin resistance was determined using the homeostasis model assessment-insulin resistance (HOMA-IR) index, calculated as:

\[ \text{HOMA-IR} = \left( \frac{\text{serum glucose level (mg/dl)} \times \text{insulin (µIU/ml)}}{405} \right) \]

Serum concentrations of total cholesterol (TC), high density lipoprotein cholesterol (HDL-C), and triglycerides (TG) were measured by enzymatic calorimetric methods using commercially available kits (Roche Diagnostic GmbH). Low density lipoprotein cholesterol (LDL-C) levels were calculated using the Friedewald equation. BMI was calculated as weight (kg) divided by height (m²). Normal weight was defined as a BMI of 19 - 24.9 kg/m² and obesity was defined as a BMI >30 kg/m².

Statistical analysis
Data analysis was performed using SPSS for Windows, version 11.5 (SPSS Inc., Chicago, IL, United States). Whether the continuous variables were normally distributed or not were determined by using Shapiro Wilk test. Data were shown as...
Obestatin levels were significantly lower in obese individuals compared with normal controls [0.65 (0.72) vs 1.10 (1.22) ng/ml; p <0.01]. Also, HOMA-IR [3.0 (1.5) vs 1.5 (1.5); p <0.001], fasting blood glucose (FBG) [96.0 (12.0) vs 86.5 (11.5) mg/dl; p <0.01], fasting insulin [13.5 (6.4) vs 9.4 (9.3) µIU/ml; p <0.01], TG [169.0 (67.7) vs 101.5 (54.2) mg/dl; p = 0.001], TC (196.8 ± 27.9 vs 173.6 ± 22.1 mg/dl; p = 0.001) and LDL-C (44.5 ± 7.8 vs 49.9 ± 8.3 mg/dl; p = 0.001) levels were found to be significantly higher and HDL-C (49.5 ± 8.5 vs 55.1 ± 7.7 mg/dl; p = 0.001) levels were found to be significantly lower before Ramadan in obese group (Table 1). When the intra-group values were compared before and after Ramadan; while obestatin [1.45 (1.22) vs 1.45 (1.22) ng/ml; p = 0.061] and LDL-C (121.0 ± 23.6 vs 103.2 ± 21.7 mg/dl; p <0.01) values were found to be significantly higher and HOMA-IR (3.0 (1.5) vs 1.5 (1.5); p <0.001), fasting blood glucose (FBG) [96.0 (12.0) vs 86.5 (11.5) mg/dl; p <0.01], fasting insulin [13.5 (6.4) vs 9.4 (9.3) µIU/ml; p <0.01], TG [169.0 (67.7) vs 101.5 (54.2) mg/dl; p = 0.001], TC (196.8 ± 27.9 vs 173.6 ± 22.1 mg/dl; p = 0.001) and LDL-C (44.5 ± 7.8 vs 49.9 ± 8.3 mg/dl; p <0.01) levels were found to be significantly lower.

When the control group’s values were compared before and after Ramadan; while obestatin [1.45 (1.22) vs 1.10 (1.22) ng/ml; p = 0.061] levels tended to be higher at the end of Ramadan, the difference was not statistically significant. At the same time, HDL-C (196.8 ± 27.9 vs 173.6 ± 22.1 mg/dl; p = 0.001) levels were found to be significantly lower before Ramadan in obese group.
There were no significant differences in HOMA-IR, levels were found to be significantly lower. mg/dl; p <0.001) and TG [95.0 (37.0) vs 101.5 (54.2) mg/dl; p <0.05] was negatively correlated with obestatin levels. After Ramadan, the data were analyzed separately for each group, BMI (r = -0.57, p = 0.001), HOMA-IR (r = -0.44, p <0.05), FBG (r = -0.52, p <0.01) and fasting insulin (r = -0.41, p <0.05) were negatively correlated with obestatin level in obese group. Obestatin levels were not correlated with any parameter in the control group.

The results of Spearman’s correlation analysis between plasma obestatin levels and selected variables are demonstrated in Table 2.

In the analysis before Ramadan for all subjects, plasma obestatin level was negatively correlated with BMI (-0.27, p <0.05), HOMA-IR (-0.29, p <0.05), TC (-0.26, p <0.05), LDL-C (-0.26, p <0.05) and FBG (-0.24, p = 0.051) levels. Both groups were examined separately before Ramadan; both in obese and the control group, obestatin levels were not associated with any parameter. In the analysis after Ramadan for all subjects, BMI (r = -0.26, p <0.05), HOMA-IR (r = -0.35, p <0.01) and fasting insulin (r = -0.37, p <0.01) levels were negatively correlated with obestatin levels. After Ramadan, when the data were analyzed separately for each group, BMI (r = -0.57, p = 0.001), HOMA-IR (r = -0.44, p <0.05), FBG (r = -0.52, p <0.01) and fasting insulin (r = -0.41, p <0.05) were negatively correlated with obestatin level in obese group. Obestatin levels were not correlated with any parameter in the control group.

DISCUSSION

In this study, plasma obestatin levels are found to be statistically low in obese individuals when compared to normal controls. This study was conducted during Ramadan. Considering Ramadan fasting, obestatin levels, and anthropometric and metabolic parameters, both before and at the end of Ramadan in obese and healthy normal weight control subjects were evaluated. Although obestatin and HDL-C levels were statistically increased at the end of Ramadan, LDL-C levels were found to be statistically decreased in obese group. While there was a tendency for obestatin levels to increase in the normal group before Ramadan, which did not reach to a statistical significance; at the end of Ramadan, a decrease in LDL-C and increase in HDL-C was determined. Thus, with an increase in obestatin and HDL-C as well as a decrease in LDL-C during the month of Ramadan, we can consider the month of Ramadan as a protective period against heart and circulation system diseases (atherosclerosis).

Obestatin is a hormone with 23 amino acids, produced in the gut. Obestatin, which is coded by ghrelin gene, was found in 2005[1,2]. Obestatin levels are not affected by age[3] and is higher in women[3]. It is reported that obestatin concentrations are lower in individuals with obesity[4,5] and type 2 diabetes mellitus[7]. Trovato et al[11] found that obestatin levels decrease along with food intake in healthy individuals.

It is reported that there was no change in TC, TG and very low density lipoprotein cholesterol (VLDL-C); an increase in LDL-C; and a decrease in HDL-C, glucose, BW and BMI for both sexes during Ramadan[8]. Then, Mansi et al[12] found that Ramadan fasting caused nonsignificant increase in blood sugar and TG levels and an increase in HDL-C as well as decrease in weight and LDL-C for healthy students in Jordan. Both groups stated that the effect of Ramadan fasting on serum lipid levels can be closely related with biochemical response to fasting or nutritional diet[8,12].

Although Al Hourani et al[9] reported a significant decrease in serum TG and insignificant increase in HDL-C during Ramadan, Sarraf Zadegan et al[14] reported that TC, TG, LDL-C, HDL-C and FBG levels did not change during Ramadan. According to Rehman et al[9], blood glucose, cholesterol, triacylglycerol and LDL-C levels were significantly decreased and HDL-C increased during Ramadan.
It is reported that these beneficial changes observed during Ramadan are temporary, and if dietary habits of Ramadan are sustained, they continue\cite{15}. There is a marked decrease in the activity of HMG-CoA-reductase during fasting, resulting in reduced synthesis of cholesterol, depicted as low blood cholesterol levels\cite{16}.

It is demonstrated that LDL-C significantly decreased at the end of fasting and there were non-significant increase in HDL-C, TG, VLDL-C and blood glucose. Ramadan fasting has a beneficial effect on LDL-C\cite{16}. In the study of Ali et al, although there is an increase in HDL-C during Ramadan, there was no change in BMI, TC and LDL-C\cite{17}. In our study, LDL-C decreased and HDL-C increased for both groups at the end of Ramadan.

Coronary artery disease is the main reason for death in the world. This disease and its relation with serum LDL-C and HDL-C are well determined. High levels of LDL-C and low levels of HDL-C are reasons for the rapid development of atherosclerosis. Compared to the time prior to Ramadan, LDL-C decreased and HDL-C increased in the middle and at the end of Ramadan. Ramadan fasting is well tolerated and an effective lipid-lowering agent\cite{18}.

There are studies which show the correlation between obestatin and BMI\cite{3,5,7}. Our results were consistent with a negative relationship between obestatin and BMI, as with most studies. In two studies\cite{19,20}, it was reported that obestatin levels are higher for obese cases. In a study with healthy normal women, obestatin and BMI, insulin and ghrelin / obestatin rate did not have a significant relation\cite{19}. In another study, a significant relation was observed between fasting obestatin level and measurements of body composition in normal weight women and of all the cohort, however significant relation was not available for obese women. It was reported that a possible reason for that was suppressed obestatin secretion as a result of obesity in obese women\cite{3}.

As previously reported, obestatin is not endogenously ligand for GPR39\cite{21,22}. Nakahara et al\cite{23} suggested that obestatin is a nutritional marker, which reflects body fat and insulin resistance. Haider et al\cite{24} demonstrated an increase in obestatin concentrations after weight loss in obese patients, like ghrelin. Observations of Green et al support the role of obestatin for regulation of metabolism by means of changes in appetite, but it shows no direct effects on glucose homeostasis or insulin secretion\cite{25}. A study of Ren et al, suggests that obestatin regulates β cell survival and insulin secretion. Therefore, ghrelin-obestatin system is referred as a promising target for treatment of diabetes and obesity\cite{26}.

Obestatin is still a debated peptide due to its most conflicting receptor(s). It was shown that obestatin is bound to pancreatic β cells and glucagon like peptide-1 receptor (GLP-1R) at adipocytes. GLP-1R has recently emerged among possible receptor candidates. It was shown that obestatin forms antiapoptotic effects on in-vitro and in-vivo β cells and islets as well as improves the insulin sensitivity. Due to strong similarity between obestatin and glucagon like peptide-1 on β-cell survival effects and activated signaling pathway, it was hypothesized that obestatin would interact with GLP-1R. Also, it was found that obestatin was bound to GLP-1R and upregulated the GLP-1R mRNA. Obestatin binding was displaced by GLP-1R agonist Ex-4\cite{23,27}. The role of obestatin on insulin secretion is still controversial, as both stimulatory and inhibitory effects were reported\cite{27}. Granata et al\cite{28} showed that obestatin increases insulin secretion in both the absence and presence of glucose. We also found apparent higher insulin levels in obese group both before and after Ramadan.

Obestatin behaves as anti-diabetogenic peptides by positively influencing glucose and lipid metabolism\cite{27,28}. It was shown that obestatin exerts effects by suppressing food intake, slowing gastric emptying and jejunal motility and reducing body weight gain, in rodents\cite{27,29}. Obestatin also regulates lipid metabolism by inhibiting lipolysis in rats\cite{27}.

This study has some restrictions. Although blood control time is appropriate for Ramadan fasting, it is not appropriate for physiological circadian during the last few days of Ramadan (08.00 a.m vs. 17.00 p.m). Therefore, it is important to note this situation during comparisons. Additionally, lipid levels can be affected by physical activities. It is known that physical activities reduce during the month of Ramadan, however we did not measure the physical activity levels. The third restriction is the measurement of ghrelin, acilghrelin and des acil ghrelin, which I wish were possible. We are now scheduling such a study.

CONCLUSION

Obestatin can be a beneficial marker for nutritional status, which reflects adiposity and insulin resistance, in the short run. In order to think of it as an endocrine marker, which can reflect changes on acute and chronic nutritional status, further studies, which shall describe the roles of obestatin and its receptor as well as showing it as a potential treatment against obesity, are needed.

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Authors Contribution: CC designed and wrote manuscript; SG collected data; YA edited manuscript.
REFERENCES


Effect of pre-gestational and gestational periodic body mass index on nausea and vomiting during spinal anesthesia for elective cesarean operation

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²Department of Anesthesiology and Reanimation, Isparta State Hospital, Isparta, Turkey

ABSTRACT

Objective: The objective of the study was to evaluate the incidence of nausea-vomiting according to the body mass index (BMI).

Design: Prospective, case-control study

Setting: Department of Anesthesiology and Reanimation, Konya Education and Research Hospital, Konya, Turkey

Subjects: We prospectively enrolled 120 parturients with term pregnancy, aged 18 - 40 years and who were scheduled for elective caesarean section (C/S) under spinal anesthesia. Patients were divided into 2 groups, as obese (BMI ≥ 30) and non-obese (BMI < 30). We also recorded the incidence of nausea and vomiting within 15 minutes after spinal anesthesia.

Intervention: Non-interventional

Main outcome measure: We have investigated the effect of obesity on the incidence of nausea-vomiting in elective C/S under spinal anesthesia.

Results: There were no significant differences between the two groups with regards to ASA physical status, age, gestational age and smoking, all measurement times (p = 0.495, p = 0.780, p = 0.268, p >0.05, respectively) and incidence of nausea-vomiting. Mean blood pressure was significantly lower in Group II compared to Group I at the beginning of surgery and 20th minute of the surgery (p <0.001 and p <0.001, respectively).

Conclusions: In the study sample, pre-gestational and gestational BMI ≥30 kg/m² was not a risk factor for nausea-vomiting after spinal anesthesia in patients undergoing C/S. However, hypotension was found to significantly influence nausea-vomiting of the patients.

INTRODUCTION

Spinal anesthesia is widely used in obstetrics, both for cesarean section (C/S) and labor analgesia[1,2]. Spinal anesthesia has lower morbidity and mortality when compared to general anesthesia that causes a higher incidence of complications, such as difficult intubation, rapid desaturation, a greater chance of aspiration, and neonatal depression[3,4].

Although spinal anesthesia is a safe anesthetic method, spinal anesthesia is not free of complications and it has limitations, like a difficult puncture in some cases, hypotension, total spinal anesthesia, postdural puncture headache, and intraoperative nausea and vomiting[5]. Spinal anesthesia in obese parturients is associated with increased risk of technical difficulty and anesthetic failure[6]. Obesity correlates with increased intra-abdominal volume. Obesity increases during pregnancy, and it is influenced by fetus size, amniotic fluid, and uterus[6]. Obesity in parturients is also associated with an increased cesarean delivery rate and risks of adverse obstetric and perinatal outcomes[5,6].

Intraoperative nausea and vomiting are associated with sudden contractions of the diaphragm, causing both patient discomfort and intra-abdominal organ displacement. These abrupt contractions add to...
the hazard of aspiration, especially in full-stomach patients. Prevention, or at least reduction, can be achieved using drugs including metoclopramide and dimenhydrinate[7,8].

The objective of this study was to analyze the frequency and severity of intraoperative nausea and vomiting in obese pregnant women and non-obese pregnant women during spinal anesthesia.

SUBJECTS AND METHODS

The study was approved by the Ethics Committee for Clinical Investigations of Necmettin Erbakan University Meram Medicine Faculty (Reference Number: 2017-823). After obtaining written informed consent, we prospectively enrolled 120 parturients with term pregnancy, with American Society of Anesthesiology physical status Class I, aged 18 - 40 years, and who were scheduled for elective C/S under spinal anesthesia. The patients were divided into two equal groups: obese (body mass index (BMI) ≥30 kg/m²) and non-obese (BMI < 30 kg/m²). We determined the sample size by calculating the power in terms of statistical significance. The exclusion criteria were doses of anticoagulants that contraindicated spinal anesthesia, thrombocytopenia, coagulopathy, congestive cardiac failure, hypertension, valvular heart disease, diabetes mellitus, epilepsy or relevant drug allergy, gastrointestinal disease or those who had received anti-emetic medication in the preceding 24 hours, preeclampsia, pregnancy-induced hypertension, multiple pregnancies and with less than 36 weeks of gestation.

All study participants were informed about the purpose of the study and the method. Patients were monitored with cardioscope, non-invasive blood pressure, and pulse oximeter. Blood pressure was measured three times at 5-minute intervals before the spinal block. Crystalloids were infused at the same time anesthesia was administered for a total of 10 mL/kg until delivery. Pre-gestational and gestational height and weight were recorded before the spinal block. Crystalloids were infused at the median approach through L3-L4 intervertebral space. A Quincke 27-gauge spinal needle was inserted. Thus, 0.5% hyperbaric bupivacaine (2.0 mL) was administered when the height was between 156 cm and 160 cm; 0.5% hyperbaric bupivacaine (2.2 mL) was administered when the height was between 161 cm and 165 cm; and 0.5% hyperbaric bupivacaine (2.4 mL) was administered when the height was between 166 cm and 170 cm. A similar clinical management was found in other studies[9,10]. No other adjunct was added.

We checked the right and left side level of cold sensation loss by using an ice cube at 1 minute, 5 minutes, 10 minutes, and 15 minutes after spinal anesthesia. As soon as the sensory level was above T5, we passively moved the parturient into a 30° head-up position in order to prevent the cephalic spread of local anesthetic. We recorded the doses of ephedrine given. The incidence of nausea and vomiting during 15 minutes was recorded after spinal anesthesia[3]. The uterus was dislocated, the volume of crystalloids infused and total doses of vasopressors were recorded. The blood pressure was recorded at 2-minute intervals for 10 minutes after the spinal injection. Hypotension was defined as a drop in systolic blood pressure to below 100 mmHg or a preoperative mean blood pressure (MAP) decrease of more than 20%. Intravenous ephedrine (10 mg) was administered when hypotension was noted. Intravenous atropine (0.4 mg) was given when the heart rate was less than 60 beats/min[3].

Statistical analyses were performed with SPSS 20 software (SPSSInstitute, Chicago, IL, USA). Continuous data were tested for normality. Normally distributed data were summarized using mean and standard deviation and were compared using unpaired two-tailed t-tests. Skewed data were summarized using median (range) and were compared using Mann-Whitney U test. Categorical data were summarized using the number and were compared using X² test or Fisher’s exact test. Repeated-measures analysis of variance was used to compare hemodynamic changes over time between the groups. Paired data were compared using paired two-tailed t-tests or signed-rank tests. A p-value <0.05 was considered statistically significant.

RESULTS

Data were collected in Konya Public Hospitals Association, University of Health Sciences, Konya Training and Research Hospital, Konya, Turkey at the operating room. A total of 120 patients were enrolled in the study and all patients completed the investigation. These 120 patients were divided into 2 groups, those who were obese comprised Group I (60 patients) and the non-obese formed Group II (60 patients). Data analysis was performed on the two groups. No patient was withdrawn from the study after induction of spinal anesthesia.

Patient demographic data were presented in Table 1 and there were no significant differences between the two groups regarding age, gestational age and smoking (p = 0.495, p = 0.780, p = 0.268, respectively). Patient’s clinical characteristics were presented in Table 2. There were no significant differences between the two groups regarding nausea and vomiting, BMI, pre-pregnancy BMI and intraoperative fluid administration (p = 0.921, p = 0.666, p = 0.495, respectively). However, intraoperative ephedrine...
usage was significantly higher in Group II [10 (0-70)] compared to Group I [5 (0-20)] (p <0.001).

Changes in heart rate are seen in Figure 1. There were no significant differences between the two groups at all measurement times (p >0.05). Changes in MAP were presented in Figure 2. MAP was significantly lower in Group II compared to Group I at the beginning of surgery and at the 20th minute of surgery (p <0.001 and p <0.001, respectively). At the other measurement times, there were no significant differences between the two groups (p >0.05).

ASA: American Society of Anesthesiologists. Data presented as mean ± SD (normally distributed data), median (range) (skewed data) or number.

Table 1: Patients’ characteristics

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Group I (n = 60)</th>
<th>Group II (n = 60)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>29.34 ± 5.20</td>
<td>30.00 ± 5.29</td>
<td>0.495</td>
</tr>
<tr>
<td>Gestational age (weeks)</td>
<td>39 (28 - 41)</td>
<td>39 (28 - 42)</td>
<td>0.780</td>
</tr>
<tr>
<td>Smoking</td>
<td>2</td>
<td>5</td>
<td>0.268</td>
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</tbody>
</table>

Table 2: Patients’ clinical characteristics

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Group I (n = 60)</th>
<th>Group II (n = 60)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI (kg/m²)</td>
<td>32.00 ± 5.66</td>
<td>31.91 ± 4.84</td>
<td>0.921</td>
</tr>
<tr>
<td>Pre-pregnancy BMI (kg/m²)</td>
<td>26.88 ± 6.12</td>
<td>27.33 ± 5.22</td>
<td>0.666</td>
</tr>
<tr>
<td>Ephedrine usage (mg)</td>
<td>5 (0 - 20)</td>
<td>10 (0 - 70)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Intraoperative fluid administration (ml)</td>
<td>2000 (900 - 3000)</td>
<td>2000 (900 - 3000)</td>
<td>0.495</td>
</tr>
</tbody>
</table>

BMI: Body mass index. Data presented as mean ± SD (normally distributed data), median (range) (skewed data).

DISCUSSION

Pregnancy causes some physiological changes in the cardiovascular system. The important increase in cardiac output, during and immediately after labor, reaches up to 75% above pre-pregnancy levels\[11,12\]. In obese patients per 100 g fat tissue growth, heart rate increases by 50 beats/min\[13\]. Besides, decreasing in afterload during pregnancy is less significant in obese pregnant women due to an increase in peripheral vascular resistance\[14\]. As a result of increased volume in those patients, a left ventricular hypertrophy was observed followed by a dilation of the myocardium against this sustained increase in blood pressure generated by the hypervolemic state\[3\].

Pre-gestational hypertension is aggravated and associated with an increase in baseline heart rate and cardiac output, and pre-gestational hypertension can lead to diastolic dysfunction. Hyperdynamic status leads to right ventricular failure and pulmonary hypertension. Supine position, sleep apnea, and hypoxemia can aggravate this clinical picture\[12\]. In addition to specific changes in the cardiovascular system, some hormonal changes are also aggravated by obesity and may overload cardiovascular functions.

Hyperinsulinemia and insulin resistance cause fat accumulation, which makes obese pregnant women more susceptible to lethal arrhythmias, leading to changes in contractility and conduction of cardiac stimulation\[11,12\]. Endothelial dysfunction and vascular inflammatory response can cause preeclampsia during pregnancy\[12\].

Previously obese pregnant women are more prone to antenatal and gestational comorbidities such as chronic hypertension, diabetes, and preeclampsia, besides the greater chance of the development of fetal cardiac anomalies, macrosomia, and fetal shoulder dystocia, an autonomous neuropathy associated with diabetic cardiomyopathy probably increase the chances of post-regional anesthesia hypotension\[14,15\].

There are few studies measuring the incidence of intraoperative nausea and vomiting. Therefore, the incidence of intraoperative nausea and vomiting is often taken from the placebo groups of studies examining the effect of antiemetic preventative measures. Some review articles included the incidence
of intraoperative nausea and vomiting during spinal anesthesia for C/S, but most of these have also included postoperative nausea and vomiting[16,17]. There are two separate centers for nausea and vomiting, medulla and chemoreceptor trigger zone[18]. The vomiting center is located in the lateral reticular formation. There are many excitatory inputs from the nerve endings of vagal sensory fibers in the gastrointestinal tract, the labyrinth via the vestibular nuclei, higher centers in the cortex, chemoreceptor trigger zone and intracranial pressure receptors. These structures are rich in dopaminergic, muscarinic, tryptaminergic, histaminic and opioid receptors, which are blocked by antiemetic drugs[18].

The only factor known to be associated with intraoperative nausea and vomiting, along with ethnicity was hypotension. The objective of this study was to analyze the frequency and severity of intraoperative nausea and vomiting in obese pregnant women when compared to non-obese pregnant women during spinal anesthesia. The aim of our study was to determine the frequency of intraoperative nausea and vomiting in obese pregnancies. Many studies have shown a correlation between blood pressure control and intraoperative nausea and vomiting. A decrease in blood pressure of >30% below baseline has been found to increase the risk of intraoperative nausea and vomiting to 60%[8].

Ngan Kee et al found the incidence of intraoperative nausea and vomiting to be 4%, 14%, and 40% with targets, as a percentage of baseline systolic blood pressure of 100%, 90%, and 80% respectively[19]. In the present study, the odds of experiencing nausea with a minimum-recorded systolic blood pressure less than 70% of baseline were 2.46 times higher than those in whom systolic blood pressure was always higher than 70% of the baseline value. There was no difference in the incidence of hypotension due to the use of oxytocin between the two groups.

Hypotension caused by neuraxial anesthesia is one of the most important causes of intraoperative nausea and vomiting[20]. In our study, a statistically significant difference was found between MAP and nausea and vomiting.

Colloids and crystalloids limited effect on hypotension, nausea and vomiting has been shown[21]. Ahmed HO et al investigated the effect of Ringer lactate on pregnant patients in different volumes. He emphasized that the use of crystalloids may be less effective than colloid because of escape to the extravascular space. However, costs and very long intravascular involvement time makes use of colloids controversial[21]. In our study, a statistically significant difference was not found between intraoperative fluid administration and nausea and vomiting.

Ephedrine, an alpha and beta-adrenergic agonist, is one of the most commonly used vasopressor agents. However, in a dose-response meta-analysis, Lee et al found that ephedrine improved hypotension, but did not reduce nausea. Also, the use of ephedrine (>14 mg) in larger doses was found to cause a slight decrease in umbilical artery pH[22]. There was a statistically significant difference between the use of ephedrine and the incidence of nausea and vomiting in our study.

CONCLUSION

In the study sample, pre-gestational and gestational BMI ≥30 kg/m² was not a risk factor for nausea-vomiting after spinal anesthesia in elective cesarean section cases. However, hypotension significantly influenced the incidence of nausea-vomiting.

REFERENCES

Clinical and radiological comparison of two classification systems in clubfoot patients who were treated by the Ponseti method

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ABSTRACT

Objective: The aim of this study is to compare the clinical and radiological assessment of the Pirani and Diméglio scoring systems in clubfoot evaluation, as well as the efficiency of the Ponseti method.

Design: Prospective study

Setting: Department of Orthopaedics and Traumatology, Erciyes University School of Medicine, Kayseri, Turkey

Subjects: Between 2010 and 2012, 41 patients (67 feet) who were diagnosed with idiopathic clubfoot and treated by the Ponseti method were evaluated clinically and radiographically. Clubfoot severity was assessed using both the Pirani score and the Dimeglio score, with each component of the scores documented.

Interventions: Ponseti method was performed for conservative treatment. Standard casting procedure was followed during treatment and each clubfoot was scored with using Dimeglio and the Pirani classification system at every visit. In accordance with the data obtained, clinical and radiological improvements were evaluated from the beginning to the end of casting.

Main outcome measure: Our hypothesis is to determine which most widely used clinical clubfoot scoring classification system is more consistent with radiologic evaluation and therefore, superior to each other and indicates both clinical and radiologic correction accurately. As secondary earning, effectiveness of Ponseti method on clubfoot was evaluated also.

Results: The average Diméglio score was 13.58. The average Pirani score was 6.3 (0.5–9.0).

Conclusion: The Diméglio and Pirani scoring systems, which are based on physical examination and used in clinical evaluation, are extremely effective in showing the clinical improvement.

INTRODUCTION

It is known that Pes equinovarus (congenital clubfoot) is the most common congenital foot deformity. In most cases, dysplasia is observed in all the tissues of the musculoskeletal system under the knee. Therefore, even with adequate treatment, it may not always be possible to obtain a completely normal limb[1]. The severity of the deformity may be different; for example, forefoot adduction and cavus may occur together with severe varus and equinus position of the whole foot or with minimal equinus and varus. Many opinions have been proposed in the treatment of clubfoot. Once the histology and pathoanatomy of the deformity was understood, various methods to treat it were developed. Nowadays, some of the previous commonly used methods of clubfoot treatment have been abandoned. The method that has the best long-term results in the treatment of clubfoot correction is the Ponseti method, which consists of manipulation and serial casting and was developed by Dr. Ignacio Ponseti[2-4]. Clubfoot assessment is important for success in results of treatment. Although there are many methods regarding the evaluation of clubfoot, agreement on a standard system is not available. According to the literature, the most popular classification systems are the Ponseti / Smoley, Harrold / Walker, Catterall, Dimeglio and Pirani classification systems[5]. The aim of this study is to compare the clinical and radiological assessment of the Pirani and Diméglio
scoring systems, as well as the efficiency of the Ponseti method.

SUBJECTS AND METHODS

Between 2010 and 2012, 41 patients (67 feet) who were diagnosed with idiopathic clubfoot and treated by the Ponseti method were evaluated clinically and radiographically. The study was approved by Erciyes University’s Ethics Committee (No:265/2010). Before treatment, systemic examination was performed in all patients. An informed consent form was obtained from parents. Clubfoot severity was assessed using both the Pirani score and the Dimeglio score, with each component of the scores documented. The Ponseti method was performed for conservative treatment.

The first casts of the cases were made to improve the cavus. One week later for the second manipulation, if the cavus deformity persisted, the first corrective plaster for the cavus was made again. In cases in whom the cavus was corrected, other clubfoot components except the equinus were corrected at the same time. After weekly casting in patients for the correction of cavus, adductus and heel varus, an Achilles tenotomy was performed if required. Tenotomy was performed percutaneously under sedation anesthesia from 1 cm proximal to the insertion of the Achilles tendon and from medial to lateral. If cavus, adductus, varus and equinus were corrected with casting, tenotomy was not performed. The last plaster was removed after 3 weeks in patients who underwent tenotomy and after 2 weeks in those without tenotomy. After the casting procedures were completed, Denis Browne orthosis was used to maintain the improvement. Patients were invited for follow-up visits in accordance with the treatment protocol. At every visit, each clubfoot was scored using the Dimeglio and the Pirani classification systems. In the Dimeglio system, the components of equinus, varus, calcaneomidfoot rotation, and midfoot adductus are each given 0 to 4 points. Posterior crease, medial crease, cavus, and abnormal musculature are each scored as 1, if present, and 0, if absent. The Pirani system involves scoring the following components as 0, 0.5, or 1: rigidity of equinus, emptiness of the heel, curvature of the lateral border, reducibility of the lateral head of the talus, and severity of the posterior and medial creases. For both systems, higher scores indicate a more severe deformity. For the evaluation of radiological improvement, anteroposterior talocalcaneal angle (AP-TCA), anteroposterior talo-first metatarsal angle (AP-TIMA) and lateral talocalcaneal angle (LAT-TCA) were measured at three different time points (before casting, at the middle of the casting period and after the last plaster). Lateral radiographs were taken in forced dorsiflexion. In accordance with the data obtained, clinical and radiological improvements were evaluated from the beginning to the end of casting. Pearson’s correlation analysis and mean ± standard deviation values were measured. Statistics and analysis were performed by using the SPSS version 16.0 software package for Windows (SPSS, Chicago, IL.).

RESULTS

Nine of 41 patients who were diagnosed with idiopathic clubfoot were female (22%) and thirty-two were male (78%). Fifteen patients had unilateral involvement (36.6%). Bilateral involvement was found in 26 patients (63.4%). Of the patients with unilateral involvement, four were on the right side and 11 were on the left side. The average time to start treatment was 20.47 (range: 4 - 90) days. The average number of casts was 6.04 (range: 4 - 7). Before the treatment, according to the Dimeglio scoring system, of the 67 feet which were diagnosed as idiopathic clubfoot, 28 were grade IV, 31 were grade III, six were grade II and two were grade I. The average Dimeglio score was 13.58. The average Pirani score was 6.3 (range: 0.5 - 9.0) (Table 1, Figures 1,2). At the middle of the casting period, according to the Dimeglio scoring system, 11 feet were grade III, 47 feet were grade II and nine feet were grade I. The average Dimeglio score was 7.47. The

<table>
<thead>
<tr>
<th>Measurements (n = 67)</th>
<th>Before the casting period</th>
<th>Mid-term of casting period</th>
<th>After the casting period</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean ± SD</td>
<td>Mean ± SD</td>
<td>Mean ± SD</td>
</tr>
<tr>
<td>Dimeglio scores</td>
<td>13.6 ± 3.0</td>
<td>7.5 ± 2.6</td>
<td>3.1 ± 1.4</td>
</tr>
<tr>
<td>Pirani scores</td>
<td>6.3 ± 2.2</td>
<td>2.9 ± 1.5</td>
<td>0.6 ± 0.7</td>
</tr>
<tr>
<td>AP-TCA angle</td>
<td>9.9 ± 4.4</td>
<td>24.0 ± 4.7</td>
<td>35.8 ± 3.9</td>
</tr>
<tr>
<td>AP-TIMA angle</td>
<td>66.7 ± 23.8</td>
<td>15.1 ± 11.3</td>
<td>8.1 ± 5.4</td>
</tr>
<tr>
<td>LAT-TCA angle</td>
<td>9.4 ± 5.9</td>
<td>14.4 ± 8.5</td>
<td>34.6 ± 5.1</td>
</tr>
</tbody>
</table>

AP-TC angle: anteroposterior talocalcaneal angle; AP-TIMA angle: anteroposterior talo-first metatarsal angle; LAT-TCA angle: lateral talocalcaneal angle

![Garfik Alan](image)

Fig 1. Change in the Dimeglio scores during the treatment
average Pirani score was 2.89 (range: 0.0 - 6.0) (Table 1, Figures 1,2). In 53 feet (79%) with corrected cavus, adductus and heel varus; Achilles tenotomy was performed percutaneously under sedation anesthesia. There was no complication due to tenotomy in any of the patients. In 14 feet, tenotomy was not necessary because their equinus deformities were corrected with casting. Following the removal of the last plaster, according to the Dimeglio scoring system 60 feet were grade I and seven feet were grade II. The average Dimeglio score was 3.07 and the average Pirani score was 0.62 (range: 0.0 - 3.0) (Table 1, Figures 1,2). In the radiological evaluation of the patients before the beginning of treatment, the average value of the AP-TC angle was 9.85 (range: 4.40 - 24.90) degrees, the average value of the AP-T1M angle was 65.67 (range: 10.00 - 114.50) degrees and the average value of the LAT-TC angle was 9.35 (range: 2.30 - 28.90) degrees (Table 1, Figure 3). At the middle of the casting period, the average AP-TC angle was 24.01 (range: 14.20 – 35.50) degrees, the average AP-T1M angle was 15.12 (range: (-2.30) - 35.70) degrees and the average value of LAT-TCA was 14.42 (range: 6.10 - 36.30) degrees (Table 1, Figure 3). After the removal of the last plaster, the average AP-TC angle was 35.82 (range: 26.6 - 44.0) degrees, the average AP-T1MA was -8.11 (range: (-20.00) - 7.10) degrees and the average LAT-TCA value was 34.63 (range: 19.00 - 45.20) degrees (Table 1, Figure 3). Correlation was evaluated between the values before treatment and after the removal of the last plaster in 67 feet (Table 2) and a statistically significant correlation was found between both clinical scoring systems and AP-T1MA (Pearson’s correlation coefficient was 0.504 for Dimeglio and 0.674 for Pirani (p <0.001)). Furthermore, there was a statistically significant correlation between Pirani scoring and LAT-TCA (Pearson’s correlation coefficient was (-)0.392; p = 0.001).

**DISCUSSION**

The Dimeglio and Pirani systems are widely used and have proven interobserver and intraobserver reliability[5]. Our hypothesis was established to prove which of the two classification systems is more consistent with the radiological findings. We also aimed to assess the efficacy of the treatment. The limitation of our study is the small number of patients.

The aim of treatment of clubfoot is to create a foot with normal flexibility and muscle balance, which is plantigrade, functional, painless and as close to normal as possible[6]. Various treatment methods have been developed. For many years, it was thought that clubfoot could not be corrected with conservative methods and surgical treatment was needed to achieve good results. Dobbs treated 45 patients (73 feet) with extensive surgical dissection and reported that quality of life declined due to stiffness of the joints, pain and arthritic changes after a long time[7]. After an understanding of the pathology of clubfoot was established, and owing to the poor long term results obtained from surgical treatment, the conservative treatment method of Ponseti, which has been shown to be an effective treatment, is now used.

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**Table 2: Correlation coefficients between clinical and radiological measurements**

<table>
<thead>
<tr>
<th>Radiological measurements</th>
<th>Clinical measurements</th>
<th>Dimeglio score changes</th>
<th>Pirani score changes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>r</td>
<td>p</td>
</tr>
<tr>
<td>AP-TC angle changes</td>
<td>-0.267</td>
<td>0.029</td>
<td>-0.173</td>
</tr>
<tr>
<td>AP-T1M angle changes</td>
<td>0.504</td>
<td>&lt;0.001</td>
<td>0.674</td>
</tr>
<tr>
<td>LAT-TC angle changes</td>
<td>-0.203</td>
<td>0.100</td>
<td>-0.392</td>
</tr>
</tbody>
</table>

AP-TC angle: anteroposterior talocalcaneal angle; AP-T1M angle: anteroposterior talo-first metatarsal angle; LAT-TC angle: lateral talocalcaneal angle
used all over the world. After Ponseti published his own series, with a success ratio of 89% and with the results of 30-year follow-up; the method has attracted attention\[2\]. However, this method aroused further interest when Cooper and Dietz published long-term results in 1995\[4\]. There are three main methods in conservative treatment of clubfoot. These are the Kite, French and Ponseti methods\[8,2\]. In the literature, the success of conservative treatment has been reported in different ratios. The initial treatment of clubfoot should always be nonsurgical and should be started at the neonatal period. In this study, conservative treatment was started early. The average age of patients at the initiation of treatment was 20.47 days. None of the cases needed extensive surgical correction. After casting, equinus deformity may improve. If the equinus deformity persists after casting, an Achilles tenotomy should be done without delay. The task of Achilles tenotomy is to prevent occurrence of iatrogenic rocker-bottom foot deformity. According to the literature, Dyer et al applied tenotomy in 42 of 70 feet (60%); Göksan applied tenotomy in 22 of 44 feet (50%); Chu et al applied tenotomy in 107 of 185 feet (57.8%); Jawadi et al applied tenotomy in 233 of 235 feet (99.1%); and Porecha et al applied tenotomy in 65 of 67 feet (95.91%)\[10-13\]. In our study, tenotomy was applied in 53 of 67 feet (79.1%). The calcaneus has equinus deformity due to a tense and short Achilles tendon. After the tenotomy, the calcaneus returns to its normal position. In the study by de Ghelder et al, the authors compared radiological data before and after application of Achilles tenotomy\[14\]. They demonstrated that the lateral tibiocalcaneal angle decreased and the lateral talocalcaneal angle increased after tenotomy. In our study, the lateral talocalcaneal angle increased rapidly after tenotomy. In a study by Wainwright et al, nine patients (18 feet) were evaluated by four different observers according to four different classification systems (Catterall, Diméglio, Harrold / Walker and Ponseti / Smoley)\[3\]. Based on their analysis, they found that the four classification systems had their own problems. In this study, it was concluded that Diméglio classification system had the best reliability, although it was complex. In the study by van Mulken et al, the authors evaluated 25 feet which were treated by operative and conservative methods (13 conservative, 12 operative) before and after treatment according to the Diméglio classification system\[15\]. They advocated that the system of Diméglio et al is an appropriate tool for evaluation from birth until the end of treatment for clubfoot\[16\]. Flynn et al evaluated 55 clubfeet in an interobserver study by the systems of Pirani and Diméglio\[15\]. They found that both classification systems had very good interobserver reliability after the initial learning phase. Although this study demonstrated reliability, it did not demonstrate efficacy. They noted that the assessment can be done successfully after a long learning period, but there may be differences in the assessment of different observers. Chu et al evaluated the correlation between the number of casts and Diméglio and Pirani scores in 185 feet of 123 patients\[11\]. They found a low correlation between both classification systems and the number of casts required to correct clubfoot. Furthermore, there was not a significant difference between the Pirani and Diméglio classification systems according to the correlation measurements. In our study, the comparison between the Pirani and Diméglio systems showed no statistically significant difference, although there was a high correlation coefficient in the Pirani system. Abulsaa et al measured the talocalcaneal angle, talo-first metatarsal angle, talocalcaneal index and calcaneo-first metatarsal angle on anteroposterior and lateral radiographs in 70 feet of 54 patients who were treated surgically\[17\]. They compared radiographic parameters and clinical outcome with the Laaveg / Ponseti evaluation system. They found a statistically significant correlation between the clinical results and two angles (the talo-first metatarsal angle on the anteroposterior radiograph and the calcaneo-first metatarsal angle on the lateral radiograph). It was concluded that these two angles should be considered when designing an evaluation system of clubfoot. According to Prasad et al and Lau et al, a statistically significant correlation was found between clinical scoring and AP-TCA\[16,19\]. In contrast, Turco and Thompson et al found no correlation between AP-TCA and functional rating\[20,21\]. Prasad et al, Turco, Thompson et al and Haasbeek et al found that the LAT-TCA correlated well with the functional rating and is a good indicator of hind-foot deformity\[18,20-22\]. In contrast, Lau et al did not find any significant correlation with LAT-TCA\[19\]. In our study, we found a statistically significant correlation of both clinical scoring systems with AP-TIMA. Furthermore, we also found a statistically significant correlation of Pirani scoring with LAT-TCA. These differences between studies could be due to difficulties in obtaining standardized radiographs in children, inaccuracies in the measurements of radiological angles, use of different functional rating systems and differences in the patient inclusion criteria.

CONCLUSION

The Diméglío and Pirani scoring systems, which are based on physical examination and used in clinical evaluation, are extremely effective in showing the clinical improvement. Both are practical and reproducible systems. AP-TIMA may correlate with both systems and LAT-TCA may correlate with the Pirani scoring system. Also, LAT-TCA may increase rapidly after Achilles tenotomy.
REFERENCES

An analysis of overall survival in patients who have undergone lung metastasectomy operations for lung metastases of colorectal cancers and malignancies other than colorectal cancer

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Department of Thoracic Surgery, Trakya University Faculty of Medicine, Edirne, Turkey

ABSTRACT

Objective: To compare the survival and factors affecting survival between patient groups with primary colorectal cancers and malignancies other than colorectal cancer, who underwent curative pulmonary metastasectomy

Design: Retrospective study

Setting: Trakya University School of Medicine, Edirne, Turkey

Subjects: Forty-four cases who underwent curative metastasectomy in our clinic between January 2006 and August 2015

Interventions: Primary colorectal cancers (Group 1 = 14 cases), malignancies other than colorectal cancer (Group 2 = 30 cases)

Main outcome measures: Age, gender, type of primary malignancy, disease-free survival, adjuvant therapy, number of radiological nodules, number and type of operations, number and site of nodules resected, presence of relapse, and mean survival

Results: Two cases (4.7%) underwent lobectomy, and a total of 123 nodules were excised in 38 cases (86.3%) using thoracotomy and in four cases (9%) using video thoracoscopic surgery. The median survival value was 33 ± 5.4 months (range:22.2 - 43.7 months) in Group 1, and 28 ± 6.8 months (range:14.5 – 41.4 months) in Group 2; the cumulative value was 33 ± 3.7 months (range:25.6 - 40.3 months). Survival did not differ significantly between the groups (p=0.738). Age (p=0.81), gender (p=0.35), disease-free survival (p=0.24), number of metastatic nodules (p=0.60), presence of synchronous-metachronous tumor (p=0.94), adjuvant chemotherapy (p=0.96), adjuvant radiotherapy (p=0.86), and relapse of disease (p=0.07) were not significantly correlated with survival.

Conclusion: Survival and factors that affected survival did not differ significantly between the two groups that underwent metastasectomy. It was indicated that the primary tumor is not an effective factor in the selection of patients who would undergo metastasectomy.

INTRODUCTION

The thorax is located on the hematological and lymphatic pathways, and it is therefore a site for frequent distant metastases. Various malign neoplasias, primarily the colorectal, breast, ovarian, urinary bladder and urogenital cancers may metastasize to the lung hilar-mediastinal lymph nodes, pleura, pericardium or chest wall[1,2]. Lung metastases have been determined in 30% of deaths related with cancer; in about 25% of these cases, metastasis has been indicated to be present only in the lungs. In the complete resection of lung metastases, a five-year survival may be 50% possible[3]. Despite developments in oncological therapies like the use of chemotherapeutic and biological agents, the surgical resection of metastases has been shown to be an efficient method of treatment. However, results...
change, depending on the histological type of the primary tumor[4]. The median five-year survival of the colorectal cancers following lung metastasectomy has been reported to be 39.6%[5]. The following four criteria are essential for metastasectomy: 1) controlled primary tumor; 2) absence of extrathoracic metastasis; 3) resectability of the metastasis; and 4) the patient’s general condition and respiratory functions to be suitable for operation[6]. In the present study, we compared the survival and factors affecting survival between patient groups with primary colorectal cancers and malignancies other than colorectal cancer, who underwent curative pulmonary metastasectomy.

MATERIALS AND METHODS

A total of 44 cases who underwent curative metastasectomy in our clinic between January 2006 and August 2015 were evaluated retrospectively. Of these cases, 17 were female (38.6%) and 27 were male (62.4%), and their mean age was 55 ± 16.7 years (range: 20 - 78 years). Depending on the site of the primary tumor, the cases were separated into two groups: the colorectal cancers (Group 1 = 14 cases; 31.8%) and the malignancies other than colorectal cancer (Group 2 = 30 cases; 68.2%). Group 2 included the following cases: 11 cases with urogenital cancers, 10 cases with sarcomas, four cases with breast cancer, three cases with head and neck cancers, and two cases with the metastases of cancers of other systems (Table 1). The two groups were compared regarding age, gender, type of primary malignity, disease-free survival, adjuvant therapy, number of radiological nodules, number and type of operations, number and site of nodules resected, presence of relapse, and mean survival. The study included cases with a controlled primary tumor and resectable metastases, without the presence of an extrathoracic metastasis, and who existed with a cardiorespiratory status related to the operation. In all cases, resections were performed with 1-cm safe surgical margins. Also, surgeries were done by the same 2 surgeons constantly.

Statistical analysis

Descriptive statistics were used in number and percentage, including mean ± standard deviation, median and range, frequencies and proportions. Newman Keuls multiple comparison test for subgroup comparison, independent t test for comparison of binary groups, and chi-square test for comparison of qualitative data were used. The results were evaluated as p <0.05 (SPSS, version 20.0, SPSS Inc., Chicago, IL, USA).

RESULTS

Following metastasectomy, the median survival and disease-free survival were 33 months (range: 25 - 40 months), and 15 ± 30.6 months (range: 1 - 132 months) respectively. Fifteen cases (34%) had a disease-free survival of more than 24 months (range: 24 - 132 months; Group 1: 4, Group 2: 11), and 29 cases (66%) had a disease-free survival of less than 24 months (range: 1 - 24 months) (Group 1: 10, Group 2: 19). None of the cases were administered neoadjuvant therapy. Thirty-five cases (79.5%) underwent adjuvant chemotherapy (Group 1: 11, Group 2: 24), and 13 cases (29.5%) underwent adjuvant radiotherapy (Group 1: 5, Group 2: 8). The tumor was metachronous in 38 cases (86.3%), and it was synchronous in six cases (13.7%). Metastasectomy was performed for one nodule in 20 cases (45%), and for two or more than two nodules (range: 2 - 12) in 24 cases (55%). A total of 123 nodules were excised in 38 cases (86.3%) by Wedge-resection with thoracotomy, and in four cases (9%) by video thoracoscopic surgery (VATS); two cases (4.7%) underwent lobectomy because of centrally located nodules (Table 1). Bilateral metastasectomy was applied in eight cases (18%). Two of them were performed simultaneously via median sternotomy and six of them were performed at different times via thoracotomy with 1 month break (Group 1: 2, Group 2: 6), and unilateral metastasectomy was applied in 36 cases (82%) (Group 1: 12, Group 2: 24). Locations of the surgically resected nodules were as follows: 42 (39%) in the upper right lobe, 22 (21%) in the lower right lobe, 21 (20%) in the lower left lobe, 18 (17%) in the upper left lobe, and three (3%) in the middle lobe. The mean number of resected metastases was 3 (range: 1 - 12). All surgical margins were reported to be negative. Twenty-three patients (52.2%) remained alive, whereas 21 cases (47.8%) were lost during follow-ups. The rate of mortality was found to be 57%
(n = 8) in Group 1, and 43% (n = 13) in Group 2. The mean relapse time was 2.5 ± 0.6 months (range: 1 - 17 months); five patients relapsed in Group 1, and 11 cases in Group 2 (Table 2). The median survival was 33 ± 5.4 months (range: 22.2 - 43.7 months) in Group 1, and it was 28 ± 6.8 months (range: 14.5 - 41.4 months) in Group 2; the cumulative value was 33 ± 3.7 months (range: 25.6 - 40.3 months). Statistically significant differences were not determined between the survival values (p = 0.738) (Figure 1).

Survival analysis was performed in all cases by applying the cox regression test, regarding the age (p = 0.81), gender (p = 0.35), disease-free survival (p = 0.24), number of metastatic nodules (p = 0.60), presence of synchronous-metachronous tumor (p = 0.94), adjuvant chemotherapy (p = 0.96), adjuvant radiotherapy (p = 0.86), and relapse of disease (p = 0.07); however no statistically significant results were obtained (Table 2).

**DISCUSSION**

Metastasis is a systemic invasion; however it has been stated that isolated pulmonary metastases have to be excluded from this consideration, and survival has been indicated to improve in the cases that underwent pulmonary metastasectomy. It is important to know the characteristics of patients for whom pulmonary metastasectomy would be useful. The criteria for undergoing metastasectomy were first defined by Ehrenhaft et al. The final regulations were made in 2005 by Kondo et al. The case selection in our study was based on the same criteria. The aim in pulmonary metastasectomy is to remove the metastatic nodules completely by optimally protecting the lung parenchyma. This procedure is conducted either by applying thoracotomy with the method of palpation, or in cases where lymphatic invasion is not suspected, with the application of VATS to resect all nodules completely by surgeons who are highly experienced with video thoracoscopy. Resectability, the number of nodules and disease-free survival were determined to be the effective factors on overall survival. In a multi-center meta-analysis study of the International Registry of Lung Metastases...
performed in 1997 and including 5,206 cases with pulmonary metastasis, prognostic factors and survival were investigated by evaluating multiple variables; in this study, metastasectomy was reported to be a safe and curative method of treatment with low cost\textsuperscript{10}. In our study, we prefer VATS in cases that the metastases were solitary, peripherally located, with no lymphatic invasion and no pleural adhesions. However, we preferred open surgery because of the advantage of palpation, especially when the millimetric nodules accompanied multiple metastases. Also, none of the factors investigated were found to be effective on survival, and no differences were determined between the group with colorectal cancers and the one with malignancies other than colorectal cancer.

In the study by Lumachi et al\textsuperscript{11}, colorectal cancers and malignancies other than colorectal cancer were compared and it was reported that the localization of the tumor was not a primary factor when considering metastasectomy, but the prognosis was found to be poor in females. In the study of Pfannschmidt et al\textsuperscript{12}, rates of survival following metastasectomy were reported to be as follows: 35.5\% - 47\% in cases of renal-cell carcinoma; 39.1\% - 67.8\% in cases of colorectal cancer; 29\% - 52\% in soft tissue sarcoma; 38\% - 49.7\% in osteosarcoma and 79\% - 94\% in seminomatous germ-cell tumors. With regard to long-term survival, they asserted that chemotherapy was more effective than surgery with the last two types of tumor.

They also revealed that case selection was extremely important on the basis of clinical stage, in association with the prognostic markers. In a meta-analysis by Gonzalez M et al\textsuperscript{13}, the following three prognostic factors were found to be related with poor prognoses: a short disease-free survival, the presence of multiple pulmonary metastases, and a high level of carcinoembryonic antigen prior to metastasectomy. However, in the studies of Younes R et al\textsuperscript{14} and Olmez OF et al\textsuperscript{15}, it was concluded that the number of pulmonary metastatic nodules does not affect survival if a complete resection has been made. Chen F et al\textsuperscript{16} reported that unilateral pulmonary metastasectomy reports as a positive prognostic factor regarding the overall survival. They have explained this result by the property of bilateral lesions to progress more rapidly, compared with unilateral ones. The following general prognostic factors in pulmonary metastases are known to prolong survival: a resectable tumor, a disease-free survival of 36 months or longer, a small number of metastases or solitary metastasis, the absence of involvement of mediastinal lymph nodes, and a metastasis of germ-cell tumor\textsuperscript{17}. Relapse is rarely seen following pulmonary metastasectomy. According to the International Registry of Lung Metastasis, the rate of relapse is 53\% in pulmonary metastases that have been completely resected. This rate is 64\% with sarcomas and melanomas, and 46\% with epithelial tumors. The five-year survival rate is 44\% for all cases, following re-operation\textsuperscript{10}. However, the five-year survival rate is 5\% to 10\% in untreated cases with pulmonary metastasis\textsuperscript{18}. In our series of cases, survivals did not differ significantly between the two groups (p = 0.738).

There are some limitations in our study. First, the most important is the retrospective study design, similar to most of the studies in the literature. Secondly, our findings are from a single institution and from a small number of case samples. The hypothesis cannot be generalized to all patient groups and all regions.

**CONCLUSION**

In conclusion, survival and factors that affected survival did not differ significantly between the two groups that underwent metastasectomy. It was indicated that the primary tumor is not an effective factor in the selection of patients who would undergo metastasectomy, and in their survival. However, the study group included a small number of cases, and further studies conducted using a larger series of patients are needed, in order to support this hypothesis.

**REFERENCES**


Can carboxyhemoglobin and total bilirubin be new prognostic indicators for determining mortality in ischemic stroke?

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Objective: The aim of this study is to determine the severity of inflammation induced by ischemic stroke via endogenous carbon monoxide and bilirubin levels.

Design: Retrospective study

Settings: The study was conducted in a tertiary care hospital serving as a stroke center.

Subjects: The epicrises of 9,251 patients hospitalized in the emergency department to the neurology clinic and neurological intensive care were reviewed using the hospital automation system between 01.01.2010 and 31.12.2016. Of these patients, 1,644 with diffusional magnetic resonance images consistent with ischemia were included.

Interventions: Non-interventional

Main outcome measures: Carboxyhemoglobin and total bilirubin levels determining mortality in ischemic stroke patients

Results: Males constituted 46.7% of the patients, and the mean age of the patients was 71.70 ± 13.897 years. The mean carboxyhemoglobin, glucose and total bilirubin values were 1.6 ± 1.0%, 149.61 ± 69.2 mg/dL, and 0.69 ± 0.55 mg/dL, respectively. Carboxyhemoglobin was not significant to determine in-hospital mortality after excluding smokers (p = 0.942). However, glucose and total bilirubin values were statistically significant in determining the rate of in-hospital mortality (p <0.05).

Conclusion: We could not detect any effect of a high endogenous carbon monoxide level on mortality. The fact that the physiology of the brain differs from that of other organs and systems in the body limits the use of carbon monoxide as a prognostic marker in stroke patients.

INTRODUCTION

Etiologically, there are two types of strokes: ischemic and hemorrhagic. The rate of hemorrhagic stroke is around 15%, while that of ischemic stroke is between 80% and 85%. It is one of the leading causes of permanent disability worldwide. The delivery of oxygen and glucose to the brain tissue is reduced during stroke, and this reduction in basic fuels leads to massive cell death. Brain injury occurring during stroke induces an inflammatory response, and whether this response has beneficial or detrimental effects is still a matter of conflict.

Carbon monoxide (CO) gas used to be considered toxic because it binds to hemoglobin with a higher affinity than oxygen. However, recently, it was recognized as a signal molecule with a regulatory role in many physiological and pathophysiological reactions within the cardiovascular, immune, and nervous systems. CO is a small gaseous molecule with a low molecular weight. The production of endogenous CO in humans occurs via heme catabolism catalyzed by microsomal heme oxygenase enzymes. Hematological catabolism and endogenous CO production take place mostly in the liver. The blood
level of carboxyhemoglobin (COHb) in non-smokers is about 1% compared to approximately 5.5% in those who smoke 20 cigarettes per day. Endogenous CO is excreted from the body through expiration, and CO is naturally synthesized in the body and has physiological functions, such as protection against inflammation and tissue damage, vasodilatation, angiogenesis, vascular remodeling, etc[4].

In this study, we aimed to detect the inflammatory response induced by ischemic stroke. The resulting inflammation will definitely cause a series of systemic reactions in our bodies. The effect of the endogenous CO created as a response to this inflammation process was investigated, as well as whether endogenous CO has an effect on mortality through this inflammatory response.

MATERIALS AND METHODS

Study design and setting

Our study has a retrospective design. It was conducted in the emergency department of the Ataturk University Faculty of Medicine, which receives approximately 120,000 admissions annually. In our region, it serves as the stroke center currently. Among our patients, those with acute infarction on diffusion-weighted magnetic resonance imaging (MRI) were included in the study.

Patients

Patient selection was carried out as follows: patients who presented to the emergency department and were hospitalized in the neurology clinic and neurological intensive care unit between the dates of 01.01.2010 and 31.12.2016 (9,251 patients) were reviewed through the automation system of our hospital. Patients whose epicrises could not be obtained (598 patients) were excluded. The epicrises of the remaining patients were assessed individually, and those with a final diagnosis of ischemic stroke (2,167 patients) were selected. In total, 6,486 patients whose final diagnosis was not ischemic stroke were excluded. The radiological images of all patients with a final diagnosis of ischemic stroke (2,167 patients) were selected. In total, 6,486 patients whose final diagnosis was not ischemic stroke were excluded. The radiological images of all patients with a final diagnosis of ischemic stroke were examined. Among those, 523 patients who did not have acute infarction on diffusion-weighted MRI or who did not undergo radiological imaging were excluded from the study. Our study was completed with 1,644 patients. The primary endpoint of patient selection was determined as in-hospital mortality and discharge from the hospital.

Measurements

The blood samples of the selected patient group were accessed using the automation system of the hospital. The blood samples taken outside the emergency department were not used in the study. The levels of COHb, glucose, and total bilirubin and the blood groups of the patients were registered retrospectively. Past medical characteristics (hypertension, diabetes mellitus, smoking status, atrial fibrillation, etc.) and exitus statuses of the patients were obtained from their discharge epicrises.

Statistics

The analyses were performed with the IBM SPSS 20 statistical analysis program. The data were expressed as the mean, standard deviation, median, minimum, maximum, percentage, and number. The normal distribution of continuous variables was analyzed with the Shapiro–Wilk test. For comparisons between two independent groups, the independent samples t-test was used when the condition of normal distribution was met and the Mann–Whitney U test was used when it was not met. A comparison between categorical variables was carried out with the chi-square and Fisher’s exact tests. A receiver operating characteristic (ROC) analysis was used to determine whether the continuous variable could be used for diagnosis. The relationship between categorical dichotomous dependent variables and independent variables was analyzed by logistic regression analysis. The statistical significance level was accepted as p <0.05.

<table>
<thead>
<tr>
<th>Table 1: Distribution of patients according to gender</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>Male</td>
</tr>
<tr>
<td>Female</td>
</tr>
<tr>
<td>Total</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 2: Past medical characteristics and in-hospital mortality rates of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Past medical characteristic</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td>Yes</td>
</tr>
<tr>
<td>No</td>
</tr>
<tr>
<td>Hypertension</td>
</tr>
<tr>
<td>Yes</td>
</tr>
<tr>
<td>No</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
</tr>
<tr>
<td>Yes</td>
</tr>
<tr>
<td>No</td>
</tr>
<tr>
<td>Smoking</td>
</tr>
<tr>
<td>Yes</td>
</tr>
<tr>
<td>No</td>
</tr>
<tr>
<td>Exitus</td>
</tr>
<tr>
<td>Yes</td>
</tr>
<tr>
<td>No</td>
</tr>
<tr>
<td>Total</td>
</tr>
</tbody>
</table>
106 years). The past medical characteristics and in-hospital mortality rates of the patients are summarized in Table 2. The biochemical values of the patients are summarized in Table 3. The distribution of the patients according to their blood types is demonstrated in Table 4. The COHb value was determined to be insignificant in determining in-hospital mortality in the statistical analysis performed after smokers were excluded (p = 0.942) (Tables 5 and 6).

In the statistical analysis including all patients, age, glucose, and total bilirubin were found to be significant in determining in-hospital mortality (p <0.05) (Tables 7 and 8). In the statistical analysis performed, after excluding the effects of age, the glucose and total bilirubin values were found to be significantly independent of age (p <0.05). The relationship between total bilirubin and exitus was shown by the ROC curve, as in Figure 1. The analysis revealed that its sensitivity (53%) and specificity (58%) were low.

Female gender, smoking, and past medical history of atrial fibrillation were found to be statistically significant in predicting in-hospital mortality (p <0.05). Being from the non-O and O blood groups (p = 0.084), having diabetes mellitus (p = 676), and having hypertension (p = 834) were not found to be statistically significant in predicting in-hospital mortality.

When the logistic regression analysis was performed, classification was made by grouping COHb values as ≤1 and >1. Finally, only the COHb value and smoking were found to be significant.

### Table 3: Biochemical values of patients

<table>
<thead>
<tr>
<th>Parameters</th>
<th>n</th>
<th>Minimum</th>
<th>Maximum</th>
<th>Mean</th>
<th>Standard deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carboxyhemoglobin</td>
<td>467</td>
<td>0.1</td>
<td>8.3</td>
<td>1.60</td>
<td>1.00</td>
</tr>
<tr>
<td>Glucose</td>
<td>1571</td>
<td>38</td>
<td>802</td>
<td>149.61</td>
<td>69.20</td>
</tr>
<tr>
<td>Total Bilirubin</td>
<td>1142</td>
<td>0.2</td>
<td>6.9</td>
<td>0.69</td>
<td>0.55</td>
</tr>
</tbody>
</table>

### Table 4: Distribution of patients according to their blood type

<table>
<thead>
<tr>
<th>Blood Group</th>
<th>n</th>
<th>Percentage of total patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARh (+)</td>
<td>212</td>
<td>12.9</td>
</tr>
<tr>
<td>ARh (-)</td>
<td>32</td>
<td>1.9</td>
</tr>
<tr>
<td>BRh (+)</td>
<td>87</td>
<td>5.3</td>
</tr>
<tr>
<td>BRh (-)</td>
<td>15</td>
<td>0.9</td>
</tr>
<tr>
<td>ABRh (+)</td>
<td>35</td>
<td>2.1</td>
</tr>
<tr>
<td>ABRh (-)</td>
<td>7</td>
<td>0.4</td>
</tr>
<tr>
<td>ORh (+)</td>
<td>162</td>
<td>9.9</td>
</tr>
<tr>
<td>ORh (-)</td>
<td>31</td>
<td>1.9</td>
</tr>
<tr>
<td>Total</td>
<td>581</td>
<td>35.3</td>
</tr>
<tr>
<td>Grand total</td>
<td>1,644</td>
<td>100.0</td>
</tr>
</tbody>
</table>

### Table 5: Analysis of COHb value in determining in-hospital mortality among surviving patients

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Surviving patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>COHb</td>
</tr>
<tr>
<td>Yes</td>
<td>COHb</td>
</tr>
</tbody>
</table>

### Table 6: Analysis of COHb value in determining in-hospital mortality among deceased patients

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Surviving patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>COHb</td>
</tr>
<tr>
<td>Yes</td>
<td>COHb</td>
</tr>
</tbody>
</table>

### Table 7: Analysis of age, glucose, and total bilirubin values in determining in-hospital mortality among surviving patients

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Surviving patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
</tr>
<tr>
<td>Age</td>
<td>71</td>
</tr>
<tr>
<td>Glucose</td>
<td>146</td>
</tr>
<tr>
<td>Total Bilirubin</td>
<td>0.66</td>
</tr>
</tbody>
</table>
DISCUSSION

Not knowing the prognosis is a major problem among many diseases. Knowing the prognosis aids in the classification of patients in the early period and in the selection of an appropriate treatment. Recently, studies on numerous prognostic biomarkers are being conducted that will aid in determining the severity of tissue damage secondary to ischemic stroke and patient prognosis. The blood–brain barrier renders the early detection of these biomarkers difficult. Ideal stroke biomarkers should be released in the early period of infarction, predict the prognosis, guide the treatment, be cost-effective, and be measured rapidly.

As far as we know, this study is the first in which the relationship between the endogenous COHb level and mortality was investigated in patients with ischemic stroke.

Endogenous COHb is produced by the enzyme heme oxygenase (HO) because of the breakdown of the heme component of heme sources. This reaction scheme is demonstrated in Figure 2. It is estimated that at least 86% of the endogenously created COHb is produced this way. Meanwhile, the remaining part is produced via photo oxidation, lipid peroxidation, and xenobiotic metabolism.

The HO enzyme has two isoforms. HO-1 is the inducible form and HO-2 is the constitutive form. HO-1 is a rate-limiting enzyme associated with heme catabolism, and it has potential anti-oxidant and anti-apoptotic effects. The expression of HO-1 is induced in a variety of pathophysiological conditions. In the normal brain, the basal expression and activity of HO-1 are at low levels. With ischemic stress, the proteins containing heme, such as hemoglobin, myoglobin, and cytochrome, increase the release of free heme. The expression of HO-1 is induced in neuronal and non-neuronal cells after cerebral ischemia. Along with the induction of HO-1, the breakdown of heme increases and therefore, the endogenous production of CO increases. It was demonstrated in experimental animals that the level of COHb in the blood can be used to estimate HO activity. In addition, an increased HO-1 expression was found to be associated with a high level of COHb. CO, which is naturally synthesized in our body, is known to have physiological functions, such as anti-inflammatory, anti-oxidative, and anti-apoptotic functions; vasodilation; angiogenesis; and vascular remodeling at low concentrations.

Recently, exogenous CO administered at low doses to mice was shown to be partially protective against focal ischemia. Zeynalov et al found that the induction of HO-1 was generated when ischemia occurred in the brain, and the healing of brain injury, which was caused by increased HO-1 activity with minimum sequelae, was enabled in the ischemic brain. The HO-1 expression protects neurons from free oxygen radicals and hypoxia-induced neurotoxicity. An increased cerebral HO-1 expression was found to be protective against cellular injury caused by ischemic stroke in studies on mice. This study was conducted through the HO-1 enzyme, which is active in many non-brain tissues. The non-brain activity of HO-1 might have caused to yield significant results in this study. In our study, the activation of HO-1 was not

### Table 8: Analysis of age, glucose, and total bilirubin values in determining in-hospital mortality among deceased patients

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Surviving patients</th>
<th>Non-surviving patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>Standard deviation</td>
<td>Mean</td>
</tr>
<tr>
<td>Age</td>
<td>76 ± 12</td>
<td>78 ± 10</td>
</tr>
<tr>
<td>Glucose</td>
<td>164 ± 75</td>
<td>145 ± 80</td>
</tr>
<tr>
<td>Total Bilirubin</td>
<td>0.83 ± 0.65</td>
<td>0.64 ± 0.14</td>
</tr>
<tr>
<td>Maximum</td>
<td></td>
<td>99 ± 12</td>
</tr>
<tr>
<td>Minimum</td>
<td></td>
<td>20 ± 7</td>
</tr>
<tr>
<td>Maximum</td>
<td></td>
<td>802 ± 50</td>
</tr>
<tr>
<td>Minimum</td>
<td></td>
<td>0.14 ± 0.04</td>
</tr>
<tr>
<td>Maximum</td>
<td></td>
<td>3.70 ± 0.25</td>
</tr>
</tbody>
</table>

Fig 1: ROC curve demonstrating the relationship between total bilirubin and mortality

Fig 2: Endogenous COHb production from HEME
assessed, whereas the value of COHb synthesized via this enzyme was investigated. In another study, administrating low doses of CO to experimental rats in which ischemic stroke was induced affected the prognosis positively. Its mechanism was considered due to the structural similarity of CO to nitric oxide (NO) and as a result, it was assumed that it could cause vasodilatation like NO[6]. In this study, when the CO gas was administered for therapeutic purposes, it was reported to affect the prognosis positively. Meanwhile, our study investigated the notion that CO, which has a positive effect on patients, can be produced by the human body.

An increased HO-1 expression and a high level of COHb were detected in patients with critical illness, chronic obstructive pulmonary disease, systemic inflammatory response syndrome, and acute respiratory distress syndrome[3,4]. A high level of COHb was considered associated with a more severe prognosis in patients with acute ischemic disease[11]. Kakavas et al detected that COHb could predict in-hospital prognosis in their study of 156 patients with a diagnosis of pulmonary embolism[11]. Since pulmonary embolism is associated with the venous system and arterial ischemic stroke is associated with the arterial system, the different pathophysiologies of these two patient groups might be effective in detecting CO as predictive of in-hospital mortality among patients with pulmonary embolism.

In the study by Kobayashi et al on 235 patients who were admitted with the symptoms of acute coronary syndrome and who underwent angiography, they found that the COHb value could not be used as a marker for the diagnosis of acute coronary syndrome, but it could be used as a marker of cardiac stress[9]. In our study, unlike this study, the usability of the COHb value for predicting in-hospital mortality was investigated. The affected organ was the brain in our study. Our study showed that COHb could be determinative of the severity of brain injury and it could not be regarded as an indicator of in-hospital mortality.

In our study, no significant relationship could be detected between the patients with ischemic stroke and COHb levels in terms of in-hospital mortality.

Bilirubin, which is derived from its metabolic precursor of biliverdin, is the final product of heme catabolism. It is known as a physiological antioxidant in non-human extracellular fluids. In addition, it was reported to cause DNA cleavage. Bilirubin has both antioxidant characteristics and pro-oxidant characteristics by causing DNA cleavage[12]. Very high bilirubin levels are definitely neurotoxic, and numerous studies indicate that slightly elevated levels of bilirubin may be beneficial. Bilirubin provides an antioxidant effect by inhibiting neutrophil chemotaxis. In addition, the evidence in support of the idea that bilirubin may contribute to observed cellular and tissue protection along with increased HO activity is increasing[13]. Bilirubin is a significant endogenous antioxidant cytoprotectant and it is protective against lipid peroxidation greatly[14].

In the light of this information, the relationship between the total bilirubin value and the in-hospital mortality in patients with ischemic stroke was investigated. When bilirubin levels in the surviving and deceased groups were compared (0.83 ± 0.65, 0.66 ± 0.51), bilirubin levels were observed to be higher in the deceased group. Even though this condition was statistically significant (p<0.05), it was clinically insignificant, as the bilirubin values of both groups were within the normal range (0.3-1.2 mg/dL). Although the antioxidant characteristic of bilirubin was mentioned in most of the conducted studies, its oxidative effect cannot be neglected. According to the findings in our study, we suggest there is an association between a high level of total bilirubin and the severity of ischemic stroke.

The effect of the distribution of blood group on mortality was also assessed in our study. The relationship between thrombosis and the ABO blood groups has been known for a long time. The non-O groups (A, B, AB) seem to have a higher incidence of ischemic stroke due to myocardial infarction, angina, peripheral vascular diseases, venous thromboembolism, and arterial occlusion compared to the O group. This is because those with the blood group of A, B, and AB are considered to have higher levels of factor 8 and von Willebrand factor (vWF), and the level of vWF is lower in the O group. However, this has not yet been completely accepted worldwide[15,16]. In our study, no significant result could be obtained in terms of determining in-hospital mortality for the non-O blood group or O blood groups. We screened blood groups through the automation system of our hospital, and the blood groups of only 35.3% of the patients included in the study were identified. This condition might have caused our study result to differ from the literature. When the past medical histories of the patients were examined, in line with the literature, a relationship was detected between poor prognosis and the parameters of a high blood glucose level, older age, and previous atrial fibrillation[17-19].

CONCLUSION

In conclusion, although exogenously administered CO was shown to decrease in patients with stroke under in vitro conditions, we could not detect any effect of a high endogenous CO level on mortality. The fact that the physiology of the brain differs from that of other organs and systems of the body limits the use of CO as a prognostic marker in stroke patients.
REFERENCES


Efficacy of surgical varicocelectomy in treating male infertility: A hospital-based retrospective study presenting a Saudi experience

Mohammed Jayed S Alenzi
Department of Surgery, Jouf University, Saudi Arabia

Kuwait Medical Journal 2019; 51 (4): 362 - 365

ABSTRACT

Objective: Infertility is one of the important common public health problems as it affects about 15% of partners in their reproductive age. One of the common causes for infertility in men is varicocele. This study aimed to determine the common post-operative complications due to surgical varicocelectomy in infertile patients and post-operative improvements in semen quality reflected as spontaneous conception in married couple.

Design: Hospital-based retrospective study
Setting: Department of Surgery, Al-Jouf regional hospital, Saudi Arabia
Subjects: The study was done among 538 married patients during the year 2015, who were treated by surgical varicocelectomy for infertility. Varicocele patients were further divided into 3 grades according to the World Health Organization grading (WHO 1993). Hormone profiling was done to rule out hormonal causes of infertility. The semen quality analysis parameters, namely, concentration, morphology and motility were done before and after varicocelectomy, during the follow-up in the Urology clinic, to detect anticipated improvements. Patient couples with primary or secondary infertility with the duration of more than one year were included in the study. The patients aged ≥40 years, with subclinical varicocele and those with idiopathic non-obstructive azoospermia were excluded.

Interventions: Blood hormonal profiling tests, surgical varicocelectomy, semen analysis

Main outcome measures: Surgical varicocelectomy post-operative complications and improvements in the quality of semen

Results: There were significant increases in semen quality considering sperm motility and concentration after varicocelectomy. Spontaneous pregnancy was ascertained for wives of 139 patients (26%) within 12-months post-operative follow-up period.

Conclusion: The treatments of varicocele were effective and minimally invasive with fewer complications, well recovery, improved semen quality and fertility reflected as 26% spontaneous pregnancy among couples enrolled.

KEYWORDS: male infertility, pampiniform plexus, semen analysis, varicocele

INTRODUCTION

Infertility is one of the important common public health problems as it affects about 15% of partners in their reproductive age. The male factor is involved in 40 - 50% of infertility cases. The most common cause of male infertility is idiopathic infertility, which is characterized by the presence of one or more abnormal semen parameters with no known cause. However, one of the common causes of male infertility is varicocele. While varicocele has an incidence of 4.4 - 22.6% in general population, 21 - 41% of men with primary infertility and 75 - 81% of those with secondary infertility have this condition.

Varicocele is defined as expansion (dilatation) of the pampiniform plexus veins in the scrotum. It is common on the left side due to anatomical differences between different sides of the human body. It seldom occurs simultaneously in both sides. Many factors explain the mechanisms of the effect of varicocele on fertility and spermatogenesis. They include increase in testicular temperature, excess intra-testicular pressure, hypoxia due to hindrance of blood flow, reflux of toxic substances, and increased prostatic pressure.
metabolites from the adrenal glands and abnormalities in the hormonal profile\cite{5-7}.

Varicocele is characterized by excess temperature of the scrotum possibly due to inflow of warm blood from the abdominal cavity. This is caused primarily by insufficiency of the internal spermatic vein valves\cite{8} and secondarily by dysfunction of the valves of the external spermatic and cremasteric veins. The mechanism by which temperature affects spermatogenesis is not clearly known. Thermal effect on the DNA and proteins in the nucleus of spermatic tubular cells and/or Leydig cells could be theoretically implicated - although reports have confirmed it\cite{6-9}.

The testicular blood flow with high vein pressure is compensated for by reduction in the arterial flow required to preserve the homeostasis of the intratesticular pressure\cite{8}. Reportedly, in men with varicocele, the mean increase in the pressure of the venous plexus of the spermatic tone was 19.7 mm Hg compared to the control group\cite{11}. Chronic vasoconstriction and subsequent malfunction of the spermatic epithelium can happen due to increases in the concentration of regressed toxic metabolites in the testes, e.g., auto-oxidizable catecholamines coming from the adrenal glands\cite{5}.

There are several methods to treat varicoceles. Surgical methods are performed sub-inguinal, inguinal, or lower abdomen (retroperitoneal). The varicocelectomy can be done by surgical laparoscopy and by an interventional radiology through venography and embolization. The current study was planned to determine the efficiency of surgical varicocelectomy considering the common post-operative complications and considering possible improvements in the fertility of infertile patients as ascertained by spontaneous pregnancy during post-operative 12-months follow-up period.

**SUBJECTS AND METHODS**

This study is a hospital-based retrospective study done among 538 married patients with age less than 40 years, who were treated by surgical varicocelectomy for infertility. The data of the patients were collected from the hospital records during the year 2015. Varicoceles patients were further divided into 3 grades according to the World Health Organization grading (WHO 1993). Grade 1 means a visible dilatation of internal spermatic veins that is palpable during Valsalva maneuver when patient is upright. Grade 2 means a palpable vein when upright without Valsalva maneuver. Grade 3 means a vein both palpable and visible through the scrotal skin when upright without Valsalva maneuver. Patients were followed-up at 6th and 12th month postoperative time points to assess sperm motility and concentration, testicles volume (with aid of ellipsoid Prader orchidometer) and occurrence of spontaneous pregnancy. Patient couples with primary or secondary infertility with the duration of more than one year were included in the study. The hormonal investigations were to rule out hormonal causes of infertility. Those patients with normal luteinizing hormone, follicular stimulating hormone, testosterone and prolactin were included in the study. Their wives were referred to obstetric and gynecological clinics for evaluation to rule out any cause of infertility, anatomical or hormonal, that could hinder pregnancy. Unilateral or bilateral (either open or laparoscopic) varicocelectomy operations were done in the Al-Jouf region hospitals for patients free from endocrine causes of infertility and their spouses were in the period from March 2009 - March 2015. On top of the pre-operative profiling, their semen analysis was conducted three times with 3 weeks intervals – each was divided into three portions for analysis in 3 independent laboratories to guard against individual bias. The pre- and post-operative semen analysis parameters (concentration, morphology and motility) were compared in the follow-up urology clinic. The hormone study was done using specific assays on an automated system.

Exclusion criteria: Patients aged ≥40 years, with subclinical varicocele and idiopathic non-obstructive azoospermia were excluded.

**Statistical analysis**

The statistical analysis was done in this study using SPSS version 21. Continuous variables were presented with mean and standard deviation. Categorical variables were presented as number and percentage.

**RESULTS**

Among the 538 patients enrolled, records of four patients were lost to follow-up. Hence, the total sample size was 534. The male patients’ mean age in this study was 29.3 ± 6.3 years and the mean age of their spouses was 25 ± 4.4 years. The mean duration of infertility among the enrolled couples was 1.8 ± 1.1 years.

<table>
<thead>
<tr>
<th>Grades</th>
<th>No</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1</td>
<td>165</td>
<td>30.9</td>
</tr>
<tr>
<td>Grade 2</td>
<td>229</td>
<td>42.9</td>
</tr>
<tr>
<td>Grade 3</td>
<td>140</td>
<td>26.2</td>
</tr>
</tbody>
</table>

Table 1 presents the different grades of varicocele among the study participants. Majority (42.9%) of the varicocele grades in the present study was grade 2, followed by grade 1 (30.9%) and grade 3 (26.2%).

The % of sperm motility before treatment among grade 1, 2 & 3 patients were 29.9%, 28.9% and 20.6%, respectively (Table 2). The statistical analysis of %
Table 2: Semen analysis for motility and concentration (before treatment, and at 6th and 12th months post-operative follow-up time points)

<table>
<thead>
<tr>
<th>Semen analysis</th>
<th>Varicocele grade</th>
<th>Number of patient (%)</th>
<th>Before treatment</th>
<th>6th month follow up</th>
<th>12th month follow up</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sperm motility (%)</td>
<td>Grade 1</td>
<td>165 (30.9)</td>
<td>29.9 ± 4.1</td>
<td>51.1 ± 1.1</td>
<td>56.3 ± 1.8</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td></td>
<td>Grade 2</td>
<td>229 (42.9)</td>
<td>28.9 ± 1.9</td>
<td>48.3 ± 4.0</td>
<td>50.3 ± 1.6</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td></td>
<td>Grade 3</td>
<td>140 (26.2)</td>
<td>20.6 ± 1.7</td>
<td>43.1 ± 3.6</td>
<td>45.3 ± 1.7</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>534 (100)</td>
<td>27.1 ± 2.4</td>
<td>49.1 ± 4.2</td>
<td>51.7 ± 1.8</td>
<td>&lt; 0.001*</td>
</tr>
<tr>
<td>Sperm concentration (millions/mL)</td>
<td>Grade 1</td>
<td>165 (30.9)</td>
<td>15.8 ± 2.9</td>
<td>35.8 ± 1.9</td>
<td>41.3 ± 4.9</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td></td>
<td>Grade 2</td>
<td>229 (42.9)</td>
<td>14.1 ± 2.2</td>
<td>32.7 ± 2.3</td>
<td>32.8 ± 2.2</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td></td>
<td>Grade 3</td>
<td>140 (26.2)</td>
<td>10.1 ± 1.9</td>
<td>18.7 ± 4.1</td>
<td>20.3 ± 2.2</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>534 (100)</td>
<td>13.5 ± 2.7</td>
<td>18.6 ± 3.9</td>
<td>23.1 ± 4.2</td>
<td>&lt; 0.001*</td>
</tr>
</tbody>
</table>

Values are presented as mean ± standard deviation. p < 0.001 is statistically significant.

Table 3: Testicular volume (mL) changes (before treatment, and at 6th and 12th months post-operative follow-up time points).

<table>
<thead>
<tr>
<th>Varicocele grade</th>
<th>Number of patient (%)</th>
<th>Before treatment</th>
<th>6th month follow up</th>
<th>12th month follow up</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1</td>
<td>165 (30.9)</td>
<td>18.8 ± 3.9</td>
<td>20.4 ± 1.8</td>
<td>21.2 ± 2.1</td>
<td>0.451</td>
</tr>
<tr>
<td>Grade 2</td>
<td>229 (42.9)</td>
<td>19.4 ± 4.9</td>
<td>20.4 ± 1.8</td>
<td>21.2 ± 2.1</td>
<td>0.386</td>
</tr>
<tr>
<td>Grade 3</td>
<td>140 (26.2)</td>
<td>17.9 ± 3.3</td>
<td>18.8 ± 2.4</td>
<td>19.8 ± 1.9</td>
<td>&lt; 0.001*</td>
</tr>
</tbody>
</table>

Values are presented as mean ± standard deviation. p < 0.001 is statistically significant.

Table 4: Surgical varicocelectomy post-operative complications (n = 534)

<table>
<thead>
<tr>
<th>Type of complication</th>
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<th>Percentage</th>
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<tr>
<td>Wound infection</td>
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<tr>
<td>Recurrence</td>
<td>8</td>
<td>1.6</td>
</tr>
</tbody>
</table>

Table 2: Semen analysis for motility and concentration (before treatment, and at 6th and 12th months post-operative follow-up time points)

Table 3: Testicular volume (mL) changes (before treatment, and at 6th and 12th months post-operative follow-up time points).

Table 4: Surgical varicocelectomy post-operative complications (n = 534)

sperm motility showed progressive increases over the follow-up 12-month period. This increase was statistically significant (p < 0.001). The mean sperm concentration (millions/mL) before treatment among grade 1, 2 & 3 varicocele patients were 15.8, 14.1 and 10.1, respectively. The statistical analysis of sperm concentration showed time-dependent increases in sperm concentration over the period of 12-month follow-up. This increase was statistically significant (p < 0.001).

Testicular volume was significantly improved among grade 3 varicocelectomy patients (Table 3) in comparison with grade 1 and grade 2 (p < 0.01). Spontaneous pregnancy was achieved in 139 couples (26%) within the post-operative 12-month follow-up period. Two patients (0.4%) were readmitted to hospital post-operatively due to signs of wound infection (Table 4). They were given the appropriate antibiotics and were completely cured. Six patients (1.1%) were complicated by hydrocele. Eight patients (1.6%) visited the clinic with recurrence of varicocele after six months post-operation.

**DISCUSSION**

The aim of this study was to evaluate post-operative complications and improvements in male fertility after surgical varicocelectomy among infertile patients with varicocele. Varicocelectomy was reported to improve semen quality among infertile men.[20] The relationship between infertility and varicocele conditions are still unclear. There is an increasing interest in the role of reactive oxygen species (ROS) and oxidative stress in the causation of male infertility.[13,14] Research performed during the last ten years has supplied rising support to the concept that oxidative stress is one of the major causes of male infertility. ROS may act through induction of apoptosis[15]. The earlier studies showed that increased nitrosative nitric oxide could be an alternative cause for varicocele-induced injury as compare to other oxidative free radicals.[16,17].

Furuya et al authenticated a blood-testis barrier and immune regulatory proteins at the level of Sertoli cells, rete testis, and efferent ductules that provide immunological protection of sperm antigens and inhibit lymphocyte proliferation and complement mediated cell lysis.[18].

A study conducted by Kim and Goldstein showed that early varicocelectomy, particularly for large varicocele, may be useful in preventing future infertility and alleviated androgen defect.[19] However, in the present study, varicocelectomy was beneficial in all the grades of varicocele considering improvement of seminal quality in terms of motility and quantity. Krishna Reddy et al[20] and Lofti[21], reported similar findings, highlighting the ability of varicocelectomy among infertile men to improve seminal quality in terms of motility and quantity.

In our study, spontaneous pregnancy was achieved in 141 (26%) couples within the post-operative 12-month follow-up period. Krishna Reddy et al[20] has reported the same. He also pointed out that there were
differences in rate of spontaneous pregnancy among the different grades of varicocele treated. The post-operative complications of varicocelectomy were very low and non-serious that must encourage conducting surgical varicocelectomy with a high hope of achieving a significant improvement in semen quality. Previous studies showed similar rate of complications\textsuperscript{22-23}.

**CONCLUSION**

From the results in this study and the literature reviews, we found that the surgical treatment of varicocele was effective, minimally invasive, and had minimal complications with excellent recovery. It improved semen quality and rate of spontaneous pregnancy among married couples enrolled.

**REFERENCES**

Original Article

Effect of SYNTAX score II on postoperative atrial fibrillation in patients undergoing off-pump coronary artery bypass grafting surgery

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Kuwait Medical Journal 2019; 51 (4): 366 - 372

ABSTRACT

Objective: Postoperative atrial fibrillation (PoAF) is a common complication after coronary artery bypass grafting (CABG). The synergy between percutaneous coronary intervention with taxus and cardiac surgery (SYNTAX) score is an angiographic scoring tool for systematically quantifying the severity of each coronary lesion. The aim of this study was to evaluate the relationship between development of PoAF and SYNTAX score II in patients undergoing off-pump CABG.

Design: Retrospective study

Setting: Department of Cardiovascular Surgery, University of Health Sciences, Bursa Yüksek İhtisas Research and Training Hospital, Bursa, Turkey

Subjects: A total of 68 consecutive patients who underwent off-pump CABG

Intervention: Predictive values of the variables were measured for the development of PoAF

Main outcome measure(s): The relationship between preoperative SYNTAX score II and PoAF in patients undergoing off-pump CABG

Results: Twenty patients with PoAF and 48 patients without PoAF were enrolled. In univariate logistic regression analysis, the PoAF was significantly correlated with age (OR=1.083, 95% CI: 1.025-1.144, p=0.004), glomerular filtration rate (OR=0.963, 95% CI: 0.940-0.987, p=0.002), hematocrit (OR=0.848, 95% CI: 0.729-0.991, p=0.038) and Syntax score II (OR=1.079, 95% CI: 1.023-1.138, p=0.005). Only hematocrit levels were identified as an independent predictor of PoAF in multivariate analysis (OR=0.829, 95% CI: 0.694–0.990, p=0.039). It was determined that a cut-off level of 22.65 for SYNTAX score II predicts PoAF (AUC: 0.733, p=0.003)

Conclusion: SYNTAX score II was not an independent predictor for the development of PoAF. However, we observed that higher SYNTAX score II was correlated with the development of PoAF.

KEYWORDS: aortocoronary bypass, cardiac arrhythmias, coronary angiography

INTRODUCTION

Postoperative atrial fibrillation (PoAF) is a common complication after coronary artery bypass grafting (CABG)[1]. PoAF has a high prevalence, affecting 20 to 45% of CABG patients[2]. This arrhythmia occurs most frequently in the first five days of the postoperative period, peaking between 24 and 72 hours, being uncommon after the first week[2]. PoAF has been associated with an increase in early and late mortality rates, hospital adverse events, particularly hemodynamic instability, thromboembolic events and heart failure progression[3]. Older age, obesity, hypertension, prior atrial fibrillation (AF) and congestive heart failure are associated with a higher risk of developing AF after cardiac surgery[4].

Intra-operative factors can be consequent to cardiac ischemia and inflammation inherent to the complexity of the surgical technique[2]. CABG with cardiopulmonary bypass appears to be associated with a higher incidence of PoAF compared to off-pump CABG[2].

The synergy between percutaneous coronary
intervention with taxus and cardiac surgery (SYNTAX) score is an angiographic scoring tool for systematically quantifying the severity of each coronary lesion and assessing its individual characteristics\(^5\). This scoring tool is used worldwide to predict long-term outcomes in patients with coronary artery disease undergoing elective percutaneous transluminal angioplasty or CABG\(^6\). Recently, some authors have used SYNTAX scores to predict major adverse cardiac and cerebrovascular events following CABG\(^6,7\). The aim of this study was to determine the relationship between preoperative SYNTAX score II and PoAF in patients undergoing off-pump CABG.

**SUBJECTS AND METHODS**

**Patients**

This retrospective observational study included 86 consecutive patients who underwent off-pump CABG between 2014 and 2016 at Department of Cardiovascular Surgery, Bursa Yüksek İhtisas Training and Research Hospital, Bursa, Turkey. The study was approved by the local institutional Ethical Committee of University of Health Sciences.

All data to be analyzed retrospectively were retrieved from the hospital medical files. The exclusion criteria were preoperative AF or flutter, previous treatment with amiodarone, presence of valvular heart disease, chronic obstructive pulmonary disease (COPD), prolonged intensive care unit (ICU) stay, redo cardiac surgery, bleeding revision, and chronic renal failure. Eighty-six patients that underwent off-pump CABG were evaluated in this study. Five patients with COPD, two patients with chronic renal failure, five patients with moderate mitral valve disease, two patients with preoperative AF, two patients with previous cardiac surgery history, one patient with postoperative bleeding and one patient with prolonged ICU stay were excluded. Thus, the remaining 68 patients with off-pump CABG were included in the study.

All data were recorded, such as age, gender, history of hypertension, diabetes mellitus, preoperative drug use (beta-blockers, statins, ACE or ARB inhibitors), smoking, ejection fraction, left atrial diameter, body mass index, body surface area, Euroscore, number of anastomosis, extubation time, postoperative bleeding amount, duration of ICU stay, and discharge time from hospital. Laboratory parameters were also studied from venous blood sample before the surgery.

**Diagnosis of PoAF**

The patients were monitored in ICU with continuous heart rhythm and invasive blood pressure monitoring. In addition, a 12-lead electrocardiography (ECG) were also obtained daily while in the ICU. Patients were monitored continuously by five-lead telemetry in the regular ward. When the patients complained of palpitation, dyspnea and angina, 12-lead ECG was taken. AF was verified using 12-lead ECG. AF was diagnosed according to the European Society of Cardiology guidelines\(^8\). Postoperative AF was described as irregular, fast oscillations, or fibrillatory waves instead of regular P waves at ECG.

An AF episode lasting longer than 5 minutes was accepted as PoAF. Standard medical cardioversion treatment was conducted with amiodarone (5 mg/kg) for 30 minutes, followed by 900 mg/day.

**SYNTAX score analysis**

SYNTAX score was performed by an experienced interventional cardiologist. For SYNTAX score II calculator, calculator version 2.28 (Cardialysis, Boston Scientific; available at: www.syntaxscore.com) was used. The vessels with a diameter of ≥1.5 mm and the lesions with ≥50% stenosis were included in the SYNTAX score calculation. Scoring was performed for each patient according to the following parameters: coronary dominance, number of lesions, segments included per lesion, the presence of total occlusion, trifurcation, bifurcation, aorto-ostial lesion, calcification, severe tortuosity, thrombus, and diffuse/small vessel disease; and lesion length >20 mm.

**Statistical analysis**

Data were analyzed with the Statistical Package for the Social Sciences (IBM SPSS Statistic Inc. version 21.0, Chicago, IL, USA). Continuous and ordinal variables were expressed as mean ± standard deviation and nominal variables were expressed as frequency and percentage. Kolmogorov-Smirnov test and Shapiro-Wilk tests of normality were used to identify distribution of variables. Student’s t test was used to compare two groups for continuous variables with normal distribution. Chi square test was used to compare two groups for nominal variables. Mann-Whitney U test was used to compare two groups for continuous variables without normal distribution. The relationship between the preoperative independent variables and the development of postoperative AF was evaluated by a binary logistic regression analysis. For all tests, a p-value <0.05 was considered statistically significant. Receiver-operating characteristic (ROC) curve was applied for the prediction of PoAF after off-pump CABG and the area under the curve was calculated for SYNTAX score II.

**RESULTS**

A total number of 20 patients in the PoAF(+) group (70% male, mean age: 66.4 ± 8.1 years) and 48 patients in the PoAF(-) group (75% male, mean age: 57.02 ± 11.8 years) were recorded in the study. The demographic and clinical properties of the subjects are summarized...
in Table 1. Both PoAF(+) group and PoAF(-) group were similar to each other with regard to demographic properties. However, ACE-I/ARB therapy and SYNTAX score II were significant in the PoAF(+) group (p = 0.007 and p = 0.02, respectively) (Table 1).

The comparison of laboratory and operative parameters are shown in Table 2. Significant differences were observed between the two groups in terms of

PoAF: Postoperative atrial fibrillation; CAD: Carotid artery disease; PAD: Peripheral artery disease; MI: myocardial infarction; ACE-I: Angiotensin-converting enzyme inhibitor, ARB: Angiotensin-receptor blocker, SYNTAX: synergy between percutaneous coronary intervention with taxus and cardiac surgery; BSA: Body surface area, BMI: Body mass index. *Student’s t test; Mann-Whitney U test; Pearson Chi-Square

in Table 1. Both PoAF(+) group and PoAF(-) group were similar to each other with regard to demographic properties. However, ACE-I/ARB therapy and SYNTAX score II were significant in the PoAF(+) group (p = 0.007 and p = 0.02, respectively) (Table 1).

The comparison of laboratory and operative parameters are shown in Table 2. Significant differences were observed between the two groups in terms of

PoAF: Postoperative atrial fibrillation; BUN: blood urea nitrogen; GFR: glomerular filtration rate; Na: sodium; K: potassium; Ca: calcium; Mg: magnesium; TSH: thyroid stimulating hormone; LDL-C: low density lipoprotein cholesterol; HDL-C: high density lipoprotein cholesterol; TG: triglyceride; ICU: Intensive care unit. *Student’s t test; Mann-Whitney U test; GFR: Glomerular Filtration Rate (According to Cockcroft-Gault Equation)
hematocrit, blood urea nitrogen, creatinin, glomerular filtration rate (GFR), free T3, time to extubation, ICU stay and hospital stay. There was a statistical difference between the two groups in terms of hematocrit, blood urea nitrogen, creatinin, GFR, time to extubation, ICU stay and hospital stay as a negative effect to PoAF(+) group (p = 0.029, p = 0.017, p = 0.015, p = 0.002, p = 0.024, p = 0.000 and p = 0.000, respectively) (Table 2). Also, ejection fraction and left atrium diameter were not significantly different between the groups (p = 0.692 and p = 0.465, respectively) (Table 2).

Factors related to the development of PoAF were included in the univariate logistic regression analysis. In unadjusted univariate logistic regression analysis, the PoAF was significantly correlated with age (Odds Ratio [OR] = 1.083, 95% Confidence interval [CI]: 1.025-1.144, p = 0.004), GFR (OR = 0.963, 95% CI: 0.940-0.987, p = 0.002), hematocrit (OR = 0.848, 95% CI: 0.729-0.991, p = 0.038) and Syntax score II (OR = 1.079, 95% CI: 1.023-1.138, p = 0.005), but was not correlated with hypertension (OR = 5.600, 95% CI: 1.626-19.290, p = 0.171), diabetes mellitus (OR = 556, 95% CI: 0.173-1.788, p = 0.324), ejection fraction (OR = 0.997, 95% CI: 0.951-1.044, p = 0.883), left atrium diameter (OR = 1.050, 95% CI: 0.923-1.191, p = 0.459) (Table 3). Only hematocrit levels were identified as an independent predictor of development of AF after off-pump CABG surgery in multivariate analysis (OR = 0.829, 95% CI: 0.694–0.990, p = 0.039) (Table 3).

Additionally, in ROC curve analysis, it was determined that a cut-off level of 22.65 for SYNTAX score II was required for predicting PoAF with a sensitivity of 80% and a specificity of 66.7% (area under the curve: 0.733, 95% CI: 0.611-0.856, p = 0.003) (Figure 1).

**DISCUSSION**

In our study, we assessed the effect of the SYNTAX score II in the development of PoAF in patients that underwent off-pump CABG. In univariate logistic regression analysis, we found that age, lower GFR, lower hematocrit levels and higher SYNTAX score II were significantly correlated with the development of PoAF. In multivariate logistic regression analysis, only hematocrit levels were detected as an independent predictor for the development of PoAF. Also, it was determined that a cut-off level of 22.65 of SYNTAX score II was needed for predicting PoAF with a sensitivity of 80% and a specificity of 66.7% in ROC analysis (Fig 1). However, in our study, SYNTAX score II was not an independent predictor for the development of PoAF.

The incidence of PoAF following CABG surgery is seen in 25 - 40% of cases[9]. However, its frequency reaches 62% following combined CABG and valve surgery[9]. Atrial fibrillation is common in patients with rheumatic and non-rheumatic valvular heart disease[10]. A previous study demonstrated that patients with mitral regurgitation were more likely to experience recurrent AF post-ablation[10]. Mariscalco

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**Table 3: Binary Logistic regression analysis to identify predictors of PoAF**

<table>
<thead>
<tr>
<th>Variables</th>
<th>p</th>
<th>Exp(B)</th>
<th>95% C.I. Lower</th>
<th>95% C.I. Upper</th>
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<th>Exp(B)</th>
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<td>0.000 - 0.000</td>
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<td>0.076</td>
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<td>0.940 - 0.987</td>
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<td>0.038</td>
<td>0.038 - 0.038</td>
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<tr>
<td>Hct</td>
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<td>0.729 - 0.991</td>
<td>0.039</td>
<td>0.829</td>
<td>0.694 - 0.990</td>
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</tbody>
</table>

PoAF: Postoperative atrial fibrillation; SYNTAX: synergy between percutaneous coronary intervention with taxus and cardiac surgery; GFR: Glomerul filtrate rate; HT: Hypertension; DM: Diabetes mellitus, EF: Ejection fraction; LAD: Left atrium diameter; Hct: Hematocrit
et al[22] identified the PoAF rates as 22.9%, 39.8%, and 45.2% for the isolated CABG, valve surgery, and combined surgery, respectively. Therefore, we excluded 5 patients with moderate mitral valve disease so that it does not affect the outcome of the study.

There have been an increased risk of new-onset AF in patients with COPD[13]. Mathew et al[14] have showed that COPD increased the incidence of both persistent and paroxysmal AF and the incidence of PoAF increased to 43% in the presence of COPD. Negative prognostic effect of AF has been demonstrated in COPD patients. For this reason, patients with COPD were excluded in order to make our results more accurate.

In their study, Kwon et al[15] found that the incidence of AF was significantly higher in patients with reduced renal function. In another study, Gursoy et al[16] investigated whether clinical SYNTAX scoring was a predictor of acute renal injury in patients undergoing on-pump and off-pump CABG and showed that high clinical syntax scoring may be a predictor in the on-pump CABG group. Similar to these studies, in our study, high urea, high creatinine levels and low GFR were statistically significant in patients with PoAF. Also, SYNTAX score II levels were higher in these patients. We found that GFR significantly correlated with the development of PoAF in univariate logistic regression analysis.

In previous studies, hypertension, diabetes mellitus, left atrium diameter and low ejection fraction have been shown to play a role in the development of PoAF[17,18]. In our study, in terms of these parameters, they were not significantly different between the groups. However, these factors which are effective in AF development, are included in the logistic regression analysis. None of these variables were significantly associated with the development of PoAF.

In our study, in univariate logistic regression analysis, we found that age significantly correlated with the development of PoAF. However, in multivariate logistic regression analysis, it was not detected as an independent predictor of the development of PoAF. Age-related changes, including atrial fibrosis and accumulation of amyloid, can cause intra-atrial reentry, which leads to the development of AF[19]. Age has been repeatedly shown to be the major risk factor for AF after cardiac surgery[20,21]. Cerit et al[22] found that age was significantly associated with development of PoAF following CABG in univariate logistic regression analysis. In another study, Geçmen et al[23] showed that age was an independent variable predicting the development of PoAF in both univariate and multivariate logistic regression analysis. Although it was not detected as an independent predictor for the development of AF in our study, when the age is considered as a risk factor, it is known that elder patients have a high risk for developing AF.

The SYNTAX score shows the complexity of coronary artery disease and is able to predict the rate of major advanced cardiovascular events after revascularization[24]. However, there are few studies about the relationship between the SYNTAX score II and PoAF. In a previous study, Geçmen et al[25] reported that advanced age, COPD, and SYNTAX score II were independent predictors of PoAF in patients undergoing isolated on-pump CABG surgery. Another study by Cerit et al[22] on patients with on-pump CABG showed that the SYNTAX score II was an independent predictor of the development of PoAF. However, a study on patients undergoing off-pump CABG reported that there was no significant difference between a higher SYNTAX score II and development of PoAF[26]. In our study, we observed that higher SYNTAX score II was correlated with the development of PoAF. However, SYNTAX score II was not an independent predictor for the development of PoAF. On the other hand, our study had homogeneity because we excluded risk factors for development of AF as COPD and valvular heart diseases. In our study, in terms of factors related to the development of PoAF such as hypertension, diabetes mellitus, left atrium diameter and low ejection fraction, there were no significant differences between the groups. In ROC curve analysis, we found that a cut-off level of 22.65 for SYNTAX score II was required for predicting PoAF with a sensitivity of 80% and a specificity of 66.7%. Therefore, the results of our study may take into consideration the relationship between high SYNTAX score and postoperative AF.

CONCLUSION

Several factors contribute to the development of AF after coronary bypass surgery. Many studies have been done on PoAF development. SYNTAX score II is a marker of the severity of preoperative coronary artery disease and may be a predictor of postoperative complications such as AF. As a result of this study, we thought that high SYNTAX score II could be a factor for the development of PoAF. We think that this factor should be taken into account before surgery.

Limitations

Our study has some limitations. The main limitation of this study is its retrospective nature and it was done in a single center. The number of patients included in the study is small and there is no record of long-term outcomes. In addition, off-pump CABG operations were not performed by a single surgeon. Further prospective studies with a larger number of patients are required.
ACKNOWLEDGMENTS

We thank Associate Professor of Cardiology Dr. Hasan Ari for his invaluable support in calculating the SYNTAX score.

Ethical statement: The material has not been published anywhere. Authors of the manuscript have no financial ties to disclose and have met the ethical adherence.

Disclosure of interest: The authors declare that they have no competing interests.

Declaration of authorship: All authors have directly participated in the planning, execution, analysis or reporting of this research paper. All authors have read and approved the final version of the manuscript.

REFERENCES


Original Article

18F-FDG PET/CT in pediatric lymphoma: Comparison of the Deauville criteria with semiquantitative analysis and CT in interim and post-treatment nodal evaluation

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2Department of Nuclear Medicine, Ege University Hospital, Bornova, Izmir, Turkey
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ABSTRACT

Objectives: To investigate and compare the role of visual assessment according to the Deauville Criteria (DC) and semiquantitative assessment by maximum standardized uptake value (SUVmax) and CT, in interim and post-therapy 18F-FDG PET/CT scans in the nodal involvement of pediatric lymphoma.

Design: Retrospective study

Setting: Training and Research Hospital

Subjects: Forty-nine PET/CT scans (15 interim, 34 post-therapy) of 30 pediatric patients [19 Hodgkin Lymphoma (HL) /11 non-Hodgkin Lymphoma (NHL)] were retrospectively reviewed. Unenhanced low-dose CT component of PET/CT were compared with data derived from DC and SUVmax and all were correlated with radiologic, pathological, laboratory records and clinical follow-up.

Main outcome measures: SUVmax, DC scores and CT findings in interim and/or post-therapy PET/CT scan

Results: In 15 interim PET/CT scans, 23 and 12 nodal disease sites were detected by CT and PET (with SUVmax and DC), respectively. In 34 post-therapy scans, 36 regions were detected by CT and metabolic assessment revealed 31 regions. In HL, specificity to predict therapy response was 77.7% and 64.4% for interim evaluation and 95.1% and 75.8% for post-therapy evaluation by metabolic assessment methods and CT, respectively. Negative predictive value (NPV) was 100% for each interim and post-therapy evaluation method. Sensitivity was 100% for post-therapy metabolic evaluation and CT. In NHL, specificity to predict therapy response was 100% and 28.5% for interim evaluation and 75% and 62.5% for post-therapy evaluation by metabolic assessment methods and CT, respectively. NPV was 100% for each interim evaluation method, 42.8% for post-therapy metabolic evaluation, 26.3% for post-therapy CT; sensitivity was 75% for post-therapy metabolic evaluation and 56.2% for post-therapy CT.

Conclusions: Our study demonstrated that the assessment according to DC and SUVmax showed concordant results and could be safely used both in interim and post-therapy PET/CT scans of pediatric patients with lymphoma. Even if metabolic evaluation is superior to CT, these methodologies are complementary to each other, and one should review them both synchronously.

KEYWORDS: Fluorodeoxyglucose F18, lymphoma, pediatrics, PET/CT

INTRODUCTION

Lymphoma is one of the most common childhood malignancies. The survival with or without disease has increased with emerging chemotherapy agents and new diagnostic modalities. Due to the fact that lymphoma has a high chance of recovery, imaging modalities are essential in the initial diagnosis, as well as follow up of the disease. There are many studies in the literature regarding the efficiency of 18F-FDG positron emission tomography (PET)/computerized tomography (CT) imaging in lymphoma. PET/CT has proven its importance in the initial staging of adult and pediatric lymphoma, in the treatment response assessment, and in the detection of recurrence[1-6].

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It has been shown that PET/CT imaging may demonstrate early metabolic changes during chemotherapy in malignant lymphomas\[7]. After 1-3 cycles of chemotherapy, PET/CT may predict the therapy response and survival. This predictability will prevent well-responding patients from aggressive chemoradiotherapy regimens, decrease long-term side effects and help to identify poor responders who will require more intense treatments. There are several studies showing a significant difference in prognosis and survival rates between positive and negative interim PET scans. PET/CT imaging is also applied at the end of the treatment protocol to determine therapy response. A negative scan may indicate that the patient is in remission and it will serve as a guide regarding the cessation of therapy. Besides, it is the ultimate imaging modality to predict progression-free and overall survival rates\[5,8-13].

In studies investigating the efficacy of PET/CT imaging in pediatric lymphoma, PET/PET-CT results were mostly compared with conventional imaging methods\[14-20]. The data comparing PET and CT component of PET/CT were limited\[21]. Interpretation of the metabolic activity in lymphoma, which is a malignancy of the lymphatic system, may be directly affected by benign inflammatory conditions and can be quiet challenging in pediatric patients. For this purpose, there are some recommended interpretation criteria\[22-25]. Deauville Criteria (DC) – Deauville 5-point scale is one of the interpretation criteria which was introduced at the 1st International Workshop on Interim PET in Lymphoma in France in 2009\[26].

The objective of this study was to assess three interpretation criteria derived from interim and late PET/CT studies in pediatric patients with lymphoma. Visual analysis using DC, the semiquantitative analysis with maximum standardized uptake value (SUVmax) and anatomic evaluation by low-dose CT component of PET/CT were compared to predict therapy response.

**SUBJECTS AND METHODS**

**Patients**

Thirty pediatric patients with lymphoma (19 Hodgkin’s lymphoma (HL)/11 non-Hodgkin’s lymphoma (NHL); 11 females and 19 males; mean age: 11.6 years; range: 3 - 17 years), who had PET/CT scan for interim and/or post-therapy evaluation from July 2009 to November 2013, were enrolled in our study. Clinical and demographic characteristics of patients are outlined in Table 1. Interim scans were performed

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<td>16</td>
<td>HL</td>
<td>MC</td>
<td>Supra/infradiaphragmatic nodal</td>
<td>IIA</td>
<td>Remission</td>
<td>12</td>
</tr>
<tr>
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<td>17</td>
<td>HL</td>
<td>NS</td>
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<td>IIA</td>
<td>Remission</td>
<td>6</td>
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<tr>
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</tr>
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<td>MC</td>
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<td>IA</td>
<td>Remission</td>
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<tr>
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<td>NS</td>
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<td>IISA</td>
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<td>IVB</td>
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</tr>
<tr>
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<td>HL</td>
<td>MC</td>
<td>Supra/infradiaphragmatic nodal, bone</td>
<td>IVB</td>
<td>Remission</td>
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</tr>
<tr>
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<td>IV</td>
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<td>Progression</td>
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<td>Burkitt</td>
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</tr>
<tr>
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<td>M</td>
<td>16</td>
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<td>AL</td>
<td>Supra/infradiaphragmatic nodal</td>
<td>III</td>
<td>Remission</td>
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</table>

after two chemotherapy cycles. Out of 49 PET/CT scans, 15 of them (10 HL, 5 NHL) were performed for interim assessment, 34 (17 HL, 17 NHL) were for post-therapy evaluation. All of the studies were performed for at least 14 days after the last administered chemotherapy cycle. A total of 88 PET/CT scans with all indications (initial staging, early-late therapy response, restaging, follow-up) were retrospectively reviewed to analyse each patient’s individual disease course. Informed consent for the PET/CT scan was obtained from the parents. The institutional ethics committee reviewed and approved the study.

PET-CT imaging

After at least six hours of the fasting period, 5.18 – 7.4 MBq/kg (0.14–0.20 mCi/kg) of ¹⁸F FDG was injected intravenously. Prior to the injection, blood glucose levels were measured (mean: 90.5 mg/dl; range: 61 to 125 mg/dl). Only oral contrast (Omnipaque 350 mg I/ml) was administered during the uptake period. Approximately one hour after injection (45 - 60 min), PET/CT scan was performed from head to the proximal thigh, using a dedicated PET/CT system (Biograph high-definition 16-slice CT, Siemens Healthcare, Erlangen, Germany). CT scans were acquired without intravenous contrast using the settings of 90 kV voltage and 120 mA tube current, 0.6 s/rotation, section thickness of 5 mm. After CT, PET imaging was performed at 1 mm/s bed position, using a matrix of 512x512. After reconstruction of PET images with iterative reconstruction methods, PET, CT and fused PET/CT images were available for review in axial, coronal and sagittal planes.

Data analysis and interpretation

PET/CT images were reviewed in consensus by two nuclear medicine physicians. Images were evaluated on a region-based analysis (cervical, mediastinal, axillary, abdominal, inguinal) as positive or negative for lymphoma involvement of nodal sites.

For anatomic evaluation with unenhanced low dose CT, the short axis of lymph nodes was measured. Mediastinal lymph nodes bigger than 0.7 cm²[29], mesenteric ones bigger than 0.8 cm²[27] and in other areas the lymph nodes bigger than 1 cm in short axis were defined as positive for disease involvement.

Semiquantitative metabolic analyses were performed by measuring FDG uptake using SUVmax. SUVmax was determined according to the injected FDG dose and the patients’ body weight. CT images were also simultaneously reviewed for correct anatomic localization of the hypermetabolic foci.

In order to define a cut-off value for SUVmax evaluation, conglomerate lymph node masses (confirmed by biopsy) in baseline PET/CT scan which showed complete metabolic and anatomic response after therapy (according to clinical evaluation and imaging findings) were selected. SUVmax both at initial and post-therapy scan were determined. Using receiver operating characteristic (ROC) curve analysis, a cut-off value was obtained to identify a lymph node as positive or negative. Lymph nodes with the SUVmax under the cut-off value were accepted as negative for disease involvement.

Visual assessment was performed using DC, which was based on a 5-point scale using mediastinal blood pool and hepatic uptake as the reference for disease involvement (1-3= PET negative, 4-5= PET positive)[24].

Tha data derived from all three methods were interpreted with follow-up scans (PET/CT, USG, contrast-enhanced diagnostic CT, MRI), histopathology (if performed), laboratory findings and clinical course (e.g. results of treatment). According to these data, patients were determined to be in remission or to have stable/progressive/recurrent disease after completion of therapy by a pediatric haematologist and this served as the standard of reference. In patients who entered remission or had no further evidence of disease, positive lesions were accepted as false positive (FP), negative ones were true negative (TN). In patients who had stable or progressive disease, positive lesions were accepted as true positive (TP) and negative lesions were false negative (FN). Sensitivity, specificity, accuracy, positive predictive value (PPV) and negative predictive value (NPV) were calculated for each of the three interpretation methods.

RESULTS

During the follow-up period (range: 6 – 31 months; mean: 18.5 months), 24 patients (17 HL, 7 NHL) were in clinical remission after therapy, three patients had progressive or recurrent disease (NHL) and three children died (one of congenital immunodeficiency-HL; two of progressive disease-HL and NHL).

ROC curve analysis determined a cut-off value for SUVmax to identify lymph nodes as positive or negative for lymphoma involvement in our patient population as 3.15 g/ml, with a sensitivity of 100% and specificity of 97.1%.

Fifteen interim PET/CT studies were applied after two cycles of chemotherapy. CT component demonstrated 23 nodal disease sites, while 12 positive regions were revealed by SUVmax and DC. In a total of 34 post-therapy scans, 36 regions were detected by CT and 31 by metabolic assessment. Performance indices of assessment methods in both interim and post-therapy scans were summarized in Table 2.

Interim PET/CT results in HL

A total of 10 interim PET/CT scans were applied in 10 patients with HL. CT depicted 16 disease sites, while 10 nodal sites were demonstrated with the
assessments based on SUVmax and DC. All three assessment methods were FP in 6 disease sites in 4 patients according to the clinical survey (3 cervical, 3 abdominal lesions, patient no:1,2,6,17). In 3 of them, post-therapy scans demonstrated no hypermetabolic foci on five sites, one patient had no scan after completion of therapy. Furthermore, none of these four patients had relapse or progression during a follow-up period of 6 - 22 months.

Twenty-five negative sites which were positive in the baseline scan were reviewed in interim PET/CT imaging by all three assessment methods. These patients were in clinical remission after the completion of the therapy, therefore they were accepted as TN. When we evaluated the conflicting results, CT depicted 10 positive sites which were negative by the metabolic assessment in 8 patients (patient no:1,2,4-7,14,16). All 8 patients underwent clinical remission at the end of the treatment. Therefore those sites were accepted as FP for CT and TN for metabolic evaluation (Fig. 1). On the contrary, there were 4 nodal sites, [three cervical and one iliac region, in 3 patients (patient no:1,5,6)] which were TN for CT imaging and FP for metabolic assessment methods. When the results were generally considered, three of 10 interim scans were positive in patients with HL. All these patients, except for one child who died due to congenital immunodeficiency syndrom-related complications, were in remission at the end of treatment. Specificity, NPV, and accuracy of both SUVmax and DC for the prediction of prognosis were 77.7%, 100%, 77.7%, respectively, as compared to 64.4%, 100%, 64.4% for CT in the interim evaluation of HL.

Post-therapy PET/CT results in HL
Seventeen post-therapy PET/CT scans were applied in 15 children with HL. CT showed 16 disease sites, while 5 sites were depicted with the metabolic

Table 2: Interim and post-therapy PET/CT results by region-based analysis in HL and NHL

<table>
<thead>
<tr>
<th>Lymphoma Type</th>
<th>TP</th>
<th>TN</th>
<th>FP</th>
<th>FN</th>
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<tr>
<td></td>
<td>SUVmax</td>
<td>DS</td>
<td>CT</td>
<td>SUVmax</td>
</tr>
<tr>
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<td>-</td>
<td>-</td>
<td>-</td>
<td>35</td>
</tr>
<tr>
<td>posttherapy</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>59</td>
</tr>
<tr>
<td>NHL interim</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>7</td>
</tr>
<tr>
<td>posttherapy</td>
<td>24</td>
<td>24</td>
<td>18</td>
<td>6</td>
</tr>
</tbody>
</table>

TP: true positive; TN: true negative; FP: false positive; FN: false negative; HL: Hodgkin lymphoma; NHL: non-Hodgkin lymphoma
assessment methods. Three positive sites were detected by all methods. Two of those nodal sites were observed in a non-responder patient (patient no:18) and were accepted as TP. The other focus was determined as FP since there was no evidence of residual and/or relapsed disease in the following scans during seventeen months follow-up (patient no:10).

In disease-free children, 45 negative sites which were positive in the previous scans were accepted as TN. The discordant results between CT and metabolic imaging in 10 children who were in clinical remission at the end of the therapy were as follows: CT demonstrated 14 positive nodal sites (1 cervical, 4 axillary, 6 mediastinal, 3 abdominal) which were negative in metabolic evaluation (patient no: 2, 4-7, 10, 15-17) while 2 positive sites with SUVmax and DC assessment were normal in CT (cervical; patient no:7) (Table 2, Fig. 1). To predict the final response to therapy in HL, the specificity of CT, SUVmax and DC were 75.8%, 95.1%, 95.1%, sensitivity and NPV were 100%, the accuracy were 76.5%, 95.3%, 95.3%; and PPV were 11.7%, 50%, 50%, respectively.

**Interim PET/CT results in NHL**

A total of 5 interim scans were applied in 4 patients with NHL. CT demonstrated 7 positive nodal regions. Two of them were detected by metabolic evaluation and were accepted as TP due to the progression of the disease (patient no:21). Five foci were FP for CT and TN for metabolic evaluation.

There were 2 regions which were negative by all assessment methods and defined as TN in a patient who is in remission (axillary, patient no:27).

When the results were generally considered, among 5 interim PET/CT scans in NHL, 3 studies were negative in patients with disease remission, while two scans were positive in patients with progressive lymphoma. Sensitivity of interim evaluation to predict therapy response was 100% for all methods due to lack of FN. Specificity of CT was 28.5% while it was 100% for metabolic assessment methods. Accuracy was 44.4% for CT and 100% for other two methods. PPV was 28.5% for CT and 100% for metabolic assessment. Finally, NPV was 100% for all.

**Post-therapy PET/CT results in NHL**

Seventeen PET/CT scans were performed for response assessment at the end of the therapy. Positive nodal regions that were revealed by CT were 21 while 26 nodal sites were determined by SUVmax and DC. In 20 nodal sites accepted as positive by all methods, 18 were TP and 2 foci (cervical, patient no:24) were FP.

Thirteen regions which were positive in previous scans have become negative by both anatomic and metabolic evaluation. Five of them were TN (patient no: 24,26,27) and 8 (patient no: 25) were FN. Six of 14 nodal sites which were negative (FN) for CT, were positive (TP) by metabolic evaluation. In addition, in a patient (patient no:27) with remission, a mesenteric nonmetabolic lymph node 1 cm in size was TN for PET and FP for CT. Sensitivity, specificity, accuracy, PPV and NPV to predict therapy response were, 56.2%, 62.5%, 57.5%, 85.7%, 26.3% for CT; 75%, 75%, 75%, 92.3%, 42.8% for both SUVmax value and DC, respectively (Table 2).

**Extranodal involvement**

In patients with HL, 2 extranodal site involvements were depicted in interim evaluation while 6 sites were detected (3 lung, 2 bone and 1 muscle) in post-therapy scans. Two cases with HL had multiple hypermetabolic pulmonary nodules which had become nonmetabolic and regressed anatomically in interim and post-therapy scans (patient no: 4,7). A pulmonary mass in a child showed partial anatomic response, while the metabolic response was complete in the post-therapy PET/CT scan (patient no:12). In one case with progressive disease, there were multiple sclerotic-lytic hypermetabolic foci on the ribs and a hypodense lesion with moderate FDG uptake in gluteal muscle. Another bone involvement was seen in a case with clinical remission (no:19). That patient had a sclerotic lesion in the thoracic spine which became nonmetabolic after therapy. There was no extranodal involvement in any of the five interim PET/CT scans of patients with NHL while 3 sites (1 subcutaneous tissue, 1 liver, 1 parotid gland) were depicted in post-therapy scans (patient no:25,28).

Three of 10 interim scans were positive in patients with HL, while nine patients entered remission after therapy completion, except one child who died because of complications related with congenital immunodeficiency syndrome. In 5 interim PET/CT scans in NHL, 3 interim studies were negative patients with disease remission, while two scans were positive in patients with progressive lymphoma.

**DISCUSSION**

Monitoring therapy response in lymphoma is essential for the separation of the patients whose therapy needs to be discontinued and who need more intensive chemoradiotherapy or different agents. For this purpose, metabolic imaging with $^{18}$F-FDG PET/CT is one of the main diagnostic modalities and has been proved to be a very effective tool in staging and evaluation of therapy response when compared to conventional imaging modalities. Interim PET/CT imaging after 1-3 cycles of chemotherapy has also been proposed to monitor therapy response to predict survival in adult lymphoma. After therapy, monitoring therapy response with FDG PET/CT imaging is challenging since tumour environment is
mostly composed of inflammatory cells which may lead to dynamic changes and false positive FDG uptake in lymphoma. Therefore, the definition of a positive scan after therapy needs to be standardised in order to decrease interobserver variability and to increase accuracy. For this purpose, various evaluation methods have been proposed to predict therapy response.

The Deauville Criteria was proposed to overcome FP results in the interim assessment of therapy response in lymphoma patients on the basis of the idea to ignore the minimal residual disease. Recent reports have also denoted the value of DC in post-therapy response evaluation[20]. In this study, we compared the efficacy of metabolic evaluation with DC and SUVmax, then found an excellent correlation between the two methods. However, in a recent study by Hussiyan et al, more significant results were reported regarding the specificity and NPV (75% vs 70.8% and 100% vs 94.4%) when the semiquantitative evaluation and DC were compared with the SUV cutoff value as 2.5 in 54 children with HL[29]. As only four discordant interim scans in a total of 54 patients yielded these results in their study, we assume that we both could gather similar results in larger series. Furthermore, our results demonstrated that metabolic assessment methods have a higher specificity than CT (77.7% vs 64%) to detect residual disease in interim PET/CT evaluation in patients with HL and NHL, concordant with the literature[5,6,14-18].

A prospective study by Illivitzki et al compared PET and low dose CT components of interim PET/CT in 34 children with HL, and reported similar results as in our study[21]. The only difference was observed in NPV for PET (89% in their study, 100% in ours), which might be explained by the lack of FN data in our series, as all of the patients with HL entered remission.

One of the few prospective studies in pediatric patients with HL was reported by Furth et al[5]. The authors evaluated the role of FDG-PET imaging in determining early and late therapy response and compared it with conventional imaging modalities (CT, MRI, USG). They reported similar results with our study in interim evaluation regarding NPV (both were 100%), specificity (77.7% vs 68%) and accuracy (77.7% vs 70%) for PET and specificity (64.4% vs 68%) and NPV (100% vs 100%) for CT. Regardless of higher values for the metabolic evaluation in post-therapy scan in our series, both studies agreed that metabolic evaluation is superior to the anatomic interpretation in interim and post-therapy assessment. The same study also emphasized that post-therapy PET results which were accepted as FP due to the remission criteria, might be TP consistent with the residual disease that cured after radiotherapy. Similarly, FP lesions in interim scans in the present study might be TP. The lesions might represent slow responding tissue, as the therapy still continues. In the current report, three interim scans were positive (3/10) in patients with HL who all had remission at the end of the therapy. Two interim studies (2/5) were positive in children with NHL, one of them had progressive disease even with a modification of therapy regimen. Defining a positive interim scan as FP may seem to be theoretically incorrect in a patient with remission after completion of therapy. However, this approach may be the correct way to show the main role of interim scan is to predict the final clinical outcome, not the current status of disease. This is a common diagnostic dilemma of interim PET/CT which cannot be easily overcome, since it is not possible to perform biopsy for all positive sites. Furthermore, it is clear that negative interim scans have a higher impact on clinical management than positive ones, since therapeutic modifications based on interim results have not been widely accepted yet.

Even if the main purpose of our study was to evaluate the correlation among the different assessment approaches of PET/CT scans, and the number of patients was not enough to elicit a significant statistic, we examined the impact of mid-therapy scans in the prediction of prognosis as well. Our results showed that interim PET/CT scans determined the patients who will enter remission after therapy completion with an excellent NPV in both HL and NHL, as expected[14]. Although the prognostic importance of a negative interim scan is widely accepted among adult patients with lymphoma, there is obviously need for more studies with a larger population in pediatric group.

A retrospective study by Riad et al reviewed PET/CT scans in order to define early and late response assessment in pediatric lymphoma and compared the findings obtained by the conventional imaging methods[14]. Their study group consisted of patients with both HL and NHL, however, they did not interpret PET/CT results according to patients’ diagnosis as HL or NHL. They carried out a scan-based analysis, while we selected a lesion-based review. Regardless of the different methodologies, both studies demonstrated that metabolic evaluation supported by CT is superior to anatomic imaging modalities in HL and NHL. Moreover, both studies concluded that PPV of the anatomic imaging methods is low due to lack of differentiation of fibrotic scar tissue from viable malignant cells. In our series for NHL, NPV of post-therapy results were found to be low for anatomical and morphologic methods comparing to the study by Bakhshi et al[6], which may be due to methodology difference of choosing region-based or scan-based analysis.

Levine et al reviewed 156 post-therapy PET scans of 34 pediatric patients with HL and concluded similar results with the current study[30]. Consistent
with several results in the literature, their PPV was low (11%)\textsuperscript{[17,31]}. They reported the factors causing high rates of FP findings are thymic hyperplasia, infection, inflammation, brown fat and muscle tension. Additionally, they indicated that recurrence rates in pediatric HL are lower compared to the adult patients, this might be another factor for lower PPV. There is an improvement in PPV in more recent studies including our report. We believe that physicians overcome challenges on interpreting scans with the help of the experience and anatomical data that CT component of PET/CT imaging provides, as well.

DC or SUVmax showed concordant results in early and late therapy response assessment of HL and NHL, suggesting that both methodologies can be safely used to predict the prognosis following the therapy. It is widely known that morphological abnormalities determined by CT are not always correlated with the active disease. In the post-therapy period, 30 - 60% of the patients have residual tissue in CT, while only 10-20% of them reveal positive histopathology, and disease relapse occurs in 18% of those cases during follow-up\textsuperscript{[32]}. In our study, there was a considerable number of cases with residual fibrotic tissue without pathological FDG accumulation (15/30, 14HL,1NHL). During follow up, there was no proof of recurrence in these cases. Current findings agree that metabolic imaging with PET is superior to CT in distinguishing active disease from scar tissue, however it is suggested that the most appropriate approach will be the evaluation of both modalities.

In our study, there were a limited number of extranodal involvement sites in interim and post-therapy scans (2 in interim, 6 in the letter). For this reason, we did not include them into statistical analysis since it requires different approaches. Regarding the regression of an extranodal lesion, for instance in bone involvement, morphological changes occur longer than the nodal regions. In a region-based analysis such as in our study, that would lead to an overestimation of FP in CT imaging. We suggest that reviewing both anatomical and the metabolic condition becomes essential in therapy response assessment, particularly in the extranodal involvement of lymphoma.

The small-sized population is one of the limitations of our study. Secondly, the methodology of disease evaluation on a region-based analysis by the assessment of only nodal findings might be the reason for the discordance with the literature. In addition, histopathological correlation was not possible for the discordance with the literature. In addition, we did not include them into statistical analysis since it requires different approaches. For this reason, we did not include them into statistical analysis since it requires different approaches. Regarding the regression of an extranodal lesion, for instance in bone involvement, morphological changes occur longer than the nodal regions. In a region-based analysis such as in our study, that would lead to an overestimation of FP in CT imaging. We suggest that reviewing both anatomical and the metabolic condition becomes essential in therapy response assessment, particularly in the extranodal involvement of lymphoma.

The small-sized population is one of the limitations of our study. Secondly, the methodology of disease evaluation on a region-based analysis by the assessment of only nodal findings might be the reason for the discordance with the literature. In addition, histopathological correlation was not possible for every positive lesion to avoid unnecessary invasive procedures. Finally, we used unenhanced low-dose CT component of PET/CT instead of contrast enhanced full-dose diagnostic CT. There are studies reporting the efficiency of low-dose CT in pediatric cases. However, diagnostic CT may be more sensitive, especially in detecting extranodal findings and in nodal sites without FDG uptake\textsuperscript{[33]}.

**CONCLUSION**

Our study offers comparative data for the pediatric literature regarding the efficacy of DC and semiquantitative evaluation in both interim and post-therapeutic estimation of lymphoma with PET/CT. Semiquantitative and visual assessments can be used both in interim and post-therapy scan safely, and both methods showed concordant results in our series. As a result, regardless of the methodological differences mentioned above, most of the studies including the current one, agreed that PET/CT is superior to anatomic imaging modalities in monitoring therapy response in pediatric patients with lymphoma.

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Trends in bariatric surgery publications worldwide

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ABSTRACT

Objective: To look at worldwide publications on bariatric surgery and the trends in the new millennium

Design: A wide literature review was performed to collect all publications on bariatric surgery from 2000-2015 using SCOPUS.

Setting: Data were analyzed according to country of origin, journals, years, trends in publications, institutions, authors, and sub-specialties.

Interventions: We looked at the highest number of publications with regards to hospitals, countries, and authors worldwide.

Main Outcome Measures: To collect present data on all papers published on bariatric surgery from 2000-2015

Results: A total of 13,173 publications were collected, 75% being original articles while the rest were reviews. The majority of studies were from North America. Most publications were from the United States (41%). The top three journals published in were Obesity Surgery (18.5%), Surgery for Obesity and Related Diseases (9.8%), and Obesity (1.2%). 95% of publications were based on medical fields. A sharp increase in publications was noted after the year 2002. Publications on sleeve gastrectomy (SG), Roux-en-Y gastric bypass, mini gastric bypass, duodenal switch, gastric band and bilio-pancreatic switch compromise 15%, 24%, 2.6%, 3.2%, 7.8%, and 5.9%, respectively. Only 312 studies were randomized controlled trials. In the last 5 years, there was an increase in SG publications; gastric bypass stayed the same, and a decrease in gastric band was noted.

Conclusions: In the past 15 years, an increasing trend in publications was seen, with a sharp increase after the year 2002. Most publications were from the USA. More randomized controlled trials need to be conducted.

INTRODUCTION

Obesity has become one of the major issues the modern world has to deal with, showing a constant increasing trend with time. The recent WHO report in 2014 has shown that globally, 39% of adults aged 18 and over are overweight, and 13% of the world’s population is obese[1].

Moreover, rise in cardiovascular diseases has been like never before, with reports in 2012 finding it as the leading cause of death worldwide in 2012[2]. Diabetes is the fourth leading cause of death worldwide according to the same report[2]. The development of both of these conditions has been clearly correlated with obesity[3].

Thus, measures to prevent the rise of preventable causes of death, mainly obesity, have been implemented. Bariatric surgery has been proven to be one of the most successful measures to fight obesity; the Swedish Obese Subjects trial has shown bariatric surgery to be associated with decreases in mortality, cardiovascular disease, diabetes, and cancer[4,5].

This study aims to evaluate the current trends in bariatric surgery and the focus of publications in the new millennium.

METHODS AND MATERIALS

A wide literature search was conducted utilizing SCOPUS to look for original articles and systematic reviews published from the year 2000 to the end of 2015. Key words entered included “bariatric surgery”, “weight loss surgery”, “surgical weight loss”, “sleeve gastrectomy”, “mini gastric bypass”, “gastric band”, “bilio-pancreatic bypass”, and “duodenal switch”. Endo-luminal weight loss publications were excluded. Abstracts, editorial notes and letters were excluded. The data was then analyzed according to country of origin, type of procedure, centers studies were

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conducted in, authors, type of study, journals, and trends in publications. In addition, closer analysis was conducted to examine trends for each type of procedure of weight loss.

**Bibliometric indicators**

The SCOPUS database uses bibliometrics shared with Elsevier when analyzing data. It measures scholarly output, citation counts and H-Index.

**RESULTS**

As seen, the majority of publications focused on Roux-en-Y gastric bypass, followed by sleeve gastrectomy (SG), and gastric band (Figure 1).

From our wide search, we collected a total of 13,173 original articles (75%) and systematic reviews (25%). The United States has contributed the most articles, giving rise to 41% of the publications, followed by the United Kingdom (6.8%), and Italy (5.8%). It has also been noted that Africa generated the least amount of publications (Figure 2).

When analyzing data according to source, it was noted that Obesity Surgery (18.5%) was the journal with the most publications on this topic, with a continuously increasing trend in the new millennium. It was followed by Surgery for Obesity and Related diseases (SOARD) (9.8%), and Obesity (1.8%). Data published in journals involving interventional techniques was excluded. Obesity Surgery and SOARD show a continuously increasing trend in the new millennium; however, other top five journals as shown in Figure 3 have a relatively steady trend.

Most of the publications were from medical fields (95%), whereas the rest were from basic sciences and nursing.

There has been an increase in the number of publications in the new millennium, with a higher velocity seen after the year 2002, in which the number of articles started to double. The speed of publications continued to increase until the year 2014, after which, a deceleration can be observed (Figure 4).

The prominent theme of studies published after...
Fig 3: Publications according to source

the year 2007 showed a trend towards “metabolic surgery” and not just “obesity”, as was the case in early publications as proven in Table 1.

Of the 13,173 articles, only 312 (2.4%) were randomized controlled trials (RCTs). Almost half of those were based on Roux-en-Y gastric bypass (Figure 5).

In the last five years, it has been observed that publications on SG were steadily increasing, those involving Roux-en-Y gastric bypass started to decrease

Fig 4: Trends in the new millennium; publications by year
in 2014, and there was no change seen in gastric band publications (Figure 6).

**DISCUSSION**

In our study, we aimed to look at the literature for publications on bariatric surgery worldwide and their trends. This assessment serves to identify and rank key countries, journals and the effect of time on the progression of the different procedures in this highly evolving field.

With increasing worldwide trends in obesity, bariatric surgery has opened up a new door for its management and treatment, as well as the co-morbidities that come along with it. While obesity itself is considered as a debilitating condition, major studies have clearly correlated it with the development of chronic metabolic disorders such as type 2 diabetes mellitus, hypertension, and hyperlipidemia. The meta-analysis performed by Buchwald H et al., which is ranked as the most cited article in bariatric surgery, comprehensively analyzed the effect of bariatric surgery on weight and co-morbidities for the first time, proving the importance of this emerging field, as well as the importance in the investment in producing publications covering this topic. Furthermore, the prominent theme of studies published after the year 2007 showed a trend towards “metabolic surgery” and not just “obesity”, as was the case in early publications as proven in Table 1.

Most weight loss surgeries today are performed using minimally invasive techniques. The most common bariatric surgery procedures are gastric bypass, SG, adjustable gastric banding, and bilipancreatic diversion with duodenal switch. A study performed by Cleveland Clinic in 2015 showed that SG has become the most popular method of weight-
loss surgery in the USA, accounting for nearly 52% of all weight-loss operations, surpassing laparoscopic gastric bypass, which had been the most common procedure for decades[8]. This is contradictory to the number of total publications of each procedure, with our results showing Roux-en-Y gastric bypass leading with 24%, followed by SG with 15%. However, the time factor needs to be taken into consideration, due to the fact that SG has recently emerged as the most popular bariatric procedure being performed, and that can be seen in the fact that publications on SG are on a steady rise since 2010, while those on gastric bypass have started to show a decreasing trend.

The “Bariatric Revolution” is known as the era where bariatric case numbers (mainly gastric bypass) and public awareness about this topic increased dramatically and has been shown to be the period from 1998-2003[9]. This period showed a bout of academic publications on this topic, with these publications contributing to the formation of modern concepts that are used nowadays in bariatric surgery. This was also proven by our study, showing a sharp increase of publications starting in 2002. However, the decreasing trend shown as of recent years can be explained by the fact that most topics to be published on have been covered, as well as the fact that this study only focuses on 3 journals covering obesity surgery as a whole, while less invasive endoscopic procedures are showing an emerging trend.

As of recently too, there has been an emergence in bariatric surgery in children and adolescents. This shift is partly due to the realization that nonsurgical approaches are of limited effectiveness for severely obese children[10], as well as the fact that bariatric surgery has been proven to be an appropriate treatment for carefully selected morbidly obese adolescents with severe comorbidities[10-13]. This increase in bariatric surgeries in this age group is paralleled to the rapid increase in these procedures among obese adults, with similar short term post-op results[14-16]. There was an overall increase in the population-based rate of procedures between the years 1996 - 2003, with a similar relative surge also seen in the year 2003 compared to the year 2000 when it came to bariatric surgeries in adolescents, with over a 3-fold higher rate of procedures performed in the former[17]. Therefore, it could be of particular interest to look into publications about bariatric surgery in this age group, and the recent trends in these studies.

Our study was also able to show that the number of publications produced by the USA exceeded those of any other country by a number significantly larger than 50%. This could be explained by the fact that, out of the western world, the USA is the leader when it comes to obesity, with 33.7% of the population classified as being obese[18], and therefore it is understandable that a lot of resources would be invested in this topic. Furthermore, the USA is known to house the majority of the biggest research institutions, drawing in physicians from all over the world, and therefore, having the ability to produce more publications than other countries. This is however an interesting finding, given that as of 2014, there are 4 multiple countries that surpass the USA in terms of obesity[16].

As demonstrated by our statistics, RCT’s proved to be the least performed study in bariatric surgery, accounting for 2.4% of all studies, even though RCT’s remain the best method to obtain unbiased estimates of treatment effects. According to Kao et al[19], fewer than 10% of all studies reported in surgical journals are RCT’s, and treatments in surgery are only half as likely to be based on RCTs as treatments in internal medicine. This could be due to the inability of surgeons to blind health care providers and patients, having small sample sizes, variations in procedural competence, and different and strong individual patient or surgeon preferences. Other factors may include a lack of expertise by surgeons in clinical trials, lack of funding for surgical trials, methodologic problems specific to surgical trials and the ability of other research designs to assess surgical therapies. Solomon et al[20] estimated that the treatment questions involving surgical procedures that are open to evaluation by RCT’s account for only 40%, even in ideal clinical settings.

The limitations of this study include the fact that only the Scopus database was used to produce these results, while there is a chance that some studies have been missed, and analysis using other database platforms may have led to a different list. Also, as mentioned earlier, only 5 journals were included in the search, while some other journals covering more specific topics may have included more recently published topics. Another limitation of this study is the fact that we did not include socio-demographics when analyzing the number of publications per country.

CONCLUSION

In the past 15 years, an increasing trend in publications on bariatric surgery was seen, with a sharp increase seen after the year 2002. Most of the publications were proven to be from the USA. Therefore, a call for more collaboration between countries for research on this topic is needed. While randomized controlled trials remain very scarce, more of them need to be utilized to be able to cover this field fully.

ACKNOWLEDGMENT

Conflict of Interest: The authors declare that they have no conflict of interest.
Informed Consent: This article does not contain any studies with human participants or animals performed by any of the authors.

Ethical Approval: This article does not contain any studies with human participants or animals performed by any of the authors.

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Original Article

Investigation on the relationship between digit ratio (2d:4d), right-left 2d:4d differences and varicocele

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ABSTRACT

Objective: To investigate the relationship between the digit measurement ratio and the incidence of varicocele

Design: Prospective study

Setting: Urology Department of Tepecik Training and Research Hospital, Izmir, Turkey

Subjects: One hundred and ninety male patients (no varicocele as group 1, n = 138; varicocele as group 2, n = 52) who presented to our urology clinic with infertility complaints between January and July 2017 were evaluated prospectively for the study.

Interventions: The right 2D, right 4D, left 2D, left 4D lengths were measured by a 1-mm precision ruler with decimal divisions. Finger measurement ratios and differences were calculated with measurement results.

Main outcome measures: Positive correlation was detected between the varicocele and the right 2D (p = 0.034), left 4D (p = 0.029), Dr-l (p = 0.01), Dr/l (p = 0.01) measurements, and negative correlation was detected between the digit asymmetry index (p = 0.01) and the varicocele. No relationship was detected between the right 2D:4D and the left 2D:4D.

Results: Positive correlation was detected between the varicocele and the right 2D, left 4D, Dr-l, Dr/l measurements, and negative correlation was detected between the digit asymmetry index and the varicocele.

Conclusion: Patients with low testosterone exposure in the prenatal period are more likely to get varicocele during adulthood and possibly because of the effect of prenatal testosterone hormone on the male genital system and the anatomical structure of the spermatic vein in the embryological period.

KEY WORDS: digit asymmetry index, Dr-l, Dr/l, varicocele, 2D:4D ratio

INTRODUCTION

There are a lot of studies on the second to fourth digit ratio in the literature. In particular, studies carried out in the field of psychology are predominant. The relationship of many psychological issues from aggression of the patients to jealousy with 2D:4D digit ratio and its derivatives was investigated and interesting relations were determined[1,2].

Based on genetics, Hoxa and Hoxd, part of the homeobox gene, play a role in the development of both extremities and genitalia in vertebrates[3]. A mutation in the Hoxa gene causes a syndrome accompanied by anatomic defects in the digits and genital region that occurs in humans[4]. It was reported that the deregulation in the Hoxd gene expression in rats affected the genital bud and digit lengths[5].

With regards to urology, it was reported that 2D:4D ratio was closely related to the testosterone level in the prenatal period, and the testosterone exposure in the prenatal period was higher in individuals for whom this ratio was lower compared to the ones with higher ratio[6]. This ratio was found to be lower in males and reproductive success was higher in females for whom this ratio was higher[7,8]. In addition to this, the relation between the penile length of the patients, premature ejaculation, male reproductive hormone levels etc. and this ratio is the subject of many studies[9,10].

Varicocele is defined as the dilatation of the scrotal veins. Varicocele in normal males and males presenting to the hospital with infertility was found to be 15% and 40%, respectively[11]. Varicocele is a disorder that causes testicular dysfunction and reduces serum
testosterone levels and causes male infertility, and the exact etiological cause of this effect is still unknown, even though it is associated with increased testicular temperature[6].

In our study, we examined the relationship between the digit measurement values discussed with so much interest in the literature and the frequently observed varicocele. The fact that there is not yet any study investigating this relationship makes our study the first in this regard.

**SUBJECTS AND METHODS**

Patients who presented to our urology clinic with infertility complaints between January and July 2017 were evaluated prospectively for the study. After the anamnesis and physical examination, patients with history of varicocelectomy, genital trauma, orchitis traumas, hand and finger surgery, patients with hypogonadotropic hypogonadism, Klinefelter syndrome and patients with pathologies other than varicocele that may affect testosterone levels were excluded from the study. Right and left hand index finger (2D) and ring finger (4D) lengths of the patients were measured. Measurement was performed by directly measuring the distance between the metacarpophalangeal joint and the fingertip from the dorsal side of the hand with the aid of a ruler, and the mean values were calculated after each measurement was made at least twice. A 1-mm precision hard plastic ruler with decimal divisions was used for measurement. Based on the values obtained, right 2D:4D ratio, left 2D:4D ratio, right 2D:4D - left 2D:4D value (Dr-l), right 2D:4D / left 2D:4D ratio (Dr/l) and 2D:4D asymmetry index [ (left 2D:4D - right 2D:4D) / (left 2D:4D + right 2D:4D) ] were calculated. The patients with no varicocele were identified as group 1 and the patients with varicocele were identified as group 2. The relationship between the varicocele groups and the digit measurements was examined by the bivariate correlation test (Spearmen), IBM Statistical Package for Social Sciences (SPSS) Statistics Software program 22 was used for statistical analysis of the study. A p-value <0.05 was regarded as statistically significant.

**RESULTS**

The age range of the 95 patients included in the study was 20 - 49 years and the average age was 33.34 ± 6.04 years. With regard to the mean digit measurement values of the patients; for Group 1 (n = 138) and Group 2 (n = 52) the measurement values are determined as follows: length range and mean ± standard deviation values for the Right 2D are respectively 85 - 112 mm and 97.24 ± 5.5 mm in group 1, 91 - 112 mm and 100.15 ± 5.54 mm in group 2 (Correlation coefficient is 0.218, p-value is 0.034); 91 - 117 mm and 102.2 ± 6.2 mm in group 1, 96 - 115 mm and 104.3 ± 5.6 mm in group 2 for the right 4D (Correlation coefficient is 0.263, p-value is 0.01); ([(-0.04) - (+0.05)] and [(-0.0087) ± 0.026] mm in group 2 (Correlation coefficient is 0.218, p-value is 0.034) were determined as Table 1: Mean data of patients

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>Group 1 (n = 138)</th>
<th>Group 2 (n = 52)</th>
<th>Total (n = 190)</th>
<th>CC</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (year)</td>
<td>Min</td>
<td>Max</td>
<td>Mean</td>
<td>Std</td>
<td>Min</td>
</tr>
<tr>
<td>Right 2D (mm)</td>
<td>85</td>
<td>112</td>
<td>97.24</td>
<td>5.5</td>
<td>91</td>
</tr>
<tr>
<td>Right 4D (mm)</td>
<td>91</td>
<td>117</td>
<td>102.2</td>
<td>6.2</td>
<td>96</td>
</tr>
<tr>
<td>Left 2D (mm)</td>
<td>84</td>
<td>109</td>
<td>96.04</td>
<td>5.27</td>
<td>89</td>
</tr>
<tr>
<td>Left 4D (mm)</td>
<td>89</td>
<td>115</td>
<td>100.97</td>
<td>6.23</td>
<td>95</td>
</tr>
<tr>
<td>Right 2D:4D</td>
<td>0.9</td>
<td>1.00</td>
<td>0.95</td>
<td>0.02</td>
<td>0.91</td>
</tr>
<tr>
<td>Left 2D:4D</td>
<td>0.9</td>
<td>1.05</td>
<td>0.95</td>
<td>0.02</td>
<td>0.89</td>
</tr>
<tr>
<td>Dr-l (mm)</td>
<td>-0.09</td>
<td>0.07</td>
<td>0.00</td>
<td>0.02</td>
<td>-0.04</td>
</tr>
<tr>
<td>Dr/l</td>
<td>0.91</td>
<td>1.07</td>
<td>1.01</td>
<td>0.02</td>
<td>0.96</td>
</tr>
<tr>
<td>Asymmetry Index</td>
<td>-0.04</td>
<td>0.05</td>
<td>-0.0001</td>
<td>0.01</td>
<td>-0.03</td>
</tr>
</tbody>
</table>

CC: Correlation coefficient

**DISCUSSION**

Varicocele etiology appears to be multifactorial. Although varicocele is rarely bilateral, left varicocele is more common than the right one, and anatomi...
laterality differences in venous return are shown as the cause[14]. Inadequacy of valves in spermatic veins is another anatomic factor that is accused in the etiology[15]. The detection of varicocele in 80% of cases of secondary male infertility makes it more important to clarify this pathology and its etiology.

In the literature, 2D:4D ratio is shown as a marker for prenatal testosterone, and patients with low ratio have been reported to be exposed to high prenatal T and low prenatal E levels[6]. In the study by Oh et al, it was found that testicular volume was lower in males with a higher 2D:4D ratio[16]. In the study by Choi et al, it was reported that the 2D:4D ratio was related to the adult penis length, and it was concluded that the adult penis length was affected by testosterone level in the prenatal period[9].

The study by Bolat et al showed that more premature ejaculation was seen in patients with low 2D:4D ratio and that prenatal high testosterone exposure was a risk for premature ejaculation in adulthood[10].

In terms of anatomical defects, the relation of the hypospadias and cryptorchidism cases with the digit ratio has become a matter of curiosity due to their relationship with the HOX gene. Abbo et al addressed this issue in their study and it was interestingly detected that 2D:4D ratio was lower in the cases with hypospadias/cryptorchidism compared to the normal cases[17]. In another study, Manning et al investigated the relationship with sexual behavior in the study and found a higher 2D:4D ratio in homosexual / bisexual men than in normal men. In the same study, this ratio was detected to be higher in whites than the black race[18]. Auger & Eustache reported that 2D:4D digit ratio was negatively correlated with testicular volume in fertile patients[19]. Choi et al found that the right index and ring fingers were not correlated with the adult penis length, but the tarse penis length was longer in the patients with lower right 2D:4D ratio[9]. When the relationship of 2D:4D ratio was examined with the adult serum testosterone levels, the obtained results are conflicting. In the study by Manning et al, it was found that especially the right 2D:4D ratio was strongly correlated with the adult serum testosterone level[9]. In the study by Muller et al, it was found that there was a negative correlation between plasma testosterone level and right 2D:4D ratio, but no relation with left 2D:4D and Dr-1 values[11]. Hönekopp et al reported that 2D:4D ratio and Dr-1 value did not correlate with adult serum sex hormone levels, and the related parameters were only correlated with the prenatal androgenesis and the related human behaviors and cognition in their meta-analysis, although 2D:4D ratio was found to correlate with adult serum sex hormone levels in some studies[20].

In the meta-analysis by Xu & Zheng, it was revealed that the right 2D:4D ratio was lower in males than females and the right 2D:4D ratio reflected the difference between sexes better compared to the left 2D:4D ratio[21]. The meta-analysis by Hönekopp et al reported that the right 2D:4D ratio reflected prenatal androgenesis better than the left 2D:4D ratio[7]. In another study by Akinsal et al, 2D:4D ratio was reported to be predictive between the group with vasal agenesis and the control group[22].

In the study by Bennett et al, it was found that low right 2D:4D ratio and low Dr-1 value were associated with high rugby performance which could be regarded as an indicator of androgenization[23]. In the study by Kilduff et al, it was found that Dr-1 value and the right 2D:4D ratio were negatively correlated with the free testosterone level after repeated sprint ability test, and reported that exercise performance was higher in these patients. This correlation was interpreted as follows: the high testosterone exposure in the prenatal period was positively correlated with the free testosterone level and exercise performance in adulthood[24]. In the study by Hill et al, it was found that people with low Dr-1 value had higher sports performance and maximum oxygen uptake value. Also in this study, this relationship could be interpreted as that the high testosterone exposure in the prenatal period was positively correlated with the circulating testosterone level in the adult period[25]. Adult serum testosterone levels were found to be higher in patients with low Dr-1 and these patients were more susceptible to testosterone. The relationship of Dr-1 value with the adult serum testosterone level seems to be lower compared to the prenatal testosterone[26]. In the study by Manning et al, testosterone and estrogen levels were found to be related to the effects (aggressivity) on the endocrine system and behavioral system in the adulthood. Patients with low Dr-1 values were found to have higher serum testosterone peaks and sports performance[27]. In the study by Coyne et al, higher aggressivity was found in female patients with low Dr-1 values, and this relationship was again associated with testosterone[2]. As a result, adult androgen hormone levels are higher in patients with negative Dr-1 values, and the success rate in hormone-related activities is higher in these patients. In a psychiatric study which we would like to mention as the digit asymmetry index is discussed in it, Venkatasubramanian et al reported that the 2D:4D asymmetry index was lower in male schizophrenia patients than the male control group, and the same relationship was not found in female patients[28].

In our study, there was no difference in terms of the right 2D:4D, left 2D:4D ratios between varicocele group and control group. It was determined that the Dr-1
value \((p = 0.01)\) and \(\text{Dr} / l\) \((p = 0.01)\) value were higher, and 2D:4D asymmetry index \((p = 0.01)\) was lower in the group with varicocele compared to the control group. In other words, patients who were exposed to low testosterone in the prenatal period were found more likely to have varicocele in adulthood. Especially \(\text{Dr}-1\) value is considered to be negatively correlated with the adult testosterone level, testosterone level is expected to be lower in the group with varicocele. The effect of prenatal androgens to the varicocele is not yet known.

As seen in many studies aforementioned, it has been shown that there is a relationship between 2D:4D ratio and prenatal testosterone level. It is known that there is a relationship between prenatal testosterone and testicular volume, penis size, secondary sex characteristics, etc.

**CONCLUSION**

Based on the findings obtained from our study, we think that patients with low testosterone exposure in the prenatal period are more likely to get varicocele during adulthood and it is possibly caused by the effect of prenatal testosterone hormone on the male genital system and the anatomical structure of the spermatic vein in the embryological period.

What makes our study interesting is that there has not been any study investigating this relationship in the literature and it is the first study conducted in this regard. However, it is clear that there is a need for prospective, randomized studies involving more patients to confirm this outcome and clarify pathophysiology more precisely.

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Original Article

Assessment of ventricular repolarization alterations in patients with Inflammatory Bowel Disease

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ABSTRACT

Objective: To evaluate the Tp-e interval and Tp-e/QT ratio as well as Tp-e/QTc ratio in patients with inflammatory bowel disease

Design: Cross sectional study

Setting: Department of Cardiology, Yüksek Ihtisas Education and Research Hospital, Ankara, Turkey

Subjects: One hundred patients with inflammatory bowel disease (51 patients had Crohn’s disease (CD) and 49 patients had ulcerative colitis (UC)) and 100 age-matched controls were enrolled in our study.

Intervention: Non-interventional

Main Outcome Measure: Tp-e interval, Tp-e/QT and Tp-e/QTc ratio were obtained from the electrocardiography.

Results: Tp-e interval (p<0.001), Tp-e/QT ratio (p=0.001) and Tp-e/QTc ratio (p=0.001) were higher in patients with CD than control subjects and it was significant. Also, Tp-e interval (p=0.001), QT interval (p=0.009), Tp-e/QT ratio (p<0.001) and Tp-e/QTc ratio (p<0.001) were significantly higher in patients with UC than control subjects. Tp-e/QTc ratio was no different between the CD and UC groups. However, Tp-e/QTc ratio was positively correlated with sedimentation rate (r= 0.209, p=0.003).

Conclusion: This study demonstrated that QT dispersion parameters were elevated in patients with IBD.

INTRODUCTION

Inflammatory bowel disorders (IBD) are chronic diseases induced by inflammation of the gastrointestinal tract. IBD mainly includes ulcerative colitis (UC) and Crohn’s disease (CD)⁴. Approximately 40% of patients with IBD have extra-intestinal complications⁵.

Individuals diagnosed with inflammatory bowel diseases have shown an increased cardiovascular disease (CVD) risk⁶. The relationship between CVD such as stroke, coronary artery disease and IBD has been reported by previous trials⁷. When compared to normal population, death from CVDs is increased in the patients with IBD⁸. Although ischemic heart disease and stroke are the main reasons in those patients, there is limited data about ventricular events or electrical abnormalities in patients with IBD.

Some of the studies have revealed that QT interval and QT dispersion were increased in patients with IBD, which are favorable markers for ventricular arrhythmias⁹. Recently, the T-peak to T-end (Tp-e) interval on 12 lead electrocardiogram (ECG) has been shown to correlate with ventricular repolarization abnormalities. Both QT and the Tp-e intervals are heart rate dependent and this dependence has also been associated with risk of ventricular arrhythmias⁹. For this reason, it has been claimed that Tp-e/QT ratio might be an important and useful indicator of ventricular repolarization and arrhythmia⁹,10. In this study, we aimed to evaluate the Tp-e interval and Tp-e/QT as well as Tp-e/QTc ratio in patients with IBD free of overt cardiac involvement.

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SUBJECTS AND METHODS

Study design
This was a cross-sectional study that was conducted at a single center in collaboration with gastroenterology and cardiology clinics. One hundred consecutive patients with IBD (51 patients had CD and 49 patients had UC) were enrolled in the study, between January 2014 and June 2015. One hundred healthy individuals were included as control group. All subjects who were investigated in this study were in sinus rhythm. All participants had no cardiac signs or symptoms. Patients with coronary artery disease, hypertension, diabetes mellitus, kidney or hepatic disease, left ventricular dysfunction, mild or severe valvular disorder, malignancy, advanced pulmonary disease, atrial fibrillation, any type of bundle branch block, and cardiac device were excluded. Basal characteristics, laboratory parameters, electrocardiographic and echocardiographic characteristics of the patients and control subjects was compared. Evaluation of the clinical activity of CD was established with Crohn’s disease activity index (CDAI). To evaluate the activity of UC, endoscopic activity index (EAI) was used. All patients underwent two-dimensional transthoracic echocardiography with the Vivid 7 system (GE Healthcare, Wauwatosa, Wisconsin). Ejection fraction was calculated by using modified Simpson method. The Institutional Research Ethics Committee approved the study and informed consent was obtained from each patient.

Electrocardiography
The 12-lead ECG of all participants were documented at amplitude of 20mm/mV and a velocity of 50mm/s (Hewlett Packard, Page-writer, USA) with the patients in supine position. The patients’ ECG examples were scanned. After that, ECGs were transferred to a personal computer to minimize the error measurements, and then used for x400% magnification by software. Two specialists who were blinded to the subjects’ information evaluated the intervals. Patients with U waves were excluded. Mean value of three measurements was obtained for each lead. The QT interval was defined as the time from the origin of the QRS complex to the termination of the T wave. Bazett formula \[ QTc = \frac{QT}{\sqrt{R-R \text{ interval}}} \] was used to assess corrected QT interval (QTc). Tp-e interval was defined as the interval between the peak and the end of T wave. Precordial leads were used to calculate Tp-e intervals\(^{(1)}\). The Tp-e/QT ratio and Tp-e/QTc ratios were calculated after the result of these measurements. Intra-observer and inter-observer coefficients were 2.9% and 2.6%, respectively.

Laboratory assessments
Peripheral venous blood was drawn from antecubital vein into ethylenediaminetetraacetic acid containing tubes for complete blood count after 12 hours of fasting in the morning. Beckman coulter was used to measure complete blood count (Florida, USA). C-reactive protein (CRP) was measured by rate turbidimetry on a Beckman Coulter (California, USA). Sodium and potassium levels were abstracted from the electronic medical records. Plasma levels of cholesterol subtypes, aspartate and alanine aminotransferase, creatinine and glucose were measured using an automated chemistry analyzer (Abbott Aeroset, USA).

Statistical analysis
The variables with a normal distribution were defined as the mean ± standard deviation and numerical variables with a skewed distribution were presented as the median (interquartile range) and categorical variables were presented as percentages. Normality of distribution was evaluated using Kolmogorov-Smirnov test. Continuous variables were compared using the independent samples t test for normally distributed variables, and the Mann-Whitney U test when the distribution was skewed. Chi-square test was used to compare the categorical variables. Pearson’s correlation analysis was done to determine the relation between Tp-e/QTc with other variables. All statistical analyses were performed with SPSS software version 20.0 (SPSS Inc., Chicago, IL). P-value less than 0.05 defined statistically significant result.

RESULTS
This study included 51 CD patients, 49 UC patients and 100 without IBD. Characteristics of participants are shown in Tables 1 and 2. The mean age of the study groups was 42.8 ± 11.8 years and 61% of patients were male. There was no difference between groups in terms of gender, age, smoking, alcohol usage and basal laboratory findings, except erythrocyte sedimentation rate (ESR) and CRP levels (p >0.05). Mean disease duration of patients with CD and UC were 6 years (1-19) and 5 years (1-27), respectively.

Heart rate, QT interval and QTc interval were similar between patients with CD and controls. Tp-e interval (72.3 ± 14.1 vs. 63.7 ± 11.9; p <0.001), Tp-e/QT ratio (0.20 ± 0.04 vs. 0.18 ± 0.03; p = 0.001) and Tp-e/QTc ratio (0.18 ± 0.03 vs. 0.16 ± 0.03; p = 0.001) were significantly different between the patients with CD and healthy controls as shown in Table 3 (the measurements were higher in the patients with CD). Additionally, heart rate and QTc interval were similar between patients with UC and control subjects. Tp-e interval (72.3 ± 10.6 vs. 63.7 ± 11.9 ms; p <0.001), QT interval (375.0 ± 33.0 vs. 360.8 ± 29.5 ms; p = 0.009), Tp-e/QT ratio (0.20 ± 0.04 vs. 0.18 ± 0.03; p <0.001) and Tp-e/QTc ratio (0.19 ± 0.03 vs. 0.16 ± 0.03; p <0.001) were significantly higher in patients with UC than in...
Seventy-three patients were treated with infliximab and azathioprine. Tp-e/QTc ratio were higher in patients treated with infliximab and azathioprine than others (0.19 ± 0.04 vs. 0.16 ± 0.03; p < 0.001). There was no correlation between Tp-e/QTc ratio and other variables as shown in Table 5. Tp-e/QTc ratio and disease duration in patients with CD and in patients with UC (r=0.008, p=0.953; r=−0.148, p=0.309, respectively) and also there were no correlation between Tp-e/QTc ratio and CDAI (r=−0.041, p=0.775) and EAI (r=−0.219, p=0.130). Also, there was no correlation between Tp-e/QTc ratio and CRP (r=0.046, p=0.523). However, there was a correlation between Tp-e/QT ratio and disease duration (r=0.267, p<0.001).

### Table 2: Basal characteristics and laboratory parameters of the patients with Ulcerative colitis and control subjects

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Ulcerative colitis (n = 49)</th>
<th>Controls (n = 100)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>45.3 ± 14.8</td>
<td>43.1 ± 8.8</td>
<td>0.247</td>
</tr>
<tr>
<td>Male (n (%))</td>
<td>33 (67.3)</td>
<td>56 (56.0)</td>
<td>0.377</td>
</tr>
<tr>
<td>Smoking (n (%))</td>
<td>7 (14.2)</td>
<td>15 (15.0)</td>
<td>0.884</td>
</tr>
<tr>
<td>Alcohol (n (%))</td>
<td>3 (6.1)</td>
<td>4 (4.0)</td>
<td>0.760</td>
</tr>
<tr>
<td>Hemoglobin (g/dl)</td>
<td>13.6 ± 2.1</td>
<td>14.0 ± 1.5</td>
<td>0.392</td>
</tr>
<tr>
<td>Creatinine (mg/dl)</td>
<td>0.9 ± 0.19</td>
<td>0.88 ± 0.12</td>
<td>0.445</td>
</tr>
<tr>
<td>Glucose (mg/dl)</td>
<td>103.9 ± 47.8</td>
<td>95.3 ± 15.8</td>
<td>0.154</td>
</tr>
<tr>
<td>Total cholesterol (mg/dl)</td>
<td>204.7 ± 51.4</td>
<td>191.2 ± 40.2</td>
<td>0.197</td>
</tr>
<tr>
<td>LDL cholesterol (mg/dl)</td>
<td>122.1 ± 44.0</td>
<td>109.7 ± 35.4</td>
<td>0.177</td>
</tr>
<tr>
<td>HDL cholesterol (mg/dl)</td>
<td>53.2 ± 26.2</td>
<td>52.0 ± 12.6</td>
<td>0.765</td>
</tr>
<tr>
<td>Triglyceride (mg/dl)</td>
<td>152.7 ± 72.3</td>
<td>146.2 ± 83.0</td>
<td>0.740</td>
</tr>
<tr>
<td>Sodium (mmol/l)</td>
<td>137.7 ± 1.9</td>
<td>138.1 ± 2.2</td>
<td>0.393</td>
</tr>
<tr>
<td>Potassium (mmol/l)</td>
<td>4.29 ± 0.40</td>
<td>4.29 ± 0.36</td>
<td>0.962</td>
</tr>
<tr>
<td>ESR, (mm/h)*</td>
<td>12 (6-29)</td>
<td>6 (4-8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Tp-e interval (ms)</td>
<td>3.7 (1.1-5.8)</td>
<td>1.8 (1.2-3.3)</td>
<td>0.016</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>72.3 ± 10.6</td>
<td>74.7 ± 12.8</td>
<td>0.988</td>
</tr>
<tr>
<td>Tp-e/QT ratio</td>
<td>0.20 ± 0.04</td>
<td>0.18 ± 0.03</td>
<td>0.001</td>
</tr>
<tr>
<td>Tp-e/QTc ratio</td>
<td>0.19 ± 0.03</td>
<td>0.16 ± 0.03</td>
<td>0.001</td>
</tr>
<tr>
<td>EF (%)</td>
<td>60.6 ± 5.3</td>
<td>61.7 ± 2.5</td>
<td>0.200</td>
</tr>
</tbody>
</table>

Data are given as mean ± SD or n (%); CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; HDL: high-density lipoprotein; LDL: low-density lipoprotein; *Median (interquartile range).
was positive correlation between Tp-e/QTc ratio and ESR \( r=0.209, p=0.003 \).

**DISCUSSION**

This study demonstrated that ventricular repolarization parameters such as Tp-e/QT and Tp-e/QTc ratios and Tp-e interval were increased in patients with IBD. This is the first study that investigated the Tp-e/QT and Tp-e/QTc ratios and Tp-e interval in patients with IBD.

Various cardiac complications could occur in patients with IBD. Pericarditis, myocarditis and thromboembolic events are rare complications in IBD\(^{[2,3]}\). It has been shown that premature coronary atherosclerosis was related with IBD\(^{[4]}\). Kristensen \textit{et al} observed that the patients with IBD had higher rate of hospitalization due to heart failure. They suggested that this relationship might be due to inappropriate immune-mediated intestinal and systemic inflammatory activity\(^{[14,15]}\). Furthermore, some trials suggested that immunosuppressive agents such as infliximab negatively affect the cardiac systolic function\(^{[16,17]}\). Cincin \textit{et al} revealed that systolic functions of the heart were impaired in UC patients\(^{[18]}\).

Ventricular arrhythmias are seen more frequently in patients with reduced left ventricular function. Prolonged ventricular repolarization parameters might cause mortality and sudden cardiac death by inducing malignant arrhythmias\(^{[19]}\). QT dispersion and prolonged QT interval are important predictors of delayed heart repolarization on electrocardiography. In literature, there is inadequate data about electrocardiographic abnormalities and ventricular tachycardia in IBD. Curione \textit{et al} demonstrated that QTc interval and QT dispersion were increased in patients with IBD\(^{[20]}\). They suggested follow up of QT changes in patients using cardiotoxic medications like infliximab, especially in presence of electrolyte imbalances, and they stated that these should not go unreported\(^{[21]}\). In contrast to this study, Dogan \textit{et al} observed that there is no heterogeneity of ventricular repolarization and cardiac involvement in patients with IBD\(^{[22]}\). Recent study has shown that both patients with UC and CD have prolonged QT dispersion, but there was no correlation between QT dispersion and 5-aminoacilic acid, steroids and immunosuppressive agents usage\(^{[23]}\). Recently, Pattanshetty \textit{et al} found that patients with IBD having a prolonged QTc interval had a higher body mass index than those with a normal QTc interval\(^{[24]}\).

Nowadays, the Tp-e interval and Tp-e/QT ratio have been studied as novel indicators of impaired ventricular repolarization dispersion\(^{[9,10,21]}\). Increased Tp-e interval was related to higher mortality rate in the patients with long QT syndrome and Brugada syndrome\(^{[10]}\). The heart rate does not affect the Tp-e/QT ratio that was accepted as more precise marker of the dispersion of ventricular repolarization, than QT dispersion, QTc dispersion and Tp-e intervals\(^{[8,22]}\). Tp-e/QT ratio is a potentially significant index of arhythmogenesis independent from the length of QT interval\(^{[10,23]}\). In our study, we showed that these markers were higher in patients with IBD than control subjects, but the mechanism which causes this condition is not clear. The inflammatory nature of the disease can be a factor that may lead to these results\(^{[24]}\) since inflammatory processes can lead to fibrosis formation and this trigger arrhythmias in left ventricle\(^{[25,26]}\). ESR and CRP levels were higher in patients with IBD than control subjects, and there was a correlation between Tp-e/QTc ratio with ESR, in our study. However, there was no correlation between Tp-e/QTc ratio and CRP. On the other hand, it has been suggested that immunosuppressive drugs such as infliximab, azathioprine and steroids may impair the conduction system of heart\(^{[27-29]}\). In this study, approximately 75\% of study patients were treated with immunosuppressive drugs and corticosteroids. Our results demonstrated that Tp-e/QTc ratio was increased in patients who were treated with infliximab and azathioprine.

**Study Limitations**

Cross-sectional design and low number of patients are the main limitations. The study is a single-center study and the patients’ follow-up data is absent. Ventricular arrhythmias of the patients were not evaluated according to the repolarization parameters. Large sample sized randomized studies are needed to establish exact role of Tp-e interval and Tp-e/QT ratio in patients with IBD who are suffering from the arrhythmias.

**CONCLUSION**

This study demonstrated that Tp-e interval, Tp-e/QT and Tp-e/QTc ratios were prolonged in patients with IBD. Our study indicates that IBD may have a negative

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**Table 5: Correlation analysis between Tp-e/QTc ratio and other variables**

<table>
<thead>
<tr>
<th>Parameters</th>
<th>r</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease duration (CD)</td>
<td>0.008</td>
<td>0.953</td>
</tr>
<tr>
<td>Disease duration (UC)</td>
<td>0.148</td>
<td>0.309</td>
</tr>
<tr>
<td>CDAI</td>
<td>-0.041</td>
<td>0.775</td>
</tr>
<tr>
<td>EAI</td>
<td>-0.219</td>
<td>0.130</td>
</tr>
<tr>
<td>C-reactive protein</td>
<td>0.046</td>
<td>0.523</td>
</tr>
<tr>
<td>Sedimentation rate</td>
<td>0.209</td>
<td>0.003</td>
</tr>
</tbody>
</table>

CD: Crohn’s disease; UC: ulcerative colitis; CDAI: Crohn’s disease activity index; EAI: endoscopic activity index

*Median (interquartile range).
effect on cardiac conduction system, which potentially may induce formation of ventricular arrhythmias. Tp-e interval and Tp-e/QT ratio are simple, easily accessible, inexpensive and non-invasive methods that can be useful markers of predicting ventricular arrhythmias in patients with IBD.

ACKNOWLEDGMENTS
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REFERENCES


Original Article

A pilot study: Does stone density affect the success of retrograde intrarenal surgery?

Yusuf Ozlem Ilbey, Mehmet Zeynel Keskin
Tepecik Training and Research Hospital, Urology Clinic, Yenişehir, Konak, Izmir, Turkey

Purpose: To examine the predictive effect of mean stone density (MSD) value for retrograde intrarenal surgery (RIRS) success

Design: Retrospective study

Setting: Urology Department, Tepecik Training and Research Hospital, Izmir, Turkey

Subjects: Sixty-three patients with solitary renal pelvic stone underwent RIRS performed by a single surgeon

Interventions: Medical records of all the patients were reviewed and data were collected retrospectively

Main outcome measures: MSD was calculated with preop CT. (MSD <1000 HU for group 1, ≥1000 HU for group 2). In postoperative CT, clinically insignificant residual size was detected as 4 mm; smaller residuals were specified as the successful group and the others were specified as the unsuccessful group. The 2x2 relation between MSD and residual groups was analyzed by the chi-square test. p<0.05 was regarded as significant.

Results: There was a statistically significant relation between the MSD groups and the residual groups (p= 0.004, Chi-square) and the treatment success in the group with high stone density (group 2) decreased by 4.74 times compared to the other group.

Conclusion: Our study is the first literature study directly investigating the relation between the RIRS success and MSD. The relation between the success rate and MSD in the patients that underwent RIRS was examined and it was found that the success rate decreased 4.74 times as the MSD value increased. There are not many studies in the literature with RIRS success and MSD predictivity and there is a need for prospective randomized studies with larger patient numbers.

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INTRODUCTION

The incidence and prevalence of renal stones increase independently of age, sex, and race all over the world[1,2]. The risk of developing lifelong renal stone disease in Western countries is 18.8% and 9.4% in males and females, respectively[3]. The renal stone density in Europe has increased from 5% to 9% in 2000s[4]. This increase in the frequency of renal stones is associated with changes in lifestyle and diet[5].

Treatment of renal stone with gradually increasing frequency has become more important, and there are numerous publications on treatment methods in the literature. Percutaneous renal stone therapy (PCNL), retrograde intrarenal surgery (RIRS), extra-corporal shock wave therapy (ESWL) and laparoscopic stone surgery are the most preferred surgical techniques today[2].

According to the guide published by the European Association of Urology, while PCNL is the first line treatment method for the renal stones ≥2 cm, RIRS and ESWL are the first line treatment for renal stones <2 cm[5]. In practice, a few cycles of RIRS treatment are safely performed for renal stones ≥2 cm and the stone-free rate (SFR) is reported to be 77 - 96.7%[6].

There are many publications in the literature about the parameters that affect the treatment success in order to increase SFR levels, but these publications are predominantly related to ESWL and PCNL. Non-contrast computed tomography (CT) is the most preferred test for the diagnosis of renal stones[7]. In the publications regarding PCNL and ESWL in the literature, the relation between SFR and parameters such as renal stone burden, mean stone density (MSD), stone localization, renal parenchymal thickness
and stone-skin distance obtained by CT has been investigated.[8-12]

In this study, we have investigated whether there is a relation between MSD and SFR in the RIRS technique.

MATERIALS AND METHODS

RIRS cases performed by a single surgeon in the urology clinic of our hospital were retrospectively reviewed between June 2013 and June 2017. The data of 197 renal stone patients who underwent RIRS with Holmium: YAG laser were retrospectively reviewed. After induction of general anesthesia, semirigid ureteroscopy (8.5/11.5 F, Wolf, Knittlingen, Germany) was performed for ureteral dilation and placing a hydrophilic guidewire to the renal pelvis. RIRS was performed by using a 7.5F flexible ureteroscope (Karl Storz Flex-X2, Tutlingen, Germany) through the ureteral access sheath (UAS). 9.5/11.5 Fr UAS placement was attempted through the ureter in all patients. In failure of the UAS, RIRS was performed without using the UAS. Holmium laser was used with a 273 μm fiber for disintegration of the stone. Holmium laser energy was set to 0.6 - 1.5 J and frequency was set to 10 - 15 Hz for all patients. The patients underwent only one RIRS procedure; basket catheter was used for stone fragments and double-J catheter was used to drop the pieces.

Patients who had a history of operation due to renal stones, stones ≥2 cm, multiple stones, stones not localized in pelvis, unaccessible preoperative CT data, renal abnormality, multiple RIRS history, trouble due to the device during surgery and whose RIRS was performed by another surgeon were excluded from the study. In conclusion, 63 patients who had a solitary stone ≤2 cm in renal pelvis and whose RIRS procedure was performed by the same operator were included in the study.

Preoperative stone densities of the patients were measured with non-contrast CTs taken before the RIRS. The measurement was performed in five different localizations. Mean values of the five densities obtained were calculated. Patients were divided into 2 groups according to the stone density. Patients with a mean stone density <1000 HU were specified as group 1 and the ones with a mean stone density of ≥1000 HU were identified as group 2. Surgery success was checked in the CT performed 3 weeks after RIRS. Presence of residual stone <4 mm was considered as surgery success; patients with residual stones <4 mm were classified as successful (clinically insignificant residual) group and the patients with residual stones ≥4 mm were identified as unsuccessful (clinically significant residual) group. The relation and the risk ratio between the MSD groups and the success groups were analyzed by chi-square test. IBM Statistical Package for Social Sciences (SPSS) Statistics Software program 22 was used for statistical analysis of the study. p <0.05 was regarded as statistically significant.

RESULTS

The age range of the 63 patients included in the study was 20 - 71 years and the average age was 45.46 ± 12.97 years. The number of male and female patients was found to be 36 and 27, respectively. In all patients, mean maximal stone size was 11.49 ± 4.17 mm (3.22 - 19.62 mm), mean stone volume was 814.04 ± 663.87 mm³ (103.15 - 3214.94 mm³). In group 1 (MSD <1000 HU) and group 2 (MSD ≥1000 HU), the number of patients were 23 and 40, and the residual stone was 0 - 9.46 mm (mean: 2.51 ± 3.2 mm) in group 1 and 0 - 14.7 mm (mean: 6.57 ± 4.61 mm) in group 2 (Table 1).

When 2x2 comparison of MSD groups with

<table>
<thead>
<tr>
<th>Properties</th>
<th>Group 1 (n = 23)</th>
<th>Group 2 (n = 40)</th>
<th>Total (n = 63)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Residual (mm)</td>
<td>0</td>
<td>9.56</td>
<td>2.51</td>
</tr>
<tr>
<td>SD (HU)</td>
<td>215</td>
<td>1592</td>
<td>860.2</td>
</tr>
</tbody>
</table>

Successful: Clinically Insignificant Residual (< 4 mm); Unsuccessful: Clinically Significant Residual (≥ 4 mm)
clinically significant/insignificant residual groups respectively was performed by the Chi-square test, it was found that there was a statistically significant relation between the MSD groups and the residual groups (p = 0.004, Chi-square) and the treatment success in the group with high stone density (group 2) decreased by 4.74 times compared to the other group (Table 3).

Table 3: Mean density and comparison of residual groups

<table>
<thead>
<tr>
<th>Residual groups</th>
<th>Group 1</th>
<th>Group 2</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinically insignificant residual (successful, ≤4mm)</td>
<td>16</td>
<td>13</td>
<td>29</td>
</tr>
<tr>
<td>Clinically significant residual (unsuccessful, &gt;4mm)</td>
<td>7</td>
<td>27</td>
<td>34</td>
</tr>
<tr>
<td>Total</td>
<td>23</td>
<td>40</td>
<td>63</td>
</tr>
</tbody>
</table>

Group 1: Mean SD < 1000 HU; Group 2: Mean SD ≥ 1000 HU
Chi-square: p = 0.004; Odds ratio: 4.74

DISCUSSION

Renal stones are one of the most common problems in urology. With technological improvements in flexible ureterorenoscopy devices in the last 10 years, the significance of RIRS technique in renal stone treatment has increased even more[13]. When the treatment modalities for renal stones were examined, the most successful technique was PCNL, whereas the RIRS outweighed ESWL based on success rate and the RIRS modality was more reliable than PCNL in terms of complication[14,15].

The RIRS technique is the first-line treatment modality especially for renal stones <20 mm and the success rate decreases for the larger stones[5]. In the study performed by Aboumarzouk et al, it has been reported that RIRS modality by experienced persons may be offered to the patients with renal stones ≥20 mm as the first option[6].

In addition to the progression of the RIRS technique in the treatment of renal stones, one of the most common problems of urology practice, the success rate of this treatment technique is very important. In our study, clinically insignificant stone size was accepted as <4 mm.

Considering the number of studies in the literature regarding the factors affecting the success in RIRS treatment, it is not as many as ESWL and PCNL. In literature studies regarding ESWL and PCNL success, MSD is emphasized[9,11].

There is a lack of studies directly examining the relation between RIRS success and MSD in the literature. There are more studies investigating the relation between ESWL/PCNL success and MSD than RIRS; various studies have reported that ESWL success decreases as MSD increases. However, there are also publications reporting no relationships. In PCNL patients, the results of studies published state that MSD is not predictive of success of treatment[8-12,16-22].

The Resorlu-Unsal stone (RUS) score developed by Resorlu et al is the only nomogram used for predicting RIRS success[13]. Subsequently, Jung et al developed the modified Seoul National University Renal Stone Complexity score (S-ReSC) by modifying the S-ReSC score used to predict the PCNL success and found a correlation with the RIRS success and reported that the modified S-ReSC score was superior to the RUS score. In the same study, Jung et al examined the predictivity of the parameters such as age, BMI, MSD in the RIRS success and found that MSD had no predictivity for RIRS success[23]. In the study by Zanetti et al, the data of 63 patients who underwent RIRS due to renal stones were examined and it was determined that BMI, stone laterality, number, localization and MSD were not predictive; but stone length, surface area and volume were predictive but not predictive of success rate[24]. D’Arrigo et al examined the stone-free rate after RIRS in the patients with multiple renal stones and found that this value was 77%, and in this study, infundibulum length, width, angle, stone burden and MSD parameters were examined in order to predict the SFR of the patients and none of them were found to have a predictive value[25]. Again in another study performed by D’Arrigo et al, stone burden and MSD were investigated in terms of predictivity in the patients who underwent semirigid ureterorenoscopy for ureteral stones and RIRS for renal stones and it was determined that the MSD parameter was predictive in determining success in the group that underwent RIRS[26].

There are limited studies regarding RIRS success and MSD predictivity in the literature. These studies, which examine the predictivity between MSD and RIRS success in the literature, include stone density as well as other parameters such as stone burden and stone localization. In addition, the RIRS procedure was performed by different surgeons, not by a single surgeon. The fact that all stones are <2 cm and present in the pelvic localization and all operations are performed by the same surgeon makes our study different from the other studies. Therefore, when considered from this point of view, our study is the first literature study objectively investigating the relation between the RIRS success and direct MSD. The relation between the success rate and MSD in the patients that underwent RIRS was examined in our study and it was found that the success rate decreased 4.74 times as the MSD value increased.

CONCLUSION

MSD value has value for predicting the success of RIRS and the success rate decreases as the MSD value increases. Our study is the first study to directly assess
the success of RIRS with MSD as there are not many studies that directly investigate this relationship in the literature. The MSD value has been taken into account with other parameters in the present studies. However, there is a need for prospective and randomized studies with more patients in order to obtain more accurate results.

REFERENCES

Case Report

Asymptomatic late lead perforation– extremely rare yet possible

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2Arrhythmia Department, Institute of Cardiology, Warsaw, Poland

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ABSTRACT

We present a case of a 39-year-old male patient with a single-chamber Biotronic implantable cardioverter-defibrillator (Biotronic, Berlin, Germany) for primary prevention of sudden cardiac death with an asymptomatic perforation of the right ventricular wall caused by defibrillator chamber lead. Disturbances in electrical parameters at routine device interrogation were the first clue of cardiac perforation. The cardiac perforation was confirmed by computed tomography scan because neither chest radiography nor transthoracic echocardiography was diagnostic of the perforation. The patient underwent a non-surgical reposition of right ventricular lead without further complications.

KEYWORDS: cardiac computed tomography, cardiac perforation, implantable cardioverter-defibrillator

INTRODUCTION

The epidemic of heart failure is likely to grow further in the upcoming decades[1]. Recommendations for cardiac implantable electronic devices (CIEDs) in patients with heart failure are becoming broader and a significant increase in the number of implantation procedure should be expected. One of the relatively rare, but sometimes serious complication is late cardiac perforation by a right ventricular pacemaker lead. When asymptomatic, it can be a challenge to diagnose.

CASE REPORT

A 39-year old patient with ischemic cardiomyopathy, with a left ventricular ejection fraction of 25%, and an implantable cardioverter-defibrillator (ICD; Biotronik Itrevia 5 VR-T, Biotronic, Berlin, Germany) implanted 6 weeks ago for primary prevention of sudden cardiac death was admitted to the hospital in order to start the participation in TELEREH-HF study (Applying telemedicine technologies in a novel model of organizing and implementing comprehensive cardiac rehabilitation in heart failure patients). Prior to the inclusion in the study, the patient underwent routine examinations for heart failure patients, among others, also ICD function assessment.

This routine device interrogation revealed significant changes in ICD pacing and sensing parameters (complete loss of capture at maximum output, low R-wave amplitude and notably abnormal lead impedance).

His medical history consisted of ST-elevation myocardial infarction six years ago, treated by angioplasty of the left anterior descending coronary artery with implanted drug-releasing stents and hypercholesterolemia.

On admission, the patient was entirely asymptomatic, denied any chest pain, dyspnoea and palpitations. Due to suspicion of cardiac perforation, chest X-ray (CXR) and transthoracic echocardiography (TTE) were performed at first. There was no evidence of cardiac perforation in the form of pleural or pericardial effusion. ICD lead migration beyond the heart silhouette or beyond the right ventricular epicardium were not detected in...
December 2019

Asymptomatic late lead perforation– extremely rare yet possible

these examinations. A contrast-enhanced computed tomography (CT), which was the next reasonable diagnostic step, revealed the right ventricular (RV) lead outside the cardiac silhouette (Fig 1). No pericardial or pleural effusions were visualized. The patient underwent non-surgical reposition of RV lead. The lead was removed out of the pericardial space and re-implanted into a septal position without further sequelae. No significant pericardial effusion was detected by TTE at the end of the procedure, and several hours and days later by transthoracic echo as well.

Device checkup at the end of the procedure and a month later revealed no abnormalities in ICD parameters.

DISCUSSION

Cardiac perforation by an implanted lead is a rare, but potentially life-threatening complication of CIEDs. The lead perforation occurs with an incidence of less than 1%[2,3]. In one of the studies the prevalence of cardiac perforation caused by defibrillator leads was 0.14%[4]. Lead perforation was more common with RV leads, especially when placed in the apex[5]. Late or delayed myocardial perforation is defined as the perforation of the lead through the myocardium more than 24 hours after the implantation procedure[6], or more than one month in one of the publications[7]. The median time from implantation to manifestation of the first symptom of perforation was 1 - 3 months in some selected analysis[2,6] but the longest period of time was 48 months[5].

It has been reported that older age (> 65 years), female sex, implantation of dual chamber ICD and apex location of RV lead have been associated with an increased perforation risk[4,5,8]. The most common symptoms attributable to cardiac perforation were chest pain, dyspnoea, palpitations, presyncope, diaphragmatic pacing or symptoms and clinical features consistent with pericardial tamponade. The asymptomatic perforation, as occurred in our patient, is very rare. Previous studies have reported overall asymptomatic lead perforation rates of 0 - 6% after pacemakers or ICD placements[2,5,8]. In such clinically occult cases, disturbances in electrical parameters on routine device interrogation may be the first clue for the diagnosis of cardiac perforation[2]. Electrical parameters (e.g. lead impedance, R wave amplitude, lead threshold, sensing) were abnormal in more than 85 - 90% of cases[2,6]. In our case, the suspicion of perforation was raised upon finding abnormal lead impedance and under-sensing of a ventricular lead.

To confirm the diagnosis of the lead perforation assessment by CXR, TTE and CT is crucial. Finding pleural or pericardial effusion or migration of the ICD lead beyond the cardiac silhouette in CXR or TTE confirms the suspicion of cardiac perforation. However, the sensitivity of 40 - 60% for CXR or TTE is not satisfactory[2]. Only CT has an excellent diagnostic capability in the setting of delayed cardiac perforation with sensitivity of 100%, specificity of 85.7% and negative predictive value of 100%[2,7].

In our case we have not found any evidence of cardiac perforation in CXR and TTE. Only chest CT demonstrated presence of ICD lead in pericardial space. The patient underwent non-surgical simple repositioning of the lead without complications.

CONCLUSION

Our report clearly indicates:
• a possibility of cardiac perforation without any clinical symptoms and without any abnormalities in CXR and TTE;
• the superiority of CT over other imaging modalities in diagnosing cardiac perforation;
• the necessity of excluding lead perforation whenever significant change in electrical ICD parameters is revealed;
• the importance of regular interrogation of the CIEDs.

ACKNOWLEDGMENT

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Fig 1: Cardiac CT shows the right ventricular apical perforation, the lead (arrow) is seen exiting the right ventricle.
REFERENCES


Case Report

Extradigital glomus tumor: A rare cause of long standing knee pain

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ABSTRACT

Background: Glomus tumors are painful and disabling soft tissue masses arising from cutaneous arteriovenous anastomoses. They often involve the nailbed of the fingers and the toes. However, the histopathologic features are the same. Extradigital glomus tumors (EGTs) are rare lesions that involve body parts other than the hands and the feet. For this reason, initial diagnosis of extradigital glomus tumor is often late and remains a challenge for the treating physicians because of this rare presentation and unusual localization.

Case report: In this report, we aimed to present a 36-year-old male with an extradigital glomus tumor around his right knee resulting in long standing pain, to raise the awareness of this uncommon entity and review the literature.

Conclusion: The diagnosis of EGTs is usually late and complicated for the treating physician because of rare presentation and unusual localization. Delayed diagnosis often results in various wrong and unnecessary treatment modalities with no chance of cure. While examining a painful, small and even benign-appearing subcutaneous lesion of the extremities, EGTs should be kept in mind to avoid delayed diagnosis and treatment.

KEYWORDS: cutaneous arteriovenous anastomose, extradigital glomus tumor, Glomus tumor, knee pain

INTRODUCTION

Glomus tumors (GTs), also called Popoff or Barre-Masson syndrome, arise from cutaneous arteriovenous anastomoses[1]. These anastomoses regulate the temperature and the tone of the vessels. They also have a role in sensory function. GTs are painful and often involve the nailbed of fingers and toes. Involvement of the extremity parts other than hands and feet are quite rare. Extradigital glomus tumors (EGTs) have the same histopathologic features as GTs, but different localization. They are rare and disabling soft tissue masses as well. EGTs are initially undiagnosed or misdiagnosed because of their rarity and unusual localization. For this reason, few cases of EGTs have been reported in the literature.

CASE REPORT

A 36-year-old man presented with long standing chronic right knee pain. He was generally healthy and had no remarkable family history. He had severe knee pain for more than a year and had taken many different treatment modalities with various diagnosis, including non-steroidal anti-inflammatory drugs, physical therapy sessions, algological techniques, and local injections with no relief. He described his pain as severe and disabling, localized on the anterolateral aspect of his right knee. Palpation was extremely tender and painful. Small, round-shaped, well-defined mass, sized approximately 0.5 x 0.5 cm was palpated subcutaneously. Physical examination of the right knee was normal otherwise.

Laboratory tests were all normal including complete blood count, C-reactive protein, erythrocyte sedimentation rate and routine biochemistry tests. Ultrasonographic examination reported a subcutaneously localized, round contoured, homogenic, hypoechoic, solid, 0.4 x 0.5 cm sized nodular mass (Figure 1). There were also vascular codings inside the lesion with the possible prediagnosis of hemangiomia or fat necrosis. Surrounding tissues were unremarkable sonographically.

The patient was scheduled for MRI with 15 ml
of i.v. gadobutrol. MRI of the extremity revealed a 0.5 x 0.5 x 0.6 cm, well-countered nodular lesion in the subcutaneous fat tissue close to the skin (Figure 2). There was no surrounding edema, but diffuse contrasting with gadobutrol (Figure 3). Although the signal intensity of the lesion was considered to be benign, there was some hesitation because of isointense contrasting on T1A and T2A.

In the operating room, complete excision of the lesion was performed under local anaesthesia. Specimen was sent for pathologic evaluation. It was a small, yellowish coloured, soft nodular lesion on macroscopic examination. Histologic sections showed dilated vascular spaces with normal endothelial cells surrounded with proliferated, small, round uniform cells with indistinct cytoplasms and round nuclei (Figure 4). There were no atypia and mitosis. Surgical margins were clear. Histologic apperance was consistent with benign glomus tumor. After immuno-histochemistry tests, the tumor was finally diagnosed as benign extradigital glomus tumor.

On the follow-up exam after one year, there was no sign of local recurrence. He was satisfied with the result and reported that he was pain free.

**DISCUSSION**

GTs were first described in detail by Masson[1]. The glomus body is a neuromyoarterial canal system of arteriovenous dermal shunts which regulates skin temperature. Local proliferation and hypertrophy of this neuroangiomatous formation results in rare, benign tumors which are often present with a triad of symptoms; attacks of extreme pain, local tenderness to palpation and hypersensitivity to cold[2]. Although the typical triad is as described, it does not occur in all patients. In our case, the patient was admitted to hospital with chronic anterior knee pain which is exhibited by pinpoint local tenderness. Other characteristic symptoms of GTs were not detected.

Approximately 70% of all cases arise in the fingertips, particularly in the subungual area. Glomus bodies are densely distributed in this area. Subungual GTs are frequently observed in middle-aged women (20 - 40 years)[3]. However, EGTs have a male sex...
predominance. In our case, the EGT developed in a 36-year-old male around the anterolateral aspect of his right knee.

There are few examples of EGTs that have been reported around the knee; lateral subcutaneous area, popliteal fossa, suprapatellar fat pad, subsynovial localization, in the patellar ligament or at the fibular head.

In contrast to digital GTs, the diagnosis of EGTs remains a challenge. Most of them are diagnosed several years after the symptoms have developed. Retrospectively, the average duration of symptoms has been found to be greater than 7 years by Schiefer et al.

In our case, the lesion was a round-shaped, well-defined small mass which was located subcutaneously around the anterolateral of the knee joint. It took more than a year from the first visit to several physicians until the correct diagnosis. The presence of the lesion around the anterolateral of the knee joint has been the cause of misdiagnosis of the condition as patellar tendinitis, meniscal pathology or neuroma and led to different treatment methods and waste of time.

In addition to the clinical examination, MRI has proved to be the most valuable, sensitive method of diagnosing EGTs. Small, well defined mass is shown isointense to hypointense on T1 and high signal intensity on T2-weighted MRI sections and strong enhancement after gadolinium injection.

MRI can be useful in efficiently identifying preoperative tumors. In a series by Schiefer et al, twelve solitary extradigital lesions were identified by MRI. As an alternative, non-invasive, easy imaging method, sonography can be used preoperatively to determine the localization and this procedure does not require administration of intravenous contrast medication. Although the sonographic findings may not be specific, in the case of a hypervascularized, well shaped, hypoechoic subcutaneous superficial mass with specific clinical features, it should be considered as a GT.

The definitive management of EGTs is curative surgical excision to obtain complete disappearance of the symptoms. Histopathological confirmation is required for final diagnosis. Incomplete removal may result in tumor recurrence within several weeks and symptoms, appearing even two to three years postoperatively. The recurrence rate after surgery was reported to range from 2% to 10.5% in EGTs.

There are also reports of alternative treatment such as sclerotherapy with sodium tetradeyl sulfate, polidocanol and hypertonic saline and ablative therapy with argon and carbon dioxide and ethanol.

CONCLUSION

The diagnosis of EGTs is usually late and complicated for the treating physician because of rare presentation and unusual localization. Delayed diagnosis often results in various wrong and unnecessary treatment modalities with no chance of cure. While examining a painful, small and even benign-appearing subcutaneous lesion of the extremities, EGTs should be kept in mind to avoid delayed diagnosis and treatment.

REFERENCES

Case Report

Low grade appendiceal mucinous neoplasm

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Kuwait Medical Journal 2019; 51 (4): 409 - 412

ABSTRACT

Tumors of the appendix are uncommon entities that comprise less than 2% of all appendectomies with an approximately 0.3% reported prevalence of mucinous neoplasm in the appendectomy specimens. We report a case of low grade appendiceal mucinous neoplasm in a 51-year-old female that was presented as lower abdominal pain. The case was managed by laparoscopic resection.

KEY WORDS: laparoscopy, low grade appendiceal mucinous neoplasm, mucocele

INTRODUCTION

Tumors of the appendix are uncommon entities that comprise less than 2% of all appendectomies with approximately 0.3% reported prevalence of mucinous neoplasm in the appendectomy specimens[1]. An appendiceal mucocele refers to a mucus-filled appendix and can be classified into the following histologic subtypes: mucosal hyperplasia, simple or retention cyst, mucinous cystadenoma, and mucinous cystadenocarcinoma[2]. The classification of appendiceal mucinous tumors is controversial and terminology can be consistent, in particular, when there is lack of overt malignant features. However, the accepted terminology for low grade neoplasm without overt features of adenocarcinoma is low grade appendiceal mucinous neoplasm (LAMN)[3]. LAMN appears to have a slight female predominance and is usually diagnosed in patients in their fifth and sixth decades of life; however, it may occur at any age[3]. Approximately 25% to 50% of LAMN are incidental findings with the initial discovery during radiologic or endoscopic examination, or during surgery[4]. We present a case of LAMN that was discovered incidentally during gynecological examination.

CASE REPORT

A 51-year-old female with no significant past medical history, presented to her primary care physician with lower abdominal pain and mucous vaginal discharge. The patient was referred to gynecological hospital where a pelvic ultrasound was performed and revealed a bilateral ovarian cyst with the presence of mass mostly originated from the right ovary. A computed tomography (CT) scan of the abdomen and pelvis (Fig 1 A, B) was carried out and showed a dilated appendix 10 x 5 cm. All routine investigations, including tumor markers, were within normal limits. The patient was referred to our hospital for further opinion by the general surgeon. The case was discussed with the patient regarding the need of excision of the mass to determine the nature and the extent of the disease. She underwent diagnostic laparoscopy by our team together with the gynecology team. A laparoscopic appendectomy with safety margin from the cecum by Endo GIA and extracted by Endo bag with bilateral ovarian cyst excision was done (Fig 2 A-C). The patient tolerated the procedure well with no postoperative complications. The histopathological examination showed a LAMN with haemorrhagic corpus luteum. After 6-month follow up with the patient, repeated CT scan of the abdomen and pelvis with tumor markers were done, which showed no evidence of recurrence.

DISCUSSION

The classification of appendiceal mucinous tumors is controversial. One of the pathologic diagnostic difficulties is appropriately distinguishing LAMN from
mucinous adenocarcinoma of the appendix. According to Misdraji et al, appendiceal mucinous tumors with destructive invasions of the appendiceal wall, complex epithelial proliferation, or high-grade course, should be classified as mucinous adenocarcinomas; others should be classified as LAMN[5]. Furthermore, some authors divide low grade mucinous neoplasm into mucinous neoplasm with low risk of recurrence and mucinous neoplasm with high risk of recurrence, with each subtype having a different clinical behavior. The one with low risk is an appendiceal tumor with histologic features of mucinous adenoma but with extra-appendiceal acellular mucin. On the other hand, the one with high risk has the morphological features of mucinous adenoma but with clear evidence of neoplastic epithelial spread beyond the muscularis propria[5]. Recently, LAMN is divided into two major classes; LAMN-I which is found in a younger group of patients, with the tumor confined to the appendix lumen. It is also described as a non-distended appendix with proliferation of mucinous epithelium, or a distended appendiceal lumen in the presence of dysplastic mucinous epithelium. LAMN-II is usually found in older patients, with mucin and/or neoplastic epithelium in the submucosa, the intestinal wall, or in the area around the appendix with or without perforation. It is also described as having mucin herniating into the appendiceal wall or the presence of extra-appendiceal mucin along the outer surface of the appendix[6]. Different types are shown in the table 1[3,5,7-10].

The major consideration regarding mucinous lesions of the appendix are the location, degree of peritoneal spread, and cytomorphology of the epithelium[7]. LAMNs localized in the appendix

Fig 1(A&B): CT scan of the abdomen showing the mucocele of the appendix.

Fig 2(A): A laparoscopic view of the mucocele.

Fig 2(B): A laparoscopic view of the ovarian cyst.

Fig 2(C): The mucocele of the appendix specimen.
Table 1: Comparisons among Classification Schemes for Appendiceal Mucinous Neoplasms and Psuedomyxoma Peritonei

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<tr>
<td>Limited to mucosa</td>
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<tr>
<td>Low-grade cytology</td>
<td>Adenoma</td>
<td>Low-grade appendiceal mucinous neoplasm</td>
<td>Adenoma</td>
<td>NA</td>
<td>NA</td>
<td>Adenoma</td>
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<tr>
<td>High-grade cytology</td>
<td>Adenoma</td>
<td>Noninvasive mucinous cystadeno-carcinoma</td>
<td>Adenoma</td>
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<td>NA</td>
<td>Adenoma</td>
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<tr>
<td>Positive surgical margin</td>
<td>Adenoma</td>
<td>Low-grade appendiceal mucinous neoplasm</td>
<td>Uncertain malignant potential</td>
<td>NA</td>
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<td>Adenoma</td>
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<tr>
<td>Neoplastic epithelium in appendix wall</td>
<td>Adenoma</td>
<td>Low-grade appendiceal mucinous neoplasm</td>
<td>Uncertain malignant potential</td>
<td>NA</td>
<td>NA</td>
<td>Adenoma</td>
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<tr>
<td>Tumor beyond appendix</td>
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<tr>
<td>Low-grade epithelium in peritoneal mucin</td>
<td>Invasive Mucinous adenocarcinoma</td>
<td>Low-grade appendiceal mucinous neoplasm</td>
<td>High-risk for recurrence</td>
<td>Disseminated peritoneal adenomucinosis</td>
<td>Low-grade mucinous carcinoma peritonei</td>
<td>Low-grade mucinous adenocarcinoma</td>
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<tr>
<td>High-grade epithelium in peritoneal mucin</td>
<td>Invasive Mucinous adenocarcinoma</td>
<td>Invasive Mucinous adenocarcinoma</td>
<td>Invasive Mucinous adenocarcinoma</td>
<td>Peritoneal mucinous carcinomatosis</td>
<td>High-grade mucinous carcinoma peritonei</td>
<td>High-grade mucinous adenocarcinoma</td>
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AJCC: American Joint Committee on Cancer; NA: not applicable; WHO: World Health Organization

typically behave as benign neoplasms. However, as soon as neoplastic epithelium escapes the appendix, there is a significant rise in morbidity and mortality, even if cytology remains bland. Pseudomyxoma peritonei is clinically defined by the presence of intraperitoneal mucin; with or without associated mucin-producing epithelium, it can be progressive and frequently fatal[11]. Macroscopically, there is an unremarkable difference between retention cyst, cystadenoma or LAMN, the appendiceal wall being fibrotic with calcification. Microscopically, a villous or flat mucinous epithelial proliferation replaces the mucosa in LAMN. The mucinous epithelial cells contain mucin, are columnar and display low-grade dysplasia. Also, the denudation of the epithelium is frequent in LAMN[12]. The preoperative diagnosis of mucocele is difficult because of its rarity and the non-specific imaging findings. There is no method to determine the diagnosis with certainty preoperatively. The differential diagnosis is made with cystic ovarian tumors, hydrosalpinx, periappendiceal abscess and mesenteric cysts[12]. An abdominal CT scan can provide useful findings, such as a round or tubular cystic mass, with calcification at the expected site of the appendix. Also, the existence of the tumor can be presumed based on colonoscopic findings as a smooth protruding mass arising from the appendiceal orifice[13]. The prognosis of LAMN is not clearly defined. Regarding appendiceal tumors overall, the course and prognosis of these rare tumors are related to the histologic subtypes. Retention cysts, mucosal hyperplasia, or cystadenoma present with excellent survival rate (91 to 100%) after standard appendectomy. In patients with appendiceal cystadenocarcinoma, five-year survival has a wide range (6 to 100%), based on the stage[8]. Open surgical resection constitutes the treatment of choice, even for a benign-appearing appendiceal mucocele, since lesions that appear to be benign on imaging studies may harbor a cystadenomcarcinoma. Laparoscopic treatment should be avoided, as there is increased risk of rupture[14]. The therapy is fundamentally surgical and is connected with the histopathology report for further management. The main purpose is to achieve negative margins[15]. For LAMN-I, which is rarely progressive, a wait and watch policy is recommended with measurement of the tumor markers, a CT of the abdomen and pelvis at six months, and an annual work up[6]. Recent studies have revealed that in LAMN, right hemicolectomy provides no survival advantage (even those that have ruptured) and appendectomy or cecectomy with negative margin is preferable[15]. Right hemicolectomy must be the therapy of choice only for tumors located at the base of the appendix[12]. Recommended treatment for LAMN-II includes hyperthermic intraperitoneal chemotherapy, prophylactic cytoreductive surgery, greater omentectomy and splenectomy, left upper quadrant peritoneectomy, right upper quadrant peritoneectomy, lesser omentectomy with cholecystectomy, pelvic peritoneectomy with...
rectosigmoid resection, and anterectum with more aggressive follow up[15]. The role of the laparoscopic approach in the management of appendiceal mucocele incidentally diagnosed during surgery is not defined clearly because of the risk of rupture and peritoneal extension of the mucin (pseudomyxoma peritonei). The risk is higher in laparoscopic surgery due to the greater possibility of inappropriate manipulation. There are few case reports in the literature, in which laparoscopy was accepted as a treatment modality for the appendiceal mucocele[12]. If there is no mucin or neoplastic epithelium in the appendiceal base or peri-appendiceal tissue (the disease is limited to the appendiceal lumen), laparoscopic appendectomy can represent an adequate operation for LAMN for experienced surgeons[12].

CONCLUSION

Appendiceal mucocele should be considered by all gynecologists or general surgeons in the differential diagnosis of a right-sided pelvic mass. Minimally invasive surgery can be safe by an experienced surgeon. A close follow up is needed.

REFERENCES

Age-Period-Cohort Modeling of Multiple Sclerosis Incidence Rates in Kuwait: 1980-2014

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BACKGROUND
Multiple sclerosis (MS) is a complex immune-mediated disorder of the central nervous system with undefined etiology. Genetic predisposition and environmental factors play an imperative role in MS causation and its sustained increasing burden worldwide. This study examined the age, period, and cohort effects on MS incidence rates in Kuwait.

METHODS
In this retrospective cohort study, data on MS cases diagnosed between January 1, 1980 and December 31, 2014 and registered in National MS Registry and reference population were obtained. Age-period-cohort (APC) analysis was conducted using a loglinear Poisson regression model to supplement the descriptive and graphical presentation. Descriptive statistics were complemented with APC parameters’ estimates including net drift, local drift, age at onset curve, and longitudinal age trend. Age effect was presented as incidence rates (per 105 person-years), whereas period and cohort effects were presented as adjusted relative rates.

RESULTS
A total of 1,131 cases were diagnosed in 1,385,923 person-years. Overall age-standardized MS incidence rate was 64.5 (95% CI 52.4-79.8). An estimated annual percentage change revealed 7.4% annual increase in MS incidence rate during the study period (Net drift = 7.4%; 95% CI 4.1-10.8%). APC “fitted” age-at-onset curve showed a bimodal pattern with peaked incidence rates at 20-24 years and 45-49 years of age. Compared with the referent period (1980-1984) and cohort (1970-1974), MS incidence rates progressively and significantly (p < 0.001) increased during subsequent time periods and in successive cohorts. Results of APC analysis are descriptive in nature and specific etiological hypotheses were not evaluated. However, the findings of this study substantiated the notion of multiplicity of genetic and/or environmental risk factors’ contributions.

CONCLUSION
A substantial increase in MS incidence rates was recorded, which significantly varied in all 3 temporal dimensions during the study period. Future studies may contemplate biological basis for recorded temporal increase in MS risk.
Candida auris in various hospitals across Kuwait and their susceptibility and molecular basis of resistance to antifungal drugs

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BACKGROUND
Candida auris, a multidrug-resistant species, has the propensity of nosocomial transmission despite normal decontamination procedures. Here, we describe the isolation of C. auris from patients in various hospitals in Kuwait during 2014-2018. Susceptibility to antifungal drugs and molecular basis of resistance to fluconazole, voriconazole and micafungin were also studied.

METHODS
Candida auris (n = 314) obtained from 126 patients in eight hospitals were studied. All isolates were identified by PCR amplification and/or PCR-sequencing of ribosomal DNA (rDNA). Antifungal susceptibility was determined by Etest. Molecular basis of resistance to fluconazole and micafungin was studied by PCR-sequencing of ERG11 and FKS1 genes, respectively.

FINDINGS
Bloodstream (n = 58), urine (n = 124), respiratory (n = 98) and other (n = 34) specimens yielded 314 C. auris isolates. The proportion of bloodstream C. auris among all yeast isolates was higher (42 of 307, 13.7%) in 2018 as compared to 2014-2017 (16 of 964, 1.7%) (P = .001). More bloodstream isolates (42 of 139) were cultured in 2018 than during 2014-2017 (16 of 175) (P = .001). Resistance to amphotericin B, fluconazole, voriconazole and micafungin was detected in 27.1%, 100%, 41.1% and 1.7% isolates, respectively. Fluconazole-resistant isolates contained either Y132F or K143R mutation in ERG11. Isolates with K143R mutation were additionally resistant to voriconazole. Micafungin-resistant isolates contained S639F mutation in hot spot 1 of FKS1.

CONCLUSIONS
Our study highlights spreading of C. auris in major hospitals across Kuwait and its increasing role as a bloodstream pathogen in 2018. Cross-resistance to voriconazole was also seen in isolates with K143R mutation in ERG11, while micafungin-resistant isolates harboured S639F mutation in hot spot 1 of FKS1.

Kuwait bone marrow transplantation activities

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Kuwait is located in the Arabian Gulf and has a population of 3.5million. The stem cell transplantation program started in 2000. Autologous peripheral blood stem cell transplantation started first, as it was easier technically to establish. In 2011, the allogeneic program started with focus on acute leukemia and hemoglobinopathies. The success of both programs required teamwork and support of health planners. The Kuwait National Bone Marrow Registry was established in 2012. The issue of donor availability and drug shortage remain the two main obstacles for expanding the bone marrow transplantation program.
Vitamin D pathway related polymorphisms and vitamin D receptor expression in breast cancer

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Vitamin D deficiency is an emerging risk factor for breast cancer suggesting its role in breast cancer pathogenesis. Recent evidence suggests vitamin D receptor (VDR) expression is a prognosis predictor in breast cancer. We set out to determine the status of VDR expression in histologically characterized breast cancers, and whether common genetic variants modify VDR expression in breast cancer. One-hundred and twenty Kuwaiti female breast cancer fixed tissues were assessed for VDR expression to identify the level and location of its expression by immunohistochemistry. VDR variants (rs731236, rs2228570), and vitamin D binding protein (VDBP) variants (rs4588, rs7041) genotypes were ascertained in breast cancer specimens using Taqman genotyping assays. VDR nuclear expression correlated with low grade tumors (p = 0.01), whereas cytoplasmic expression correlated with lymph node positive tumors (p = 0.03). Absence of VDR expression was a marker for high-grade dedifferentiated tumors (p = 0.01). VDBP rs7041 associated with breast cancer risk (OR 1.92, 95% CI: 1.34 - 2.73; p = 0.0004), and VDR rs2228570 correlated with increased VDR cytoplasmic expression (p < 0.0001). In conclusion, VDR expression is altered in breast cancer confirming its involvement in breast cancer progression. Genetic factors appear to play a role in breast cancer risk, and may modify tumor sensitization to vitamin D.

Pattern of Renal Blood Flow and Renovascular Parameters in Adult Patients With Sickle Cell Disease

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OBJECTIVES
To evaluate renal blood flow patterns and renovascular parameters in adult patients with sickle cell disease (SCD) without laboratory evidence of renal impairment.

METHODS
Sixty-five steady-state adult patients with SCD (50 hemoglobin SS [HbSS], 12 HbSβ0, and 3 HbSD) and 30 age- and sex-matched healthy controls were studied. The kidney length, echo pattern, peak systolic velocity (PSV), end-diastolic velocity, renal-to-aortic ratio, resistive index (RI), acceleration time (AT), and renal vein velocity were acquired, recorded, and analyzed with a 1-5-MHz curvilinear transducer through the abdomen.

RESULTS
The mean age ± SD of the patients with SCD was 32.89 ± 13.89 years. The highest means for the ultrasound-measured renal length and cortical thickness in the SCD and control groups were 11.78 ± 1.30 and
Teenagers’ Awareness of Peers’ Substance and Drug Use in Kuwait

Omu FE1, Bader AW, Helen D, Slabeeb S, Safar H, Omu AE
1Florence E. Omu, PhD, MEd, BSN, RN, Al-Wadaany Bader, MSN, BSN, Delles Helen, BSN, Shukriya Slabeeb, PhD, and Hanan Safar, MSN, BSN, College of Nursing, The Public Authority for Applied, Education and Training, Kuwait. Alexander E. Omu, MBBS, FRCOG, Faculty of Medicine, Kuwait University, Kuwait.


BACKGROUND
Teenage substance use is a global challenge, and youths residing in Kuwait are not immune from it. Tobacco products are licit; however, alcohol and other mood-altering illicit substances are prohibited with severe penalties including imprisonment. Youths residing in Kuwait are being initiated into the use of mood-altering substances like tobacco at an early age, and it is postulated that, as they grow older, they may progress into using alcohol and other prohibited illicit drugs.

AIMS
The aim of this study was to determine licit and illicit substance use by teenagers residing in Kuwait. The study will also explore their awareness of substance use among their peers.

DESIGN
A cross-sectional survey using a snowball sampling technique was used to recruit 190 teenagers aged 15-18 years residing in Kuwait. Data were collected using the 130-item questionnaire adapted from 1998 New Jersey Triennial Public High School Survey of Drug and Alcohol Use. Data collection was from September 2012 to June 2013.

DATA ANALYSIS
The Statistical Package for Social Sciences Version 22 for Windows was used. Pearson’s chi-square, Kruskal-Wallis, and Mann-Whitney U tests were used to test the hypotheses.

RESULTS
Tobacco was the most commonly used substance by these teenagers; 8.4% were current smokers, and 50% had experimented. Age of initiation for 21% was before 14 years old. Hashish (marijuana) was the most commonly used illicit drug, with 3.7% current users and 5.3% claiming to have used it. More male than female teenagers in Grade 9 were using tobacco products ($\chi^2 = 27.428$, df = 5, p < .001).

CONCLUSION
The use and abuse of mood/mind-altering licit and illicit substances appear to be increasing among older teenagers. Intensifying campaigns about the hazards of substance use and drug testing should start from the primary school level.
Forthcoming Conferences and Meetings

Compiled and edited by
Vineetha Elizabeth Mammen

Kuwait Medical Journal 2019; 51 (4): 417 - 423

MicroCon 2019  
Nov 29 - Dec 01, 2019  
India / Mumbai, Maharashtra  
Contact: Indian Association Of Medical Microbiologists (IAMM)  
King Edward Memorial (KEM) Hospital and Seth Gordhandas Sunderdas Medical College (GSMC)  
Lokmanya Tilak Municipal Medical College and General Hospital (LTMMC & GH)  
Phone: +91 80975 76061  
Email: srikant@cimglobal.net

28th Update in Critical Care for Physiotherapists  
Nov 30 - Dec 01, 2019  
United Kingdom / London, England  
Contact: Hartley Taylor Medical Communications Ltd  
Phone: ++44 (0)1565 621967  
Email: derry@hartleytaylor.co.uk

Occupational Stress: Understanding and Management  
2019 by NCORE  
Dec 02, 2019  
United Kingdom / Derby, England  
Contact: National Centre of Rehabilitation Education (NCORE)  
Phone: (01332) 254679  
Email: dhft.ncore@nhs.net

Scholars International Conference on Pharmaceutics and Drug Delivery Research  
Dec 02 - 03, 2019  
Spain / Madrid, Madrid  
Contact: Scholars International Limited  
Phone: +44 2035140512  
Email: pharmaceutics@scholarsmeetings.org

British Society for Immunology (BSI) Congress 2019  
Dec 02 - 05, 2019  
United Kingdom / Liverpool, England  
Contact: British Society for Immunology (BSI)  
Phone: +44 (0)20 3019 5901  
Email: j.sessenwein@immunology.org

Radiation in Everyday Life by The Society for Radiological Protection (SRP)  
Dec 03 - 04, 2019  
United Kingdom / Glasgow, Scotland  
Contact: The Society for Radiological Protection (SRP)  
Phone: 01803 866743  
Email: admin@srp-uk.org

Effective Clinical Supervision Course  
Dec 04, 2019  
United Kingdom / Derby, England  
Contact: National Centre of Rehabilitation Education (NCORE)  
Phone: (01332) 254679  
Email: dhft.ncore@nhs.net

International Society of Orthopaedic Surgery and Traumatology / Societe Internationale de Chirurgie Orthopédique et de Traumatologie (SICOT) 40th Orthopaedic World Congress  
Dec 04 - 07, 2019  
Oman / Muscat, Muscat  
Contact: International Society of Orthopaedic Surgery and Traumatology / Societe Internationale de Chirurgie Orthopédique et de Traumatologie (SICOT)  
Phone: +32 2 648 68 23  
Email: congress@sicot.org

28th Annual Course in Advanced Gynecologic Surgery  
Dec 05 - 07, 2019  
United States / La Jolla, California  
Contact: Society of Gynecologic Surgeons (SGS)  
Phone: 414-253-3463  
Email: nancy@sgsonline.org

6th Annual Gulf Obesity & Metabolic Surgery Society (GOSS) Conference 2019  
Dec 05 - 07, 2019  
Oman / Muscat, Muscat  
Contact: MCI Middle East  
Phone: +971 4 311 6300  
Email: goss@mci-group.com

Antimicrobial Resistance Summit Asia 2019  
Dec 05, 2019  
Singapore / Singapore  
Contact: The Economist Group  
Phone: +65 64282603  
Email: fionayim@economist.com

CARF Workshop 2019  
Dec 05 - 06, 2019  
United Arab Emirates / Abu Dhabi, Abu Dhabi  
Contact: Medetarian Conferences Organizing (MCO)  
Phone: +971 02 658 8717  
Email: it@mco.ae
World Congress on **Pathology and Cancer** Diagnosis 2019
Dec 06 - 07, 2019
*United Arab Emirates / Dubai, Dubai*
Contact: NMC Healthcare | BioGenesis Health Cluster
Phone: +91-9886327807
Email: info@pathologycancersummit.com

**Pediatric Tongue Ties and Lip Ties** Course
Dec 07, 2019
*United States / College Park, Maryland*
Contact: Full Spectrum Seminars
Phone: 212-255-5730
Email: LaserBobDDS@Gmail.com

**General Anesthesia & Deep Sedation**
Dec 08 - 09, 2019
*United States / Chicago, Illinois*
Contact: American Dental Society of Anesthesiology (ADSA)
Phone: 312.664.8270
Email: adsahome@icloud.com

Hot Topics in **Neonatology** 2019
Dec 08 - 11, 2019
*United States / Prince Georges, Maryland*
Contact: Nemours children’s Health system
Phone: 302-651-6750
Email: kbidus@nemours.org

**Middle East Healthcare Social Media Summit 2019**
Dec 09 - 10, 2019
*United Arab Emirates / Dubai, Dubai*
Contact: Mayo Clinic
Phone: 507-284-2511
Email: cme@mayo.edu

**Introduction to Ophthalmic Surgery** course
Dec 11, 2019
*United Kingdom / London, England*
Contact: The Royal College of Ophthalmologists (RCOphth)
Phone: +44 (0) 20 7329 0171
Email: info@bps.ac.uk

**Emirates Society of Emergency Medicine Conference (ESEM19)**
Dec 11 - 14, 2019
*United Arab Emirates / Abu Dhabi, United Arab Emirates*
Contact: MCI Middle East | Emirates Society of Emergency Medicine (ESEM)
Phone: +971-4-311-6300
Email: esem@mci-group.com

**Pediatric Pathology** for General Surgical Pathologists
Dec 11 - 13, 2019
*United States / Palm Springs, California*
Contact: United States and Canadian Academy of Pathology (USCAP)
Phone: (706) 733-7550
Email: help@uscap.org

**Annual Meeting on Gastroenterology and Endoscopy**
Dec 11 - 12, 2019
*United Arab Emirates / Dubai, Dubai*
Contact: BioLEAGUES Worldwide
Phone: +91 - 9087388242
Email: gastrosummit@bioleagues.com

**Acute Pain and Persistent Pain** After Surgery Course
Dec 12 - 13, 2019
*United Kingdom / London, England*
Contact: The Royal Marsden NHS Foundation Trust
Phone: 020 7352 8171
Email: conferenceteam@rmh.nhs.uk

**4th Middle East Camp for Parkinson’s, Movement Disorders and Neuromodulation**
Dec 13 - 14, 2019
*United Arab Emirates / Dubai, Dubai*
Contact: International Parkinson and Movement Disorder Society (MDS)
Phone: +1 (414) 276-2145
Email: info@movementdisorders.org

**Pharmacology 2019 by British Pharmacological Society (BPS)**
Dec 15 - 17, 2019
*United Kingdom / Edinburgh, Scotland*
Contact: British Pharmacological Society (BPS)
Phone: + 44 (0)20 7239 0171
Email: info@bps.ac.uk

International Conference on **Nanotechnology** 2019
Dec 16 - 18, 2019
*United Arab Emirates / Dubai, Dubai*
Contact: Impact Conferences
Phone: 13028277933; 3028277933
Email: impactconferences9@gmail.com

International **Medicine & Health Sciences Congress** (IMedHSC) 2019
Dec 26 - 29, 2019
*France / Paris, Ile-de-France*
Contact: KumGroup Congress and Meeting Organization / KumGroup Kongre ve Toplant Organizasyonu
Phone: +905070619537
Email: info@kumgroup.net
6th International Conference On Public Mental Health and Neurosciences (ICPMN - 2019)  
Dec 26 - 27, 2019  
Indonesia/ Bali  
Contact: Sarvasumana Association  
Email: info@sarvasumana.in

Cardiology and Sports Medicine for Primary Care  
Dec 28 - 30, 2019  
United States / New York City, New York  
Contact: MCE Conferences  
Phone: 1 888 533 9031; 858-566-1500  
Email: info@mceconferences.com

Society for Integrative & Comparative Biology (SICB)  
Annual Meeting 2020  
Jan 03 - 07, 2020  
United States / Austin, Texas  
Contact: Society for Integrative & Comparative Biology (SICB)  
Phone: 703-790-1745; 1-800-955-1236  
Email: Questions@SICB.org

Multi-Specialty Conference in Medicine  
Jan 05 - 07, 2020  
Philippines / Makati, Metro Manila  
Contact: American Academy of Family Medicine (AAFM)  
Phone: 714 907 0872; 011 63 908 451 3700  
Email: aafm123@gmail.com

The Fertility 2020 Conference  
Jan 09 - 11, 2020  
United Kingdom / Edinburgh, Scotland  
Contact: Profile Productions Ltd  
Phone: +44(0)20 3725 5840  
Email: fertility@profileproductions.co.uk

Introduction to Obstetrics - 2 Day Course  
Jan 09 - 10, 2020  
Australia / Gold coast, Queensland  
Contact: Australian Institute of Ultrasound (AIU)  
Specialties : Obstetrics and Gynecology  
Phone: +61 7 552 66655  
Email: info@aiu.edu.au

Mental Health Issues in the Classroom: Practical Strategies for Helping Children and Adolescents Succeed  
Jan 13, 2020  
United States / Rockford, Illinois  
Contact: PESI HealthCare  
Phone: (800) 844-8260  
Email: info@pesi.com

Society for Technology in Anesthesia (STA) 2020 Annual Meeting  
Jan 15 - 18, 2020  
United States / Austin, Texas  
Contact: Society for Technology in Anesthesia (STA)  
Phone: (414) 389-8600  
Email: STAhq@STAhq.org

Recognising post traumatic stress in clients 2020 by NCORE  
Jan 15, 2020  
United Kingdom / Derby, England  
Contact: National Centre of Rehabilitation Education (NCORE)  
Phone: (01332) 254679  
Email: dhft.ncore@nhs.net

Singapore Live 2020: 29th Annual Live Interventions in Vascular Endotherapy  
Jan 15 - 17, 2020  
Singapore / Singapore  
Contact: National Heart Centre Singapore (NHCS)  
Phone: 6704 2389; +65 6704 2389  
Email: slive@nhcs.com.sg

10th Emirates Otorhinolaryngology Audiology and Communication Disorders Congress  
Jan 15 - 17, 2020  
United Arab Emirates / Dubai, Dubai  
Contact: MCI Middle East  
Phone: +971 4 311 6300  
Email: eroc@mci-group.com

14th SEHA International Paediatric Conference  
Jan 16 - 18, 2020  
United Arab Emirates / Abu Dhabi, Abu Dhabi  
Contact: Mena Conference  
Phone: +971 2 4919888; +971 56 5033747  
Email: afsal@menaconference.com

The 8th Pan Arab Human Genetics Conference (PAHGC)  
Jan 17 - 20, 2020  
United Arab Emirates / Dubai, Dubai  
Contact: Sheikh Hamdan Bin Rashid Al Maktoum Award for Medical Sciences  
Phone: + 971 4 3986777  
Email: info@hmaward.org.ae

American Academy of Anti-Aging Medicine (A4M) India Conference  
Jan 18 - 19, 2020  
India / New Delhi, Delhi  
Contact: American Academy of Anti-Aging Medicine (A4M)  
Phone: 561-997-0112; 888-997-0112  
Email: info@a4m.com
Glasgow **Neuroradiology** Workshop for Stroke Physicians  
Jan 18, 2020  
*United Arab Emirates / Dubai, Dubai*  
Contact: Radicon Radiology Courses (RRC)  
Phone: 971 4 514 7475  
Email: info@radiologycourses.org

**Cancer** Evolution and Combinatorial Cancer Therapies: Concepts and Challenges (L1)  
Jan 19 - 23, 2020  
*Canada / Banff, Alberta*  
Contact: Keystone Symposia on Molecular and Cellular Biology  
Phone: +1 800-253-0685  
Email: info@keystonesymposia.org

**Autism:** De-Escalate Meltdowns and Diffuse Explosive Behaviors in Children and Adolescents  
Jan 24, 2020  
*United States / Tacoma, Washington*  
Contact: PESI HealthCare  
Phone: (800) 844-8260  
Email: info@pesi.com

**Endocrinology** for Primary Care 2020  
Jan 24 - 26, 2020  
*United States / Orlando, Florida*  
Contact: Medical Education Resources (MER)  
Phone: 303-798-9682; 1-800-421-3756  
Email: info@mer.org

**7th EMINS Congress**  
Jan 24 - 25, 2020  
*United Arab Emirates / Dubai, Dubai*  
Contact: DiaEdu Management Consultancy  
Phone: +971 4 453 2975  
Email: contact@diaedu.com

The Society of **Thoracic Surgeons** (STS) 56th Annual Meeting  
Jan 25 - 28, 2020  
*United States / New Orleans, Louisiana*  
Contact: The Society of Thoracic Surgeons (STS)  
Phone: 312-202-5800  
Email: meetings@sts.org

Updated **Neuroimaging** for Acute Ischemic Stroke Conference  
Jan 25, 2020  
*Canada / Toronto, Ontario*  
Contact: Ontario Association of Radiologists (OAR)  
Phone: 905-337-2680; 800-616-6277  
Email: mail@oarinfo.ca

**Cancer** Epigenetics: New Mechanisms and Therapeutic Opportunities (J4)  
Jan 26 - 30, 2020  
*United States / Keystone, Colorado*  
Contact: Keystone Symposia on Molecular and Cellular Biology  
Phone: +1 800-253-0685  
Email: info@keystonesymposia.org

**Hospital Medicine:** Management of the Hospitalized Adult Patient 2020  
Jan 27 - 31, 2020  
*United States / Sarasota, Florida*  
Contact: American Medical Seminars (AMS)  
Phone: 941-388-1766; 1-866-267-4263  
Email: mail@ams4cme.com

63rd All India Congress of **Obstetrics and Gynaecology** (AICOG)  
Jan 29 - Feb 02, 2020  
*India / Lucknow, Uttar Pradesh*  
Contact: Concept Conferences Pvt. Ltd.  
Phone: +91 9319789003  
Email: contact@concepttc.com

**Endocrinology and Rheumatology:** The Most Practical and Useful Topics from Two Specialties 2020  
Feb 03 - 07, 2020  
*United States / Sarasota, Florida*  
Contact: American Medical Seminars (AMS)  
Phone: 941-388-1766  
Email: mail@ams4cme.com

Canadian Coronary **Physiology and Invasive Imaging** Symposium CPI 2020  
Feb 04 - 05, 2020  
*Canada / Dorval, Quebec*  
Contact: Xpertize Meeting Management  
Phone: (514) 696-6699  
Email: xpertize@xpertize.com

**DF Clinical Symposia Advances in Dermatology** 2020  
Feb 05 - 09, 2020  
*United States / Naples, Florida*  
Contact: Dermatology Foundation (DF)  
Phone: (847) 328-2256  
Email: dfgen@dermatologyfoundation.org

**Cranial Eval** & Adjusting Protocols for the Infant and Child  
Feb 08 - 09, 2020  
*United States / Atlanta, Georgia*  
Contact: International Chiropractic Pediatric Association (ICPA)  
Phone: (610) 565-2360  
Email: info@icpa4kids.com
2020 Canadian Critical Care Conference (CCCC)  
Feb 10 - 13, 2020  
Canada / Whistler, British Columbia  
Contact: Canadian Critical Care Conference (CCCC)  
Phone: 604.834.9362  
Email: Zena.davidson@vch.ca

Paediatric sleep Course  
Feb 10 - 11, 2020  
England / London  
Contact: Imperial College London  
Phone: +44 (0)20 7589 5111  
Email: cpd@imperial.ac.uk

10th neonatal palliative and end of life care conference  
Feb 11, 2020  
United Kingdom / Leeds, England  
Contact: Child Bereavement UK  
Phone: 01494 568 900  
Email: enquiries@childbereavementuk.org

RCOG Basic Practical Skills in Obstetrics and Gynaecology 2020  
Feb 11 - 12, 2020  
United Kingdom / London, England  
Contact: Royal College of Obstetricians and Gynaecologists (RCOG)  
Phone: +44 (0)207 772 6281  
Email: adias@rcog.org.uk

UCSF CME: 53rd Annual Recent Advances in Neurology  
Feb 12 - 14, 2020  
United States / San Francisco, California  
Contact: The University of California, San Francisco (UCSF) Office of Continuing Medical Education  
Phone: 415-476-4251  
Email: info@cme.ucsf.edu

Behavioral Treatment of Chronic Pain: Evidence-Based Techniques to Move People from Hurt to Hope  
Feb 11, 2020  
United States / East Lansing, Michigan  
Contact: PESI HealthCare  
Phone: (800) 844-8260  
Email: info@pesi.com

Intra- and Intercellular Mechanisms of Aging (B2)  
Feb 09 - 13, 2020  
Canada / Vancouver, British Columbia  
Contact: Keystone Symposia on Molecular and Cellular Biology  
Phone: +1 800-253-0685  
Email: info@keystonesymposia.org

8th Pediatric & Neonatal International Conference UHS  
Feb 13 - 14, 2020  
United Arab Emirates / Dubai, Dubai  
Contact: CME Conferences Organizing  
Phone: 971 52 9977 290  
Email: Info@dubaicme.com

The 46th Annual Vail OB-GYN Conference  
Feb 16 - 21, 2020  
United States / Vail, Colorado  
Contact: University of Colorado, Department of Obstetrics and Gynecology | University of Colorado School of Medicine  
Phone: (303) 724-3866  
Email: VailOBGYN@UCDenver.edu

Navigating Ethical Challenges in Mental Health Practice: Current Guidelines for Clinicians  
Feb 17, 2020  
United States / Tinley Park, Illinois  
Contact: PESI HealthCare  
Phone: (800) 844-8260  
Email: info@pesi.com

Extracellular Vesicles and Stem Cells Summit 2020  
Feb 17 - 18, 2020  
United States / San Diego, California  
Contact: Select Biosciences Limited  
Phone: +1 510 857 4865  
Email: enquiries@selectbio.com

Clinically Relevant Vascular & Endovascular Surgery (CARVE) 2020  
Feb 18 - 20, 2020  
United States / Vail, Colorado  
Contact: Clinically Relevant Vascular & Endovascular Surgery (CARVE)  
Phone: +1 763-398-2221

Advanced OB-GYN Ultrasound Seminar 2020  
Feb 19 - 22, 2020  
United States / Lake Buena Vista, Florida  
Contact: American Institute of Ultrasound in Medicine (AIUM)  
Phone: 301-498-4100; 800-638-5352  
Email: accreditation@aium.org

Changing the ADHD Brain: Moving Beyond Medication  
Feb 19, 2020  
United States / Thousand Oaks, California  
Contact: PESI HealthCare  
Phone: (800) 844-8260  
Email: info@pesi.com
Stromal Cells in Immunity and Disease (Q5)
Feb 19 - 23, 2020
Canada / Victoria, British Columbia
Contact: Keystone Symposia on Molecular and Cellular Biology
Phone: +1 800-253-0685
Email: info@keystonesymposia.org

World Congress on Physical Therapy and Rehabilitation Medicine (PTRM 2020)
Feb 22 - 23, 2020
United Arab Emirates / Dubai, Dubai
Contact: GSE Academy
Phone: +1 214 275 9747
Email: info@physicaltherapyconferences.org

26th Annual Conference of Indian Society of Critical Care Medicine Criticare
Feb 26 - Mar 01, 2020
India / Hyderabad, Telangana
Contact: Indian Society of Critical Care Medicine (ISCCM)
Phone: 022-24444737 / 022-24460348
Email: conferencecoordinator@isccm.org

Computational and Systems Neuroscience (COSYNE) 2020
Feb 27 - Mar 03, 2020
United States / Denver, Colorado
Contact: Computational and Systems Neuroscience (COSYNE)
Email: leslie.weekes@cosyne.org

Multi-Specialty Conference in Medicine
Mar 01 - 03, 2020
Philippines / Makati, Metro Manila
Contact: American Academy of Family Medicine (AAFM)
Phone: 011 63 908 451 3700
Email: afm123@gmail.com

14th International Society of Physical and Rehabilitation Medicine (ISPRM) World Congress 2020
Mar 04 - 09, 2020
United States / Orlando, Florida
Contact: International Society of Physical and Rehabilitation Medicine (ISPRM)
Phone: +41 22 908 04 83; +41 22 906 91
Email: isprmoffice@kenes.com

International Academy of Oral Medicine and Toxicology (IAOMT) 2020 Joint Meeting
Mar 05 - 07, 2020
United States / Dallas, Texas
Contact: International Academy of Oral Medicine and Toxicology (IAOMT)
Phone: (863) 420-6373
Email: info@iaomt.org

Mar 07 - 12, 2020
United States / Amelia Island, Florida
Contact: North American Neuro-Ophthalmology Society (NANOS)
Phone: 952-646-2037; (952) 646-2033
Email: info@nanosweb.org

Gulf Thoracic 2020
Mar 11 - 14, 2020
United Arab Emirates / Dubai, Dubai
Contact: Saudi Thoracic Society (STS)
Phone: +966-11-2488966; +966506426704
Email: sts.exo@gmail.com

5th International Dermatology and Cosmetology (INDERCOS) Congress
Mar 12 - 15, 2020
Turkey / Istanbul, Istanbul
Contact: Figur Congress & Organizations
Phone: +90 212 381 46 00
Email: indercos@figur.net

Dubai Derma - Dubai World Dermatology and Laser Conference & Exhibition 2020
Mar 16 - 18, 2020
United Arab Emirates / Dubai, Dubai
Contact: INDEX Conferences & Exhibitions
Phone: 00971 4 520 8888
Email: info@dubaiderma.com

American Society for Clinical Pharmacology and Therapeutics (ASCPT) 121st Annual Meeting
Mar 17 - 21, 2020
United States / Houston, Texas
Contact: American Society for Clinical Pharmacology and Therapeutics (ASCPT)
Phone: 703 836 6981
Email: info@ascpt.org

7th World Conference on Pharmaceutical Science and Drug Manufacturing
Mar 18 - 19, 2020
United Arab Emirates / Dubai, Dubai
Contact: Bioleagues Worldwide
Phone: +91-9884076645; +1 (212) 305-2500
Email: info@pharma-dubai.com

8th International Maternal & Fetal Nutrition in the first 1000 days
Mar 19 - 21, 2020
Turkey / Cankaya, Ankara
Contact: FTS Tourism Congress Organization / FTS Turizm Kongre Organizasyon, Halit Riza Ozturk
Phone: +90 312 439 68 04
Email: first1000days2020@ftskongre.org
AOTrauma - Seminar Complex **Pediatric Fractures**
Mar 20, 2020  
*Jordan / Amman*  
Contact: AOTrauma  
Phone: +41 81 414 27 00 ext. 700  
Email: EGuiterrez@aotrauma.org

Royal College of Obstericians and Gynaecologists (RCOG) World Congress 2020  
Mar 25 - 28, 2020  
*Oman / Muscat, Muscat*  
Contact: MCI Middle East  
Phone: +971 4 311 6300  
Email: rcog2020@mci-group.com

International Conference on **Gastroenterology and Hepatology** (ICGH2020)  
Mar 25 - 26, 2020  
*United Kingdom / London, England*  
Contact: Scietech International  
Phone: +65 31634905  
Email: info@scietechconferences.com

12th Annual McMaster University Review Course in **Internal Medicine**  
Mar 25 - 27, 2020  
*Canada / Hamilton, Ontario*  
Contact: McMaster University  
Specialties: Internal Medicine  
Phone: 905-525-9140 x20052  
Email: castewa@mcmaster.ca

**Clinical Immunology** Society (CIS) 2020 Annual Meeting  
Apr 02 - 05, 2020  
*United States / Denver, Colorado*  
Contact: Clinical Immunology Society (CIS)  
Phone: (414) 224-8095  
Email: info@clinimmssoc.org

Emirates **Critical Care** Conference (ECCC) 2020  
Apr 02 - 04, 2020  
*United Arab Emirates / Dubai, Dubai*  
Contact: InfoPlus Events LLC (IPE)  
Phone: +971 4 4218996  
Email: Plus@InfoPlusEvents.com

2020 - 4th Annual Dubai International **Paediatric Neurology** Congress  
Apr 09 - 11, 2020  
*United Arab Emirates / Dubai, Dubai*  
Contact: Maarefah Management  
Phone: +971 4 361 9616  
Email: info@ipncongress.com

**Cardiac Arrhythmias**  
Apr 10, 2020  
*United States / Minneapolis, Minnesota*  
Contact: University of Minnesota - Continuing Professional Development  
Phone: 612-626-7600; 1-800-776-8636  
Email: cme@umn.edu

Enhancing **Pediatric Neuroplasticity** - Vancouver  
Apr 18 - 19, 2020  
*Canada / Vancouver, British Columbia*  
Contact: International Chiropractic Pediatric Association (ICPA)  
Phone: (610) 565-2360  
Email: info@icpa4kids.com

**Radiology** in Lyon, France  
Apr 26 - May 02, 2020  
*France / Lyon, Auvergne-Rhone-Alpes*  
Contact: Radiology International, Inc.  
Phone: 860-225-1700  
Email: nadine@radiologyintl.com

**Emergency Medicine:** An Evidence-Based Approach To Adult Care 2020  
Apr 27 - May 01, 2020  
*United States / Longboat Key, Florida*  
Contact: American Medical Seminars (AMS)  
Phone: 941-388-1766  
Email: mail@ams4cme.com

**Euroanaesthesia 2020 Congress**  
May 30 - Jun 01, 2020  
*Spain / Barcelona, Catalonia*  
Contact: European Society of Anaesthesiology (ESA)  
Email: info@esahq.org

**Nutrition 2020**  
May 30 - Jun 02, 2020  
*United States / Seattle, Washington*  
Contact: American Society for Nutrition (ASN)  
Phone: (240) 428-3650  
Email: meetings@nutrition.org
WHO-Facts Sheet

1. Falls
2. Hypertension
3. Influenza (seasonal)
4. Listeriosis
5. Schizophrenia

Compiled and edited by
Vineetha E Mammen

Kuwait Medical Journal 2019; 51 (4): 424 - 432

1. FALLS

KEY FACTS
- Falls are the second leading cause of accidental or unintentional injury deaths worldwide.
- Each year an estimated 646,000 individuals die from falls globally of which over 80% are in low- and middle-income countries.
- Adults older than 65 years of age suffer the greatest number of fatal falls.
- 37.3 million falls that are severe enough to require medical attention occur each year.
- Prevention strategies should emphasize education, training, creating safer environments, prioritizing fall-related research and establishing effective policies to reduce risk.

A fall is defined as an event which results in a person coming to rest inadvertently on the ground or floor or other lower level. Fall-related injuries may be fatal or non-fatal(1) though most are non-fatal. For example, of children in the People’s Republic of China, for every death due to a fall, there are 4 cases of permanent disability, 13 cases requiring hospitalization for more than 10 days, 24 cases requiring hospitalization for 1–9 days and 690 cases seeking medical care or missing work/school.

The problem
Globally, falls are a major public health problem. An estimated 646,000 fatal falls occur each year, making it the second leading cause of unintentional injury death, after road traffic injuries. Over 80% of fall-related fatalities occur in low- and middle-income countries, with regions of the Western Pacific and South East Asia accounting for 60% of these deaths. In all regions of the world, death rates are highest among adults over the age of 60 years.

Though not fatal, approximately 37.3 million falls severe enough to require medical attention occur each year. Such falls are responsible for over 17 million DALYs (disability-adjusted life years) lost (2). The largest morbidity occurs in people aged 65 years or older, young adults aged 15–29 years and children aged 15 years or younger.

While nearly 40% of the total DALYs lost due to falls worldwide occurs in children, this measurement may not accurately reflect the impact of fall-related disabilities for older individuals who have fewer life years to lose. In addition, those individuals who fall and suffer a disability, particularly older people, are at a major risk for subsequent long-term care and institutionalization.

The financial costs from fall-related injuries are substantial. For people aged 65 years or older, the average health system cost per fall injury in the Republic of Finland and Australia are US$ 3611 and US$ 1049 respectively. Evidence from Canada suggests the implementation of effective prevention strategies with a subsequent 20% reduction in the incidence of falls among children under 10 years of age could create a net savings of over US$ 120 million each year.

Who is at risk?
While all people who fall are at risk of injury, the age, gender and health of the individual can affect the type and severity of injury.

Age
Age is one of the key risk factors for falls. Older people have the highest risk of death or serious
injury arising from a fall and the risk increases with age. For example, in the United States of America, 20–30% of older people who fall suffer moderate to severe injuries such as bruises, hip fractures, or head trauma. This risk level may be in part due to physical, sensory, and cognitive changes associated with ageing, in combination with environments that are not adapted for an aging population.

Another high risk group is children. Childhood falls occur largely as a result of their evolving developmental stages, innate curiosity in their surroundings, and increasing levels of independence that coincide with more challenging behaviours commonly referred to as ‘risk taking’. While inadequate adult supervision is a commonly cited risk factor, the circumstances are often complex, interacting with poverty, sole parenthood, and particularly hazardous environments.

**Gender**

Across all age groups and regions, both genders are at risk of falls. In some countries, it has been noted that males are more likely to die from a fall, while females suffer more non-fatal falls. Older women and younger children are especially prone to falls and increased injury severity. Worldwide, males consistently sustain higher death rates and DALYs lost. Possible explanations of the greater burden seen among males may include higher levels of risk-taking behaviours and hazards within occupations.

Other risk factors include:

- occupations at elevated heights or other hazardous working conditions;
- alcohol or substance use;
- socioeconomic factors including poverty, overcrowded housing, sole parenthood, young maternal age;
- underlying medical conditions, such as neurological, cardiac or other disabling conditions;
- side effects of medication, physical inactivity and loss of balance, particularly among older people;
- poor mobility, cognition, and vision, particularly among those living in an institution, such as a nursing home or chronic care facility;
- unsafe environments, particularly for those with poor balance and limited vision.

**Prevention**

Fall prevention strategies should be comprehensive and multifaceted. They should prioritize research and public health initiatives to further define the burden, explore variable risk factors and utilize effective prevention strategies. They should support policies that create safer environments and reduce risk factors. They should promote engineering to remove the potential for falls, the training of health care providers on evidence-based prevention strategies; and the education of individuals and communities to build risk awareness.

Effective fall prevention programmes aim to reduce the number of people who fall, the rate of falls and the severity of injury should a fall occur. For older individuals, fall prevention programmes can include a number of components to identify and modify risk, such as:

- screening within living environments for risks for falls;
- clinical interventions to identify risk factors, such as medication review and modification, treatment of low blood pressure, vitamin D and calcium supplementation, treatment of correctable visual impairment;
- home assessment and environmental modification for those with known risk factors or a history of falling;
- prescription of appropriate assistive devices to address physical and sensory impairments;
- muscle strengthening and balance retraining prescribed by a trained health professional;
- community-based group programmes which may incorporate fall prevention education and Tai Chi-type exercises or dynamic balance and strength training;
- use of hip protectors for those at risk of a hip fracture due to a fall.

For children, effective interventions include multifaceted community programmes; engineering modifications of nursery furniture, playground equipment, and other products; and legislation for the use of window guards. Other promising prevention strategies include: use of guard rails/gates, home visitation programmes, mass public education campaigns, and training of individuals and communities in appropriate acute pediatric medical care should a fall occur.

1. Within the WHO Global Health Estimates database, fall-related deaths and non-fatal injuries exclude falls due to assault and self-harm; falls from animals, burning buildings, transport vehicles; and falls into fire, water and machinery.
2. The disability-adjusted life year (DALY) extends the concept of potential years of life lost due to premature death to include equivalent years of “healthy” life lost by virtue of being in states of poor health or disability.
2. HYPERTENSION

KEY FACTS

- Hypertension - or elevated blood pressure - is a serious medical condition that significantly increases the risks of heart, brain, kidney and other diseases.
- An estimated 1.13 billion people worldwide have hypertension, most (two-thirds) living in low- and middle-income countries.
- In 2015, 1 in 4 men and 1 in 5 women had hypertension.
- Fewer than 1 in 5 people with hypertension have the problem under control.
- Hypertension is a major cause of premature death worldwide.
- One of the global targets for noncommunicable diseases is to reduce the prevalence of hypertension by 25% by 2025 (baseline 2010).

What is hypertension?

Blood pressure is the force exerted by circulating blood against the walls of the body’s arteries, the major blood vessels in the body. Hypertension is when blood pressure is too high.

Blood pressure is written as two numbers. The first (systolic) number represents the pressure in blood vessels when the heart contracts or beats. The second (diastolic) number represents the pressure in the vessels when the heart rests between beats.

Hypertension is diagnosed if, when it is measured on two different days, the systolic blood pressure readings on both days is ≥140 mmHg and/or the diastolic blood pressure readings on both days is ≥90 mmHg.

What are the risk factors for hypertension?

Modifiable risk factors include unhealthy diets (excessive salt consumption, a diet high in saturated fat and trans fats, low intake of fruits and vegetables), physical inactivity, consumption of tobacco and alcohol, and being overweight or obese.

Non-modifiable risk factors include a family history of hypertension, age over 65 years and co-existing diseases such as diabetes or kidney disease.

What are common symptoms of hypertension?

Hypertension is called a “silent killer”. Most people with hypertension are unaware of the problem because it may have no warning signs or symptoms. For this reason, it is essential that blood pressure is measured regularly.

When symptoms do occur, they can include early morning headaches, nosebleeds, irregular heart rhythms, vision changes, and buzzing in the ears. Severe hypertension can cause fatigue, nausea, vomiting, confusion, anxiety, chest pain, and muscle tremors.

The only way to detect hypertension is to have a health professional measure blood pressure. Having blood pressure measured is quick and painless. Individuals can also measure their own blood pressure using automated devices, however, an evaluation by a health professional is important for assessment of risk and associated conditions.

What are the complications of uncontrolled hypertension?

Among other complications, hypertension can cause serious damage to the heart. Excessive pressure can harden arteries, decreasing the flow of blood and oxygen to the heart. This elevated pressure and reduced blood flow can cause:

- Chest pain, also called angina.
- Heart attack, which occurs when the blood supply to the heart is blocked and heart muscle cells die from lack of oxygen. The longer the blood flow is blocked, the greater the damage to the heart.
- Heart failure, which occurs when the heart cannot pump enough blood and oxygen to other vital body organs.
- Irregular heart beat which can lead to a sudden death.

Hypertension can also burst or block arteries that supply blood and oxygen to the brain, causing a stroke.

In addition, hypertension can cause kidney damage, leading to kidney failure.

Why is hypertension an important issue in low- and middle-income countries?

The prevalence of hypertension varies across the WHO regions and country income groups. The WHO African Region has the highest prevalence of hypertension (27%) while the WHO Region of the Americas has the lowest prevalence of hypertension (18%).

A review of current trends shows that the number of adults with hypertension increased from 594 million in 1975 to 1.13 billion in 2015, with the increase seen largely in low- and middle-income countries. This increase is due mainly to a rise in hypertension risk factors in those populations.

How can the burden of hypertension be reduced?

Reducing hypertension prevents heart attack, stroke, and kidney damage, as well as other health problems.

Prevention

- Reducing salt intake (to less than 5g daily)
- Eating more fruit and vegetables
• Being physically active on a regular basis
• Avoiding use of tobacco
• Reducing alcohol consumption
• Limiting the intake of foods high in saturated fats
• Eliminating/reducing trans fats in diet

Management
• Reducing and managing mental stress
• Regularly checking blood pressure
• Treating high blood pressure
• Managing other medical conditions

What is the WHO response?
In 2016, WHO and the United States Centers for Disease Control and Prevention launched the Global Hearts Initiative to support governments to prevent and treat cardiovascular diseases.

Of the five technical packages that comprise the Global Hearts Initiative, the HEARTS technical package aims to improve the prevention and management of cardiovascular diseases, including hypertension detection and management. The five modules of the HEARTS technical package (Healthy-lifestyle counselling, Evidence-based treatment protocols, Access to essential medicines and technology, Team-based care, and Systems for monitoring) provide a strategic approach to improve cardiovascular health in countries across the globe.

Fifteen countries have started implementing the HEARTS technical package (Barbados, Bhutan, Colombia, Chile, China, Cuba, Ethiopia, India, Iran, Morocco, Nepal, Philippines, Tajikistan, Thailand, and Viet Nam). By scaling up protocol-based management, improving access to medicines and technologies, and better measuring outcomes, successes are already being achieved.

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3. INFLUENZA (SEASONAL)
Seasonal influenza is an acute respiratory infection caused by influenza viruses which circulate in all parts of the world.

The pathogen
There are 4 types of seasonal influenza viruses, types A, B, C and D. Influenza A and B viruses circulate and cause seasonal epidemics of disease.

• Influenza A viruses are further classified into subtypes according to the combinations of the hemagglutinin (HA) and the neuraminidase (NA), the proteins on the surface of the virus. Currently circulating in humans are subtype A(H1N1) and A(H3N2) influenza viruses. The A(H1N1) is also written as A(H1N1)pdm09 as it caused the pandemic in 2009 and subsequently replaced the seasonal influenza A(H1N1) virus which had circulated prior to 2009. Only influenza type A viruses are known to have caused pandemics.

• Influenza B viruses are not classified into subtypes, but can be broken down into lineages. Currently circulating influenza type B viruses belong to either B/Yamagata or B/Victoria lineage.

• Influenza C virus is detected less frequently and usually causes mild infections, thus does not present public health importance.

• Influenza D viruses primarily affect cattle and are not known to infect or cause illness in people.

Signs and symptoms
Seasonal influenza is characterized by a sudden onset of fever, cough (usually dry), headache, muscle and joint pain, severe malaise (feeling unwell), sore throat and a runny nose. The cough can be severe and can last 2 or more weeks. Most people recover from fever and other symptoms within a week without requiring medical attention. But influenza can cause severe illness or death especially in people at high risk (see below).

Illnesses range from mild to severe and even death. Hospitalization and death occur mainly among high risk groups. Worldwide, these annual epidemics are estimated to result in about 3 to 5 million cases of severe illness, and about 290 000 to 650 000 respiratory deaths.

In industrialized countries most deaths associated with influenza occur among people age 65 or older (1). Epidemics can result in high levels of worker/school absenteeism and productivity losses. Clinics and hospitals can be overwhelmed during peak illness periods.

The effects of seasonal influenza epidemics in developing countries are not fully known, but research estimates that 99% of deaths in children under 5 years of age with influenza related lower respiratory tract infections are found in developing countries (2).

Epidemiology
All age groups can be affected but there are groups that are more at risk than others.

• People at greater risk of severe disease or complications when infected are: pregnant women, children under 59 months, the elderly, individuals with chronic medical conditions (such as chronic cardiac, pulmonary, renal, metabolic, neurodevelopmental, liver or hematologic diseases) and individuals with immunosuppressive conditions (such as HIV/AIDS, receiving chemotherapy or steroids, or malignancy).
• Health care workers are at high risk acquiring influenza virus infection due to increased exposure to the patients and risk further spread particularly to vulnerable individuals.

In terms of transmission, seasonal influenza spreads easily, with rapid transmission in crowded areas including schools and nursing homes. When an infected person coughs or sneezes, droplets containing viruses (infectious droplets) are dispersed into the air and can spread up to one meter, and infect persons in close proximity who breathe these droplets in. The virus can also be spread by hands contaminated with influenza viruses. To prevent transmission, people should cover their mouth and nose with a tissue when coughing, and wash their hands regularly.

In temperate climates, seasonal epidemics occur mainly during winter, while in tropical regions, influenza may occur throughout the year, causing outbreaks more irregularly.

The time from infection to illness, known as the incubation period, is about 2 days, but ranges from one to four days.

Diagnosis

The majority of cases of human influenza are clinically diagnosed. However, during periods of low influenza activity and outside of epidemics situations, the infection of other respiratory viruses e.g. rhinovirus, respiratory syncytial virus, parainfluenza and adenovirus can also present as Influenza-like Illness (ILI) which makes the clinical differentiation of influenza from other pathogens difficult.

Collection of appropriate respiratory samples and the application of a laboratory diagnostic test is required to establish a definitive diagnosis. Proper collection, storage and transport of respiratory specimens is the essential first step for laboratory detection of influenza virus infections. Laboratory confirmation of influenza virus from throat, nasal and nasopharyngeal secretions or tracheal aspirate or washings is commonly performed using direct antigen detection, virus isolation, or detection of influenza-specific RNA by reverse transcriptase-polymerase chain reaction (RT-PCR). Various guidance on the laboratory techniques is published and updated by WHO. (3)

Rapid influenza diagnostic tests (RIDTs) are used in clinical settings, but they have lower sensitivity compared to RT-PCR methods and their reliability depends largely on the conditions under which they are used.

Treatment

Patients with uncomplicated seasonal influenza:

Patients that are not from a high risk group should be managed with symptomatic treatment and are advised, if symptomatic, to stay home in order to minimize the risk of infecting others in the community. Treatment focuses on relieving symptoms of influenza such as fever. Patients should monitor themselves to detect if their condition deteriorates and seek medical attention. Patients that are known to be in a group at high risk for developing severe or complicated illness, (see above) should be treated with antivirals in addition to symptomatic treatment as soon as possible.

Patients with severe or progressive clinical illness associated with suspected or confirmed influenza virus infection (i.e. clinical syndromes of pneumonia, sepsis or exacerbation of chronic underling diseases) should be treated with antiviral drug as soon as possible.

• Neuraminidase inhibitors (i.e. oseltamivir) should be prescribed as soon as possible (ideally, within 48 hours following symptom onset) to maximize therapeutic benefits. Administration of the drug should also be considered in patients presenting later in the course of illness.

• Treatment is recommended for a minimum of 5 days, but can be extended until there is satisfactory clinical improvement.

• Corticosteroids should not be used routinely, unless indicated for other reasons (e.g. asthma and other specific conditions); as it has been associated with prolonged viral clearance, immunosuppression leading to bacterial or fungal superinfection.

• All currently circulating influenza viruses are resistant to adamantane antiviral drugs (such as amantadine and rimantadine), and these are therefore not recommended for monotherapy. WHO GISRS monitors resistance to antivirals among circulating influenza viruses to provide timely guidance for antiviral use in clinical management and potential chemoprophylaxis.

Prevention

The most effective way to prevent the disease is vaccination. Safe and effective vaccines are available and have been used for more than 60 years. Immunity from vaccination wanes over time so annual vaccination is recommended to protect against influenza. Injected inactivated influenza vaccines are most commonly used throughout the world.

Among healthy adults, influenza vaccine provides protection, even when circulating viruses do not exactly match the vaccine viruses. However, among the elderly, influenza vaccination may be less effective in preventing illness but reduces severity of disease and incidence of complications and deaths. Vaccination is especially important for people at high risk of influenza complications, and for people who live with or care for the people at high risk.
WHO recommends annual vaccination for:

- pregnant women at any stage of pregnancy
- children aged between 6 months to 5 years
- elderly individuals (aged more than 65 years)
- individuals with chronic medical conditions
- health-care workers.

Influenza vaccine is most effective when circulating viruses are well-matched with viruses contained in vaccines. Due to the constant evolving nature of influenza viruses, the WHO Global Influenza Surveillance and Response System (GISRS) – a system of National Influenza Centres and WHO Collaborating Centres around the world – continuously monitors the influenza viruses circulating in humans and updates the composition of influenza vaccines twice a year.

For many years, WHO has updated its recommendation on the composition of the vaccine (trivalent) that targets the 3 most representative virus types in circulation (two subtypes of influenza A viruses and one influenza B virus). Starting with the 2013–2014 northern hemisphere influenza season, a 4th component is recommended to support quadrivalent vaccine development. Quadrivalent vaccines include a 2nd influenza B virus in addition to the viruses in trivalent vaccines, and are expected to provide wider protection against influenza B virus infections. A number of inactivated influenza vaccines and recombinant influenza vaccines are available in injectable form. Live attenuated influenza vaccine is available as a nasal spray.

Pre-exposure or post-exposure prophylaxis with antivirals is possible but depends on several factors e.g. individual factors, type of exposure, and risk associated with the exposure.

Apart from vaccination and antiviral treatment, the public health management includes personal protective measures like:

- Regular hand washing with proper drying of the hands
- Good respiratory hygiene – covering mouth and nose when coughing or sneezing, using tissues and disposing of them correctly
- Early self-isolation of those feeling unwell, feverish and having other symptoms of influenza
- Avoiding close contact with sick people
- Avoiding touching one’s eyes, nose or mouth

**WHO response**

WHO, through the WHO GISRS system, in collaboration with other partners, monitors influenza activity globally, recommends seasonal influenza vaccine compositions twice a year for the Northern and Southern hemisphere influenza seasons, guides countries in tropical and subtropical areas to choose vaccine formulations (Northern hemisphere vs. Southern hemisphere), to support decisions for timing of vaccination campaigns, and to support Member States to develop prevention and control strategies.

WHO works to strengthen national, regional and global influenza response capacities including diagnostics, antiviral susceptibility monitoring, disease surveillance and outbreak responses, and to increase vaccine coverage among high risk groups and prepare for the next influenza pandemic.


**4. LISTERIOSIS**

**KEY FACTS**

- Listeriosis is a serious, but preventable and treatable disease.
- Pregnant women, the elderly or individuals with a weakened immune system, such as people with immuno-compromised status due to HIV/AIDS, leukaemia, cancer, kidney transplant and steroid therapy, are at greatest risk of severe listeriosis and should avoid high risk foods.
- High risk foods include deli meat and ready-to-eat meat products (such as cooked, cured and/or fermented meats and sausages), soft cheeses and cold smoked fishery products.
- Listeria monocytogenes are widely distributed in nature. They can be found in soil, water, vegetation and the faeces of some animals and can contaminate foods.
- Listeriosis is an infectious disease caused by the bacterium Listeria monocytogenes.
- Foodborne listeriosis is one of the most serious and severe foodborne diseases. It is caused by the bacteria *Listeria monocytogenes*. It is a relatively rare disease with 0.1 to 10 cases per 1 million people per year depending on the countries and regions of the world. Although the number of cases of listeriosis is small, the high rate of death associated with this infection makes it a significant public health concern.

Unlike many other common foodborne diseases...
causing bacteria, *L. monocytogenes* can survive and multiply at low temperatures usually found in refrigerators. Eating contaminated food with high numbers of *L. monocytogenes* is the main route of infection. Infection can also be transmitted between humans, notably from pregnant women to unborn babies.

*L. monocytogenes* are ubiquitous in nature and found in soil, water and animal digestive tracts. Vegetables may be contaminated through soil or the use of manure as fertilizer. Ready-to-eat food can also become contaminated during processing and the bacteria can multiply to dangerous levels during distribution and storage.

Food most often associated with listeriosis include:

- foods with a long shelf-life under refrigeration (*L. monocytogenes* can grow to significant numbers in food at refrigeration temperatures when given sufficient time); and
- foods that are consumed without further treatment, such as cooking, which would otherwise kill *L. monocytogenes*.

In past outbreaks, foods involved included ready-to-eat meat products, such as frankfurters, meat spread (paté), smoked salmon and fermented raw meat sausages, as well as dairy products (including soft cheeses, unpasteurized milk and ice cream) and prepared salads (including coleslaw and bean sprouts) as well as fresh vegetables and fruits.

### The disease

Listeriosis is a series of diseases caused by the bacteria *L. monocytogenes*, outbreaks of which occur in all countries. There are two main types of listeriosis: a non-invasive form and an invasive form.

Noninvasive listeriosis (febrile listerial gastroenteritis) is a mild form of the disease affecting mainly otherwise healthy people. Symptoms include diarrhoea, fever, headache and myalgia (muscle pain). The incubation period is short (a few days). Outbreaks of this disease have generally involved the ingestion of foods containing high doses of *L. monocytogenes*.

Invasive listeriosis is a more severe form of the disease and affects certain high risk groups of the population. These include pregnant women, patients undergoing treatment for cancer, AIDS and organ transplants, elderly people and infants. This form of disease is characterized by severe symptoms and a high mortality rate (20%–30%). The symptoms include fever, myalgia (muscle pain), septicemia, meningitis. The incubation period is usually one to two weeks but can vary between a few days and up to 90 days.

The initial diagnosis of listeriosis is made based on clinical symptoms and detection of the bacteria in a smear from blood, cerebrospinal fluid (CSF), meconium of newborns (or the fetus in abortion cases), as well as from faeces, vomitus, foods or animal feed. Various detection methods, including polymerase chain reaction (PCR), are available for diagnosis of listeriosis in humans. During pregnancy, blood and placenta cultures are the most reliable ways to discover if symptoms are due to listeriosis.

Pregnant women are about 20 times more likely to contract listeriosis than other healthy adults. It can result in miscarriage or stillbirth. Newborn may also have low birth weight, septicaemia and meningitis. People with HIV/AIDS are at least 300 times more likely to get ill than those with a normally functioning immune system.

Due to the long incubation period, it is challenging to identify the food which was the actual source of the infection.

### Treatment

Listeriosis can be treated if diagnosed early. Antibiotics are used to treat severe symptoms such as meningitis. When infection occurs during pregnancy, prompt administration of antibiotics prevents infection of the foetus or newborn.

### Control methods

The control of *L. monocytogenes* is required at all stages in the food chain and an integrated approach is needed to prevent the multiplication of this bacteria in the final food product. The challenges for controlling *L. monocytogenes* are considerable given its ubiquitous nature, high resistance to common preservative methods, such as the use of salt, smoke or acidic condition in the food, and its ability to survive and grow at refrigeration temperatures (around 5 °C). All sectors of the food chain should implement Good Hygienic Practices (GHP) and Good Manufacturing Practices (GMP) as well as implement a food safety management system based on the principles of Hazard Analysis Critical Control Points (HACCP).

- Guidelines on the application of general principles of food hygiene to the control of Listeria monocytogenes in ready-to-eat foods [PDF]

Food manufacturers should also test against microbiological criteria, as appropriate, when validating and verifying the correct functioning of their HACCP based procedures and other hygiene control measures. In addition, producers manufacturing food associated with risks of Listeria must conduct environmental monitoring to identify and eliminate niche environments, including areas that favor the establishment and proliferation of *L. monocytogenes*.

Modern technologies using genetic fingerprint - Whole Genome Sequencing (WGS) - allow for more rapid identification of the food source of listeriosis.
outbreaks by linking *L. monocytogenes* isolated from patients with those isolated from foods.

**Prevention**

*L. monocytogenes* in food are killed by pasteurization and cooking.

In general, guidance on the prevention of listeriosis is similar to guidance used to help prevent other foodborne illnesses. This includes practicing safe food handling and following the WHO Five Keys to Safer Food (1. Keep clean. 2. Separate raw and cooked. 3. Cook thoroughly. 4. Keep food at safe temperatures. 5. Use safe water and raw materials.)

- Poster: Five Keys to Safer Food
- Persons in high risk groups should:
  - Avoid consuming dairy products made of unpasteurized milk; deli meats and ready-to-eat meat products such as sausages, hams, patés and meat spreads, as well as cold-smoked seafood (such as smoked salmon);
  - Read and carefully follow the shelf life period and storage temperatures indicated on the product label.

It is important to respect the shelf-life and storage temperature written on labels of ready-to-eat foods to ensure that bacteria potentially present in these foods does not multiply to dangerously high numbers. Cooking before eating is another very effective way to kill the bacteria.

**WHO response**

WHO promotes the strengthening of food safety systems, good manufacturing practices and educating retailers and consumers on appropriate food handling and avoiding contamination. Educating consumers, especially those in high risk groups, and training of food handlers in safe food handling are among the most critical means to prevent foodborne illnesses including listeriosis.

WHO and FAO have published an international quantitative risk assessment of Listeria in ready-to-eat foods. This has formed the scientific basis for the Codex Alimentarius Commission Guidelines on the Application of General Principles of Food Hygiene to the Control of *Listeria Monocytogenes* in Foods. This guidance includes microbiological criteria (i.e. maximum limits for the presence of *L. monocytogenes* in foods).

WHO’s main tool to assist Member States in surveillance, coordination and response to outbreaks is the International Network of Food Safety Authorities (INFOSAN) which links national authorities in Member States in charge of managing food safety events. This network is managed jointly by WHO and FAO.

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**5. SCHIZOPHRENIA**

**KEY FACTS**

- Schizophrenia is a chronic and severe mental disorder affecting more than 21 million people worldwide.
- Schizophrenia is characterized by distortions in thinking, perception, emotions, language, sense of self and behaviour. Common experiences include hallucinations - hearing voices or seeing things that are not there and delusions – fixed, false beliefs.
- Worldwide, schizophrenia is associated with considerable disability and may affect educational and occupational performance.
- People with schizophrenia are 2-3 times more likely to die early than the general population. This is often due to preventable physical diseases, such as cardiovascular disease, metabolic disease and infections.
- Stigma, discrimination and violation of human rights of people with schizophrenia is common.
- Schizophrenia is treatable. Treatment with medicines and psychosocial support is effective.
- Facilitation of assisted living, supported housing and supported employment are effective management strategies for people with schizophrenia.

**Symptoms**

Schizophrenia is a psychosis, a type of mental illness characterized by distortions in thinking, perception, emotions, language, sense of self and behaviour. Common experiences include:

- Hallucination: hearing, seeing or feeling things that are not there.
- Delusion: fixed false beliefs or suspicions not shared by others in the person’s culture and that are firmly held even when there is evidence to the contrary.
- Abnormal Behaviour: disorganised behavior such as wandering aimlessly, mumbling or laughing to self, strange appearance, self-neglect or appearing unkempt
- Disorganised speech; incoherent or irrelevant speech
- Disturbances of emotions: marked apathy or disconnect between reported emotion and what is observed such as facial expression or body language

**Magnitude and impact**

Schizophrenia affects more than 23 million people worldwide but is not as common as many other mental disorders. It is more common among males (12 million), than females (9 million). Schizophrenia also commonly starts earlier among men.
Schizophrenia is associated with considerable disability and may affect educational and occupational performance.

People with schizophrenia are 2-3 times more likely to die early than the general population. This is often due to physical illnesses, such as cardiovascular, metabolic and infectious diseases.

Stigma, discrimination and violation of human rights of people with schizophrenia is common.

**Causes of schizophrenia**

Research has not identified one single factor. It is thought that an interaction between genes and a range of environmental factors may cause schizophrenia.

Psychosocial factors may also contribute to schizophrenia.

**Services**

More than 50% of people with schizophrenia are not receiving appropriate care. Ninety per cent of people with untreated schizophrenia live in low- and middle-income countries. Lack of access to mental health services is an important issue. Furthermore, people with schizophrenia are less likely to seek care than the general population.

**Management**

Schizophrenia is treatable. Treatment with medicines and psychosocial support is effective. However, the majority of people with chronic schizophrenia lack access to treatment.

There is clear evidence that old-style mental hospitals are not effective in providing the treatment that people with mental disorders need and violate basic human rights of persons with mental disorders. Efforts to transfer care from mental health institutions to the community need to be expanded and accelerated. The engagement of family members and the wider community in providing support is very important.

Programmes in several low- and middle-income countries (e.g. Ethiopia, Guinea-Bissau, India, Iran, Pakistan, Tanzania) have demonstrated the feasibility of providing care to people with severe mental illness through the primary health-care system by:

- training primary health-care personnel;
- providing access to essential drugs;
- supporting families in providing home care;
- educating the public to decrease stigma and discrimination;
- enhancing independent living skills through recovery-oriented psychosocial interventions (e.g., life skills training, social skills training) for people with schizophrenia and for their families and/or caregivers; and
- facilitating independent living, if possible or assisted living, supported housing and supported employment for people with schizophrenia. This can act as a base for people with schizophrenia to achieve recovery goals. People affected by schizophrenia often face difficulty in obtaining or retaining normal employment or housing opportunities.

**Human rights violations**

People with schizophrenia are prone to human rights violations both inside mental health institutions and in communities. Stigma of the disorder is high. This contributes to discrimination, which can in turn limit access to general health care, education, housing and employment.

**WHO response**

WHO’s Mental Health Gap Action Programme (mhGAP), launched in 2008, uses evidence-based technical guidance, tools and training packages to expand service in countries, especially in resource-poor settings. It focuses on a prioritized set of conditions, directing capacity building towards non-specialized health-care providers in an integrated approach that promotes mental health at all levels of care. Currently mhGAP is implemented in more than 100 Member States.

The WHO QualityRights Project involves improving the quality of care and human rights conditions in mental health and social care facilities and to empower organizations to advocate for the health of people with mental disorders.

WHO’s Mental Health Action Plan 2013-2020, endorsed by the World Health Assembly in 2013, highlights the steps required to provide appropriate services for people with mental disorders including schizophrenia. A key recommendation of the Action Plan is to shift services from institutions to the community.
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