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**IN THE NAME OF ALLAH,
THE MOST GRACIOUS,
THE MOST MERCIFUL**

Kingdom of Saudi Arabia
Ministry of Education
Majmaah University



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The Majmaah Journal of Health Sciences shall be an international peer reviewed journal, which intends to serve researchers through prompt publication of significant advances, and to provide a forum for the reporting and discussion of news and issues concerning health sciences.

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To lead the debate on health and to engage, inform, and stimulate the academicians, researchers, and other health professionals in ways that will improve outcomes for patients.

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Majmaah Journal of Health Sciences

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Editorial



From Editor's Desk.....

It's a great pleasure in reaching you through this eleventh issue of MJHS. It is a great privilege bestowed upon me to be the editor in chief of MJHS.

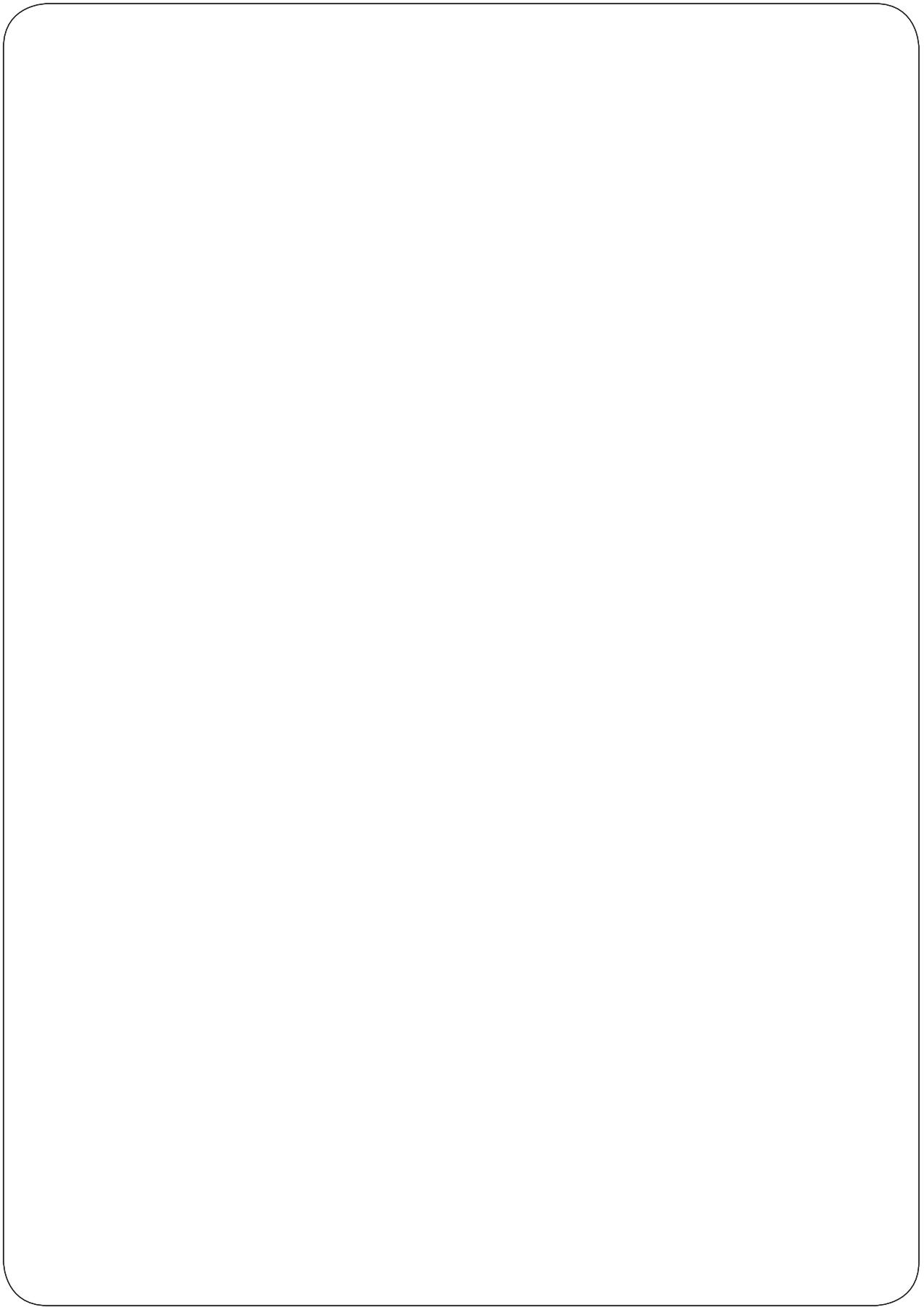
MJHS always strive to be the platform for students, faculties and researchers to exhibit their intellectual thinking and writing skills. Special efforts will be taken to include student research in every issue. I am very happy to inform that MJHS has got facilities for online submission and tracking system for articles through EJ manager. Facilities are made to submit articles through the MJHS site in our University website or directly through EJ manager web site. From Nov 2018 issue onwards, online submission of articles is made mandatory. MJHS is receiving more articles from scholars from other universities all over the Kingdom. Insha Allah expects soon to attract research articles from scholars all over the world.

MJHS had a remarkable journey of good standing of publications for the last five years, half yearly with ten issues to its credit. It is the policy decision to include 1 or 2 review article, 6-8 original researches and 1-2 case reports. From 2018 MJHS intend to publish three issues per year. Now with online submission facilities and a strong backup of peer reviewers, the goal is set to get more reputable indexing and establish an international standard.

We value your positive and negative feedback, which would help us improve.

Dr. Khalid Bin Mohamed Alabdulwahab

Editor in Chief



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Original article

Relationship Between Vitamin-D and Obesity in Pediatric Outpatients, at King Khalid General Hospital, Majmaah, Saudi Arabia

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Abstract:

Background: In many countries, overweight and obesity are becoming a serious threat to the health of the population. Several studies have found a strong independent relationship between vitamin D levels and several metabolic complications of obesity. However, it is still not known if vitamin D deficiency is directly responsible in the pathogenesis of these complications or just a secondary consequence of obesity. With an increasing number of research studies, it is evident that improvement of Vitamin D status could lead to good health outcomes especially related to obesity. **Aims:** This study sought to find any possible association between body mass index (BMI) and serum level of vitamin D in 6-13 year-old children attending the outpatient department (OPD) at King Khalid Hospital, Majmaah, KSA. **Settings and Design:** This cross-sectional observational study was done on 86 children who were 6 to 13 years old attending the OPD from March 2016 to February 2017. **Materials and Methods:** Anthropometric indices (weight, height and waist circumference) were assessed by using identical instruments. The hematological profile of all study participants was also evaluated for biochemical parameters such as fasting blood sugar, insulin, total cholesterol (LDL, HDL, triglycerides). **Results:** This study revealed a high prevalence (83.7%) of vitamin D deficiency and insufficiency, with 50 (58.1%) children with vitamin D levels in the deficiency range (<20 nmol/L), 22 (25.6%) in the insufficiency range (20-30 nmol/L), and only 14 (16.3%) with adequate, or sufficient, vitamin D levels (>30 nmol/L). There were significant differences in vitamin D deficiency between male and female children; with females more deficient in Vitamin D than males. Vitamin D levels and BMI status were not significant between the vitamin D level and BMI; although there was significant inverse correlation between waist circumference and vitamin D levels. **Conclusion:** Vitamin D deficiency is common in children, and is more prevalent in females as compared to males. There was a significant relationship between waist circumference and vitamin D. More exposure to sunlight and prescription Vitamin D pediatric supplements and/or food fortification is recommended.

Keywords: Obesity, BMI, vitamin D. Pediatrics.**المخلص:**

خلفية: في كثير من البلدان، أصبحت زيادة الوزن والبدانة تهديدا خطيرا لصحة الانسان. وقد وجدت العديد من الدراسات وجود علاقة مستقلة قوية بين مستويات فيتامين (د) وعدد من مضاعفات التمثيل الغذائي للبدانة. ومع ذلك، فإنه لا يزال غير معروف ما إذا كان نقص فيتامين (د) هو المسؤول مباشرة في التسبب في هذه المضاعفات أو مجرد نتيجة ثانوية من السمنة. أوضحت عدد من الدراسات البحثية أن تحسين حالة فيتامين (د) يمكن أن يؤدي إلى نتائج صحية جيدة تتعلق بالبدانة. الأهداف: هدفت هذه الدراسة إلى العثور على أي ارتباط ممكن بين مؤشر كتلة الجسم ومستوى فيتامين (د) في أمصال الأطفال الذين تتراوح أعمارهم ما بين 6-13 عاما، والذين يعادون قسم العيادات الخارجية في مستشفى الملك خالد، الجامعة، المملكة العربية السعودية. وقد تم إجراء هذه الدراسة الرصدية المستعرضة على 86 طفلا تتراوح أعمارهم بين 6 و 13 عاما في الفترة الزمنية من مارس 2016 إلى فبراير 2017. المواد والطرق: تم تقييم المؤشرات الأنتروبومترية (الوزن والطول ومحيط الخصر) باستخدام صكوك مماثلة. تم تقييم الشخصية الدموية لجميع المشاركين في الدراسة بالإضافة الي موسمات الكيمياء الحيوية مثل تركيز سكر الدم عند الصيام، الأنسولين، الكوليسترول الكلي (الدهون منخفضة الكثافة، الدهون مرتفعة الكثافة، الدهون الثلاثية). النتائج: كشفت هذه الدراسة ان 83,7% من الاطفال يعانون نقص وعدم كفاية فيتامين (د) وهذا يعتبر معدل انتشار مرتفع. مع وجود 50 (58,1%) من الأطفال يعانون نقص مستويات فيتامين (د) في نطاق اقل من 20 نانو مول / لتر، بينما 22 (25,6%) يعانون من عوز وقصور مستوي فيتامين (د) (20-30 نانو مول / لتر)، و فقط 14 (16,3%) كانوا ضمن المستوى الكافي والطبيعي لفيتامين (د) (أكثر من 30 نانو مول / لتر). وكان هناك نقص معنوية في مستويات فيتامين (د) للأطفال الإناث عند مقارنتهم بالذكور. بينما كانت العلاقة بين مستويات فيتامين (د) وحالة مؤشر كتلة الجسم غير معنوية. على الرغم من وجود علاقة عكسية كبيرة بين محيط الخصر ومستويات فيتامين (د). الاستنتاج: نقص فيتامين (د) شائع لدى الأطفال، وهو أكثر انتشارا في الإناث مقارنة بالذكور. كانت هناك علاقة كبيرة بين محيط الخصر وفيتامين (د). يوصى بزيادة التعرض لأشعة الشمس وتناول الأطفال لوصفات طبية تحتوي على كميات غذائية غنية بفيتامين (د).

الكلمات الرئيسية: السمنة، مؤشر كتلة الجسم، فيتامين (د)، الأطفال.

Background:

Childhood obesity affects both developed and developing countries of all socioeconomic groups, irrespective of age, sex or ethnicity. As per data from the International Obesity Task Force, at least 155 million school-age children worldwide are overweight or obese.^[1] The traditional Middle Eastern diet, characterized by high-fiber content and low in fatty acids, cholesterol and sodium, has changed to a “westernized” diet with high intake of energy-dense foods rich in fat, cholesterol, free sugars, and sodium, and low in dietary fiber.^[2] As such the Middle Eastern populations are at great risk of vitamin D deficiency due to a diet low in vitamin D and low sunshine exposure. Obesity is also a risk factor for vitamin D deficiency since vitamin D is sequestered in body fat.^[1] Vitamin D deficiency is pandemic, and has been implicated in a wide variety of disease states.^[3] Vitamin D deficiency is estimated to affect approximately 30-50% of people worldwide.^[4] Middle Eastern populations are known to be at risk of vitamin D deficiency due to a diet low in vitamin D and limited exposure to sunshine.^[5] It is established fact that vitamin D plays a significant role in the absorption of calcium and phosphorous. Recently, the focus has been on growing evidence of an association between vitamin D insufficiency and various chronic diseases, mainly cardiovascular disease. In the recent past, it was found that impaired glucose homeostasis is also associated with vitamin D deficiency and more common in overweight and obese children.^[6,7]

While the relationship between vitamin D status and obesity is well documented, there is confusion as to whether vitamin D deficiency has a direct effect on obesity or results as a consequence of obesity.^[8,9] This confusion is perpetuated by mixed results seen not only in human but also animal studies investigating the effectiveness of vitamin D supplementation to reduce body weight and adiposity^[10-12]. Therefore, this study was designed to determine the possible relationship between body mass index (BMI) and serum level of vitamin D in 6-13-year-old children attending the outpatient department (OPD) at King Khaled Hospital, Majmaah, Saudi Arabia. The current study is believed to be the first to examine the relationship between vitamin D and obesity among 6-13-year-old children.

Hypothesis:

Vitamin D will be lower in underweight and overweight/obese children. In overweight children, excess body fat may cause increased Vitamin D sequestration and result in low Vitamin D availability and, as a consequence, low serum 25(OH)D levels. BMI and waist circumference will show an inverse association with vitamin D that is Low serum 25(OH)D levels are associated to higher BMI.

Methods:**Ethical Principles**

Ethics committee approval was provided by the Majmaah University Scientific Committee. Self-designed questionnaires were completed after receiving a written informed consent from parents/guardians of participants. Addi-

tionally, verbal consent was received from all children who participated in the study.

Participants

Included in this study were 86 children (48 female and 38 male), aged 6-13 years, visiting the OPD of King Khaled Hospital. This was a cross-sectional study having quantitative variables. Exclusion criteria for both obese and normal weight children were 1) use of an anticonvulsant or systemic glucocorticoid, 2) use of a vitamin D supplement more than 400 IU/d, 3) hepatic disease, 4) renal disease, or malabsorptive disorder, 5) disorder of bone or calcium metabolism (including known vitamin D deficiency) and 6) obesity due to a genetic disorder.

Anthropometric parameters

Height was calculated on all respondents using a fixed stadiometer with a vertical backboard and a moveable headboard.^[13] Participant's weight was taken with a digital scale.^[13] BMI was calculated using the universal formula (weight in kilograms divided by height in meters squared). Waist circumference was measured in centimeters on all participants using a measuring tape using the standard World Health Organization (WHO) protocol midpoint between last floating rib and top of the iliac crest in midaxillary line.^[14] To reduce subjective error, all measurements were taken by one individual.

Biochemical parameters

Fasting venous blood sample was examined for fasting plasma glucose and lipid profile by auto analyzer with standard

kits. Plasma insulin was measured by radioimmunoassay (RIA), specific for human insulin and less than 0.2% cross-reactivity with human proinsulin and no cross reactivity with c-peptide or insulin-like growth factor. Vitamin D levels were determined by a chemiluminescence assay using the LIAISON 25-hydroxy vitamin D TOTAL assay (DiaSorin, Ltd.). The lower and upper detection limits are 10 nmol/L and 375 nmol/L, respectively.^[15] In-house testing estimated the assay coefficient of variation within runs as 3.2% to 8.5% and between runs as 6.9% to 12.7%.^[15] For quality control purposes, 10% of samples were run in duplicate. Vitamin D levels less than 20 nmol/L were grouped as a deficiency, levels between 20-30 nmol/L were grouped as inadequate and those ≥ 30 nmol/L were considered as sufficient.^[16]

Classification of BMI

Pediatric BMI is age and sex specific and uses growth curves for diagnosis.^[17] WHO growth curves are based on optimal growth conditions.^[14] Children whose BMI is $< 5\%$ is categorized under, those having BMI between 5% to 84.99% as normal weight, and those having BMI from 85 % to $< 95\%$ as overweight and $\geq 95\%$ as obese using the Centers for Disease Control and Prevention growth curves from the year 2000.^[18]

Statistical Analysis

Data were described as mean \pm standard deviation and percentage. Independent student's t-test was done to compare the two groups. A P-value of ≤ 0.05 was considered as statistically significant. Statistical Package for

Social Sciences (SPSS) 20.0 and MS Excel were used for the data analysis. SAS (Statistical Analysis Systems) software was used that considers bootstrap weights. To take account of the multiplicity of analysis, a conservative alpha level of <0.001 was defined as the threshold of statistical significance. To find the significance of study parameters on the categorical scale between two or more groups Chi-square/Fisher Exact test was used.

Results:

Baseline characteristics of both male and female children are represented in Table 1. The levels of vitamin D in females and males were 16.07 ± 6.71 and 19.63 ± 7.26 nmol/L, respectively. This difference was statistically significant ($p = 0.014$). Significant difference was also found in waist circumference, insulin level, total cholesterol and LDL between males and females.

Table 1. Baseline characteristics of study subjects by sex

Parameters	Female (n = 48) Mean±SD	Male (n = 38) Mean±SD	P value
Vitamin D	16.07±6.71	19.63±7.26	0.042*
BMI (kg/m ²)	23.63±12.82	19.78±7.80	0.314
WC (cm)	59.47±13.82	59.25±13.60	0.028*
FBS (mmol/L)	5.21±0.95	5.06±0.82	0.429
Insulin	45.37±31.51	120.27±51.83	0.008*
Cholesterol	165.32±21.48	184.78±34.80	0.049*
HDL (mmol/L)	52.06±11.08	50.75±13.27	0.803
LDL (mmol/L)	135.87±36.99	121.02±27.58	0.037*
TG (mmol/L)	108.06±44.99	131.46±50.81	0.748
SBP (mm Hg)	110.08±6.50	114.16±8.04	0.624
DBP (mm Hg)	74.67±6.61	78.32±12.96	0.913

Abbreviations: BMI, body mass index; WC, Waist circumference; FBS, Fasting blood sugar; HDL-C, high-density lipoprotein-cholesterol; TG, triglyceride; SBP, systolic blood pressure; DBP, diastolic blood pressure.

Table 2. Prevalence and intensity of vitamin D deficiency

Vitamin D Status*	Number	Percent (%)
Deficiency	50	58.1
Insufficiency	22	25.6
Sufficiency	14	16.3
Total	86	100

*Level of <20 nmol/L was considered as deficiency, 20-30 nmol/L as insufficiency, and ≥ 30 ng/mL as sufficiency.^[16]

In the selected sample of 86 children, most (83.7%) of them showed lack in the level of vitamin D. Vitamin D deficiency was observed in more than half of children (58.1%) and it was insufficient in one quarter of children (25.6%) (Table 2).

Table 3: Body mass indices categories*

Body Mass Index (kg/m ²)	Total N (%)	Male = 38 N (%)	Female = 48 N (%)
<5% (underweight)	8 (9.3)	4 (10.5)	4 (8.3)
5% to 84.99% (normal weight)	52 (60.5)	24 (63.2)	28 (58.3)
85% to <95% (overweight)	20 (23.3)	8 (21.1)	12 (25.0)
$\geq 95\%$ (obese)	6 (7.0)	2 (5.3%)	4 (8.3)

*As per Centers for Disease Control and Prevention growth curves from the year 2000. The majority of children (60.5%) had normal weight, one quarter (23.3%) were categorized as overweight; whereas a small percentage of children were underweight (9.3%) or obese (7%). BMI was not significantly correlated with vitamin D ($r = -0.114$, $p = 0.674$) (Table 3).

Significant inverse correlation was observed between waist circumference (WC) and vitamin D levels showing that as WC increases the level of vitamin D decreases and vice versa ($r = -0.519$, $p = 0.031$).

Discussion:

Lack of vitamin D could be a pathological condition for many diseases, mainly cardiovascular disease, cancer and autoimmune diseases.^[19-22] In contrast, sufficient vitamin D levels are beneficial to the cardiovascular system. So, a close monitoring vitamin D levels has been suggested to be protective to reduce cardiovascular disease and hypertension.

The present study of 86 children observed a lack of vitamin D 83.7% of cases. Cultural and religious practices and norms are the most common reasons why Middle Eastern.^[23,24] Because of these norms and practices, people in many countries such as India, Australia, Brazil and the Middle East have a high prevalence of vitamin D deficiency.^[25,26] There are several causes of vitamin D deficiency among women in the Gulf region, such as clothing style, lack of foods rich in vitamin D, lack of vitamin D supplements, multiparity and obesity.^[27]

Various methods are available for the measurement of vitamin D including liquid chromatography-tandem mass spectrometry, high performance liquid chromatography, radioimmunoassays (IDS and DIASORIN) and chemiluminescent assays (IDS, Advantage, LIASON).^[28] Methods are comparable across laboratories, using liquid chromatography-tandem mass spectrometry as a gold standard.^[29] However, a limitation of immunoassays is the inability to distinguish between vitamin D2 and D3.

This study showed deficient vitamin D levels in half of all subjects. In addition, there

was a significant difference between vitamin D levels in male and female children. Vitamin D deficiency was more prevalent in females. Insufficient studies show the difference between men and women in terms of vitamin D deficiency. Some studies considered vitamin D deficiency based on gender, but with no actual comparison between both genders in terms of vitamin deficiency and its risk factors.^[30] In this study, based on the WHO criteria for classification of obesity in children, the majority of children had normal weight, one quarter of children were categorized as overweight, and a small percentage of children were underweight or obese. Further, this study showed that BMI did not significantly correlate with vitamin D in either group. There is a well-established inverse association between body fat mass and serum 25(OH)D levels in both adults and children.^[31] The central dogma surrounding this inverse relationship is that circulating vitamin D, derived from both cutaneous and dietary sources, is sequestered by adipose tissue prior to hepatic hydroxylation and is therefore unavailable to be converted to 25(OH)D.^[3,9,32] Porcine studies have demonstrated upwards of 65% of vitamin D is stored in adipose tissue.^[32,33] In addition to lower circulating levels of 25(OH)D seen in cases of excess adiposity, Lee et al. noted a similar inverse relationship between BMI and vitamin D status in adults receiving daily vitamin D supplementation.^[6] These results were consistent with the findings of Heaney et al., who reported that obese individuals require approximately twice as

much vitamin D to produce the same rise in vitamin D status as lean individuals. The present study found the correlation between WC and vitamin D was significantly inverse.

BMI is used as an indicator of body fat accumulation, but BMI is not ideal because it does not differentiate fat tissue from other tissues, such as muscle mass. A further complexity is that in many studies BMI was calculated from self-reported height and weight. This may have introduced systematic bias.^[34,35] Central fat mass, central obesity or abdominal obesity can be measured by WC.^[36,37] Distribution of adipose tissue predicts obesity-related health risks, including type 2 diabetes, atherogenic dyslipidemia, hypertension and cardiovascular disease.^[38] Abdominal obesity is a component of metabolic syndrome, also called syndrome X.

Conclusion:

The present study supported previous findings from numerous Middle Eastern and international studies that revealed a high prevalence of vitamin D deficiency and insufficiency among Middle Eastern populations. The best predictors of vitamin D status seem to be WC relating to metabolic status. Currently, there is a paucity of well-designed, placebo-controlled clinical trials investigating how improving vitamin D status can impact some of these health outcomes. A large survey on a national scale, especially with good design and appropriate standardized methodology is needed to provide a clear picture of the situation in KSA.

Limitations of the study

A limitation of this study is that vitamin D deficiency and insufficiency was defined only by 25(OH)D levels. Further, there is no consensus defining an optimal status of vitamin D in children. In addition, the sample size was small although the study was conducted for a period of one year; and it was very difficult to get consent from parents for a blood sample. Since this study was conducted in a single center, its findings could not be generalized which is a potential limitation. Additionally, keeping in mind the sedentary lifestyle of children and the cultural influence of society, innovative approaches are required to engage children in outdoor activities.

Competing interests

The authors declare no conflicts of interest.

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Original article

Prevalence of Hypertriglyceridemia in Patients Attending Primary Health Care Centers in, Majmaah, Saudi Arabia

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Abstract

Background: Hypertriglyceridemia (HTG) is a characteristic of several metabolic disorders like dyslipidemias, diabetes mellitus and metabolic syndrome.

Objectives: The study aimed to determine the prevalence of HTG among adult patients attending Primary Health Care Centers in, Majmaah, Saudi Arabia and to determine its association with diabetes mellitus, obesity, physical activity and high-density lipoprotein (HDL).

Methods: The study was a descriptive cross-sectional. The participants were chosen from five primary health care centers in Majmaah, Saudi Arabia by systematic random sampling. The sample size was 353 participants. The data were collected by a structured and pre-tested questionnaire.

Results: The prevalence of HTG was 33.7%. There was a significant association between HTG and diabetes mellitus. The study showed a significant inverse association between HDL cholesterol and HTG, 46.8% of the participants had hypertriglyceridemia with low level of HDL. There was a significant association between hypertriglyceridemia and smoking, 22.9% of smokers had high level of Triglycerides.

Conclusion: The prevalence of HTG in patients attending Primary Health Care Centers in, Majmaah was high (33.7%).

Keywords: Hypertriglyceridemia, smoking, high density lipoprotein, diabetes mellitus, Majmaah, Saudi Arabia

المخلص:

خلفية: ترتفع الدهون الثلاثية في عدد من الامراض اهمها متلازمة الايض ومرض السكري وارتفاع الكوليسترول

تهدف هذه الدراسة لمعرفة مدى انتشار ارتفاع الدهون الثلاثية لدى مراجعي مراكز الرعاية الصحية الأولية بمحافظة المجمعة وتحديد العلاقة بين الدهون الثلاثية من جهة ومرض السكري والسمنة والنشاط البدني والدهون عالية الكثافة من جهة أخرى

منهجية الدراسة: هذه دراسة مقطعية أجريت في مدينة المجمعة بالمملكة العربية السعودية. تم حساب عينة البحث لتبلغ ثلاثمائة وثلاثة وخمسون. تم جمع البيانات عن طريق الاستبيان وقياس الوزن والطول لتحديد معدل كتلة الجسم كما تم قياس نسبة الدهون الثلاثية والدهون عالية الكثافة بالدم.

النتائج: معدل انتشار ارتفاع الدهون الثلاثية بين البالغين الذين يترددون على مركز الرعاية الأولية بمحافظة المجمعة هو 33.7%. وجدت الدراسة ان هناك علاقة بين الإصابة بمرض السكري وارتفاع الدهون الثلاثية. وجدت علاقة عكسية بين ارتفاع الدهون الثلاثية والكوليسترول عال الكثافة حيث أن 46% ممن لديهم ارتفاع في الدهون الثلاثية ينخفض لديهم الكوليسترول عال الكثافة. وجدت الدراسة أيضا ان أكثر من 22% من المدخنين لديهم ارتفاع في الدهون الثلاثية.

الخلاصة: خلصت الدراسة ان نسبة انتشار ارتفاع الدهون الثلاثية لدى مراجعي مراكز الرعاية الصحية الأولية بمحافظة المجمعة 33.7%.

Introduction

Hypertriglyceridemia (HTG) is defined as: “an increased level of plasma triglyceride above the ninety fifth percentile for age and sex”^[1-2]. It is referred to as an abnormal concentration of triglyceride in the blood according to the National Cholesterol Education Program Adult Treatment Panel (NCEP ATP III) guidelines. A normal triglyceride level is 150 mg/dL^[3]. HTG, which may be primary or secondary in nature, could occur by primary or secondary causes. The primary HTG is the result of genetic defects. Secondary HTG is caused by hypothyroidism, some medications, obesity and diabetes mellitus. HTG is associate with pancreatitis; up to 1 to 4% of acute pancreatitis is caused by HTG^[4].

HTG is a characteristic of several metabolic disorders together with dyslipidemias, diabetes mellitus and metabolic syndrome, it is also a general risk for cardiovascular disorders (CVD) and increasingly important in the setting of current insulin resistance and obesity epidemics^[5]. Postprandial hypertriglyceridemia can be crucial element for causing atherosclerosis^[5]. Meta-analyses of hundreds of sufferers observed up for more than 10 years confirmed that a triglyceride elevation of 1 mmol/L increased threat of cardiovascular sickness by means of 32% in men and 76% in women^[6]. This is because hypertriglyceridemia is suggested to lower the serum degree of excessive-density lipoprotein (HDL), at the same time as it will increase the remnant lipoproteins and small dense LDL (low density lipoprotein), these could result in throm-

bogenesis and promote atherosclerosis^[7].

Hypertriglyceridemia is the most common lipid abnormalities among patients with chronic kidney disease(CKD). The concentration of triglyceride-lipoproteins begins to rise in early stages of CKD despite normal level of creatinine^[8, 9]. HTG prevalence varies in different population, surveys conducted in the United States of America (USA) showed a prevalence of HTG as 33% and 30% respectively^[10 - 12].

According to national health survey conducted in Saudi Arabia in 2008 to study coronary artery disease risk factors found HTG constituted 40.3%^[13]. A study done in KSA found that HTG as a risk factor for coronary artery diseases was 49.6% and 65.4% in AL Qassim and Riyadh respectively. Another study found 39% among those patients^[14,15]. Significant association between diabetes mellitus (DM) and HTG was shown in a study done in KSA^[16]. According to an epidemiological study in KSA, serum triglyceride was higher among male obese patients^[17]. The current study aimed to determine the prevalence of HTG among patients attending Primary Health Care Centers in, Majmaah, Saudi Arabia and to study the association of HTG with diabetes mellitus, obesity, physical activity and high-density lipoprotein (HDL).

Materials and methods

This study is a descriptive cross-sectional, to determine the prevalence of HTG in patients attending Primary Health Care Centers in Majmaah, Saudi Arabia. Five primary health centers (Al Majmaah, Hai Al-

matar, Alfaiha, Al Yarmok and Alfaisalya) were chosen randomly for the study. The Study population was male and female Saudi adults, between 20-70 years of age attending the selected primary health care Centers in Majmaah. The participants were chosen from the selected primary health care centers by systematic random sampling. The sample size was calculated as 353. The data were collected by a pre-tested questionnaire. A written informed consent was obtained from each respondent after obtaining the ethics approval.

The height and weight were measured to calculate the body mass index according to the formula $\{BMI = \text{weight (kg)}/\text{height (m)}^2\}$. The subject is considered overweight if it was between 25 to 29.9 and obese it was above 30. The serum triglyceride and HDL level were measured in the laboratory of King Khalid Hospital, Majmaah. The reference range for HTG is considered high if the serum triglyceride level is above 150 mg/dl (> 1.7 mmol/l).

The data were analyzed using SPSS 22.0. Mean \pm SD was given for quantitative variables. Frequencies and percentages were done for qualitative variables. Pearson Chi-Square was applied to determine the associations between qualitative variables. A p-value of <0.05 was considered as statistically significant.

Results:

A total of 353 participants (46.5%) were males and (53.5%) were females, aged between 20-70 years, most of them (57.2%) were between 40-59 years of age as shown in table 1. Most of the participants (62.9%) were obese

and 24.4% had history of dyslipidemia. The prevalence of HTG was 33.7%. Forty-six (41.4%) of participants who had high HTG had low level of HDL ($P < 0.001$). The study showed that there is a significant association between HTG and diabetes mellitus ($P=0.001$). Most participants with high TG had a long duration of tobacco smoking ($p < 0.001$). The results showed no significant association between HTG and physical activity ($p=.942$). The results showed that 34.3% of participants with HTG consume fatty food and 33.8% were obese.

Table 1: Socio – demographic characteristics of patients

	n (%)		n (%)
PHC's		Monthly Income	
Alfasaliya	66 (18.7)	< 5000	165 (46.7)
Alfiha	25 (7.10)	5000 - 10,000	100 (28.3)
Alyarmook	67 (19.0)	10,001 - 15,000	80 (22.7)
Almajmaah	94 (26.6)	> 15,000	08 (2.30)
Almataar	101 (28.6)		
Age/ years		Occupation	
20 – 29	55 (15.6)	Government employee	121 (34.3)
30 – 39	54 (15.3)	Private employee	12 (12.4)
40 – 49	102 (28.9)	Business	10 (2.80)
50 – 59	100 (28.3)	Military	07 (2.00)
60 – 69	24 (6.80)	House wife	148 (41.9)
≥ 70	18 (5.10)	Student	29 (8.20)
		Others	26 (7.40)
Gender		Regular physical activity	
Male	164 (46.5)	Yes	90 (25.5)
Female	189 (53.5)	No	263 (74.5)
Education Level		Marital Status	
Illiterate	93 (26.3)	Single	48 (13.6)
Primary	64 (18.1)	Married	273 (77.3)
Intermediate	53 (15.0)	Divorced	09 (2.50)
Secondary	56 (15.9)	Widow	23 (6.5)
University and Above	87 (24.6)		

Table 2: Risk Factors

Variables	n = 353	Percent
Smoking		
Yes	35	9.9
No	318	90.1
Diabetes		
Yes	122	34.6
No	231	65.4
Hypertension		
Yes	72	20.4
No	281	79.6
Dyslipidemia		
Yes	85	24.1
No	268	75.9
Coronary Artery Disease		
Yes	12	3.4
No	341	96.6
Metabolic Syndrome		
Yes	157	55.5
No	196	44.5

Table 3: Lipid Profile of patients

	n (%)		n (%)
BMI		Monthly Income	
Underweight	09 (2.50)	< 5000	165 (46.7)
Normal	44 (12.5)	5000 - 10,000	100 (28.3)
Over weight	78 (22.1)	10,001 - 15,000	80 (22.7)
Obese	222 (62.9)	> 15,000	08 (2.30)
LDL		Triglycerides	
Optimal	109 (30.9)	Desirable	162 (45.9)
Near optimal	105 (29.7)	Borderline high	72 (20.4)
Borderline	59 (16.7)	High	81 (22.9)
high			38 (10.8)
High	21 (5.9)	Very high	
Very high	59 (16.7)		
Cholesterol		HDL	
Desirable	315 (89.2)	Low	111 (31.4)
High	38 (10.8)	Average	160 (45.3)
		High	82 (23.2)

Discussion

The increasing prevalence of dyslipidemia has emerged as a global public health problem, and the prevalence varies extensively according to the ethnic traits, socioeconomic status and cultural characteristics. In our study, the reported prevalence of HTG (≥ 150 mg/dl) was 33.7%. This prevalence shows that the prevalence of hypertriglyceridemia in patients attending Primary Health Care Centers in Majmaah, Saudi Arabia is high comparing to international studies, but lower relative to most other local studies. The corresponding figure is 40.3% in Saudi Arabia [18-19]. This may be due to different life style and socioeconomic status in this city. In USA the prevalence is around 25% [20]. In Asia, the prevalence of HTG is reported to be 26.35% in Taiwanese aged 40-65 years of age and 29.3% in Malaysia [21,22]. Report from the Middle Eastern countries vary: 41.6% in Iraq, 35.3% in Lebanon, 30.4% in Turkey and 20.7% in Oman [23-26].

In our research, the gender -adjusted occurrence of HTG was higher for male (54.3%) than for female (45.7%), which may be related to the differences in the body mass index. Our results became in conformity with different studies, which additionally confirmed the prevalence of HTG is more in diabetic and smoker participants and inversely associated with HDL. Furthermore, a significant influence of these risk factors for coronary heart disease showed how importance the detection of HTG. This finding indicated that effective screen-

ing program for blood lipid levels should be implemented effectively in high risk group. Although our study shows no significant relation between physical activity and HTG, it is still important to encourage the physical activity as it shows positive effect in cardiovascular risk prevention [27]. The study recommends an urgent need for health educations program for promoting awareness of health care providers and public about HTG and to implement an appropriate community-based prevention strategy emphasizing the risks of HTG with behavioral changes, especially promoting physical activity

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Original Article:

Prevalence of Brucellosis in Hawtat Sudair City, Riyadh Province, Saudi Arabia

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Abstract

Background: Brucellosis is a zoonotic disease caused by the bacterium known as Brucella. Consumption of unpasteurized dairy products, inhalation of aerosol carrying the bacteria and occupational contact with infected livestock are the main causes of infection. This paper discusses the brucellosis prevalence among patients visiting the Howtat Sudair General Hospital during the period from December 2012 to January 2017.

Methods: The data of samples tested serologically for Brucella spp. infection were collected from the microbiology laboratory at Hawtat Sudair General Hospital, Riyadh, Saudi Arabia and analyzed statistically looking at socio-demographic (i.e. age) in relation to cases of brucellosis.

Results: 1286 samples tested for Brucella spp. (*B. melitensis* and *B. abortus*), 489 (38.03%) samples were positive for Brucella spp. with various age groups having different levels of infected cases. The majority of cases were in the age group from 30 to < 50 years with less cases in the younger age groups <18 and from 18 to < 30 years. We found more cases of *B. abortus* infection compared to *B. melitensis* infection with 88.1% of the samples were positive for both *B. melitensis* and *B. abortus*.

Conclusion: The study confirms that brucellosis is still endemic in Hawtat Sudair city, Riyadh, Saudi Arabia.

Keywords: Brucella spp., brucellosis, zoonotic, prevalence, Hawtat Sudair city.

المخلص:

الخلفية: الحمى المالطية هي مرض يصيب الحيوان تسببه البكتيريا المعروفة باسم البروسيلا. ويعد استهلاك منتجات الألبان غير المبسترة واستنشاق الهواء الجوي الذي يحمل البكتيريا بالإضافة الي الاتصال المهني مع الماشية المصابة من الأسباب الرئيسية للعدوى. تناقش هذه الورقة انتشار الحمى المالطية بين المرضى الذين يعاودون مستشفى حوطة سدبير العام خلال الفترة من ديسمبر ٢٠١٢ إلى يناير ٢٠١٧.

الطريقة: تم جمع عينات الدراسة من مختبر الاحياء الدقيقة في مستشفى حوطة سدبير العام، الرياض، المملكة العربية السعودية. تم جمع البيانات من عينات اختبرت سيروولوجيا للتحقق من الاصابة بعدوي البروسيلا. كما تم تحليل البيانات إحصائيا للنظر في العلاقة الديموغرافية الاجتماعية (العمر) والاصابة بداء البروسيلا.

النتائج: تم اختبار ١٢٨٦ عينة لوعين من البروسيلا (بروسيلا ملينتسيس وبروسيلا أبورتوس)، كانت ٤٨٩ (٣٨,٠٣٪) من العينات بمختلف الفئات العمرية لديها ايجابية البروسيلا بمستويات مختلفة من حالات الاصابة. وكانت غالبية الحالات في الفئة العمرية من ٣٠ إلى ٥٠ سنة مع حالات أقل في الفئات العمرية الأصغر سنا من ١٨ سنة، ومن ١٨ إلى أقل من ٣٠ سنة. وجدنا المزيد من حالات عدوى البروسيلا أبورتوس بالمقارنة مع عدوى البروسيلا ملينتسيس مع ٨٨,١٪ من العينات كانت ايجابية لكل من البروسيلا ملينتسيس والبروسيلا أبورتوس.

الخلاصة: تؤكد الدراسة أن الحمى المالطية مازالت مستوطنة في مدينة حوطة سدبير، الرياض، المملكة العربية السعودية.

الكلمات الرئيسية: بروسيلا، الحمى المالطية، الحيوانية المنشأ، انتشار، مدينة حوطة سدبير.

Introduction

Brucellosis is one of the most important worldwide zoonotic bacterial infection affecting livestock and humans [1,2]. It is caused by the Gram-negative facultative intracellular bacterium of the genus *Brucella*. The four important species of *Brucella* that are pathogenic to humans are *Brucella melitensis*; found primarily in goats, sheep and camels; *Brucella abortus* found in cows; *Brucella suis* found in pigs; and *Brucella canis* found in dogs [3,4]. For humans, *Brucella melitensis* is the most pathogenic and invasive among the different *Brucella* spp., followed by *Brucella suis*, *Brucella abortus*, and *Brucella canis* [5].

Brucellosis remains an important public health concern in many parts of the world [6,7]. The bacterial transmission to humans occurs by the ingestion of raw or unpasteurized milk and other dairy products, direct contact with infected animal tissues, or the accidental inhalation, ingestion or injection of *Brucella* [8,9].

Humans infected with *Brucella* spp. may develop various symptoms including irregular fever, profound sweating, fatigue, anemia, depression and headache [10,11]. The most common diagnostic method for the identification of *Brucella* spp. infection is the serological screening method (i.e. the serum agglutination test; SAT). However, this needs further confirmation by the isolation of the bacteria from the blood. Other diagnostic approaches include the indirect fluorescence antibody assay (IFA), the anti-human globulin test and the enzyme-linked immunosorbent assay (ELISA) [11,12].

Brucellosis causes more than 500,000 human infections annually worldwide [13]. Although, brucellosis has a limited geographic distribution, it remains endemic causing major public health problems in areas such as western Asia, the Mediterranean region, Africa and Latin America [2,13]. The majority of developed countries were successful in implementing disease eradication protocols. However, brucellosis remains a health concern, as there is no human vaccination available yet and the difficulty of controlling the huge number of livestock importation between countries [14,15]. In Saudi Arabia, different regions have different prevalence of brucellosis, with values of about 8% had been reported [16]. Brucellosis in Saudi Arabia is highly endemic, with an estimated incidence of 5.4 per 1000 per year was reported [9]. In addition, Memish and Mah (2001) reported that there is an annual estimation of more than 8000 cases of brucellosis reported by the Saudi Arabian Ministry of Health. The majority of incidence found in the Riyadh province and the area around it. These areas are famous for farms owners where they keep and raise livestock animals such as camels, goats, and cows. Furthermore, it is a very strong part of the people tradition in these areas to consume the animal milk and dairy products raw or unpasteurized, which makes the persistent of the disease in such areas [3,17,18].

In Saudi Arabia, there is a lack of prevalence data on brucellosis for most provinces. Therefore, this study will assess the disease prevalence in Hawtat Sudair city,

northern part of Riyadh province. In this study, an estimate of the prevalence of human brucellosis in Hawtat Sudair city from samples tested for Brucella infection in Hawtat Sudair General Hospital (HSGH) is reported.

Methods:

Data collection

This study was carried out in HSGH, Hawtat Sudair city, Riyadh, Saudi Arabia. Data were collected from the logbook of the hospital's microbiology laboratory covering the period from December 2012 to January 2017. Data collected are serological testing of the Brucella spp. (*B. melitensis* and *B. abortus*) using the tube agglutination test from Crescent Diagnostics (Febrile antigens used were; FB850-10 *B. melitensis* and FB850-9 *B. abortus*). According to the manufacture instructions, titers $\geq 1/180$ indicate infection. In addition, socio-demographic data (i.e. age) of the patients were obtained from laboratory logbook.

Statistical analysis

Descriptive statistics were used to estimate the prevalence of brucellosis screening and demographic characteristics. Frequencies and cross-tabulations were used by Chi-square and Spearman Correlation tests were also used to assess these relationships. Statistical significance was evaluated at $\alpha = 0.05$ (see supplementary data). Statistical percentages were calculated and schematically presented using the Microsoft excel program.

Results:

In this study a total number of 1286 samples tested for Brucella spp. (*B. melitensis* and *B. abortus*) were collected including

204 (15.86%) samples in the age group <18, 246 (19.13%) samples in the age group from 18 to < 30, 535 (41.6%) samples in the age group from 30 to < 50, 297 (23.09%) samples in the age group from 50 to < 90 and 4 (0.31%) sample in the age group >90 (Table 1). Table 1. Samples represented as age groups and the total number of the negative and positive tests with their percentages.

Parameters		Frequency	Percentage
Age	< 18	204	15.86%
	From 18 to < 30	246	19.13%
	From 30 to < 50	535	41.60%
	From 50 to < 90	297	23.09%
	> 90	4	0.31%
<i>B. melitensis</i>	Negative	1049	81.57%
	Positive	237	18.43%
<i>B. abortus</i>	Negative	1034	80.40%
	Positive	252	19.60%

Out of 1286 samples tested for Brucella spp. (*B. melitensis* and *B. abortus*), 489 (38.03%) samples were positive for Brucella spp.; 237 (18.43%) were positive for *B. melitensis* and 252 (19.6%) were positive for *B. abortus* (Table 1).

Out of the 237 *B. melitensis* positive cases, 48 samples (3.73%) were in the age group less than 18 years, 49 samples (3.81%) were in the age group 18 to <30 years, 96 samples (7.47%) were in the age group 30 to <50 years, 44 samples (3.42%) were in the age group 50 to <90 years (Table 2 and Fig 1).

Table 2. Samples tested for *B. melitensis* represented as age groups showing the numbers of the negative and positive tests with their percentages.

Parameters	<i>B. melitensis</i>	
	Negative	Positive
< 18	156 (12.13%)	48 (3.73%)
From 18 to < 30	197 (15.32%)	49 (3.81%)
From 30 to < 50	439 (34.14%)	96 (7.47%)
From 50 to < 90	253 (19.67%)	44 (3.42%)
> 90	4 (0.31%)	0 (0.00%)
Total	1049 (81.57%)	237 (18.43%)

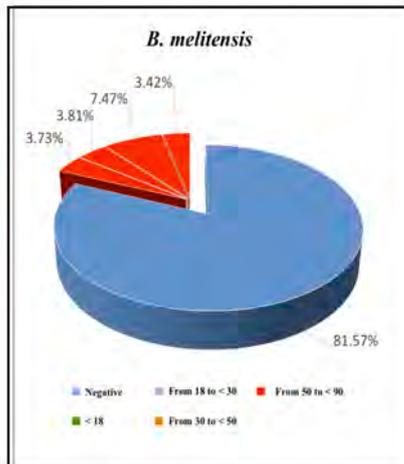


Fig 1. Samples tested for *B. melitensis* represented as age groups showing the percentages of the negative and positive tests in a schematic diagram.

Out of the 252 *B. abortus* positive cases, 43 samples (3.34%) were in the age group less than 18 years, 54 samples (4.20%) were in the age group 18 to <30 years, 104

samples (8.09%) were in the age group 30 to <50 years, 51 samples (3.97%) were in the age group 50 to <90 years (Table 3 and Fig 2). Table 3. Samples tested for *B. abortus* represented as age groups showing the numbers of the negative and positive tests with their percentages.

Parameters	<i>B. abortus</i>	
	Negative	Positive
< 18	161 (12.52%)	43 (3.34%)
From 18 to < 30	192 (14.93%)	54 (4.20%)
From 30 to < 50	431 (33.51%)	104 (8.09%)
From 50 to < 90	246 (19.13%)	51 (3.97%)
> 90	4 (0.31%)	0 (0.00%)
Total	1034 (80.40%)	252 (19.60%)

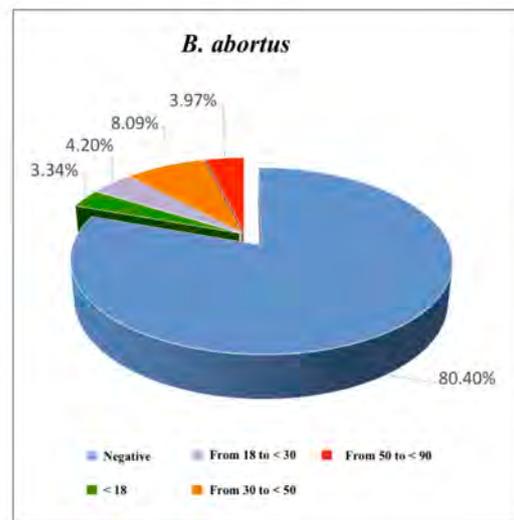


Fig 2. Samples tested for *B. abortus* represented as age groups showing the percentages of the negative and positive tests in a schematic diagram.

Table 4 shows that out of the 1286

samples tested for *Brucella* spp. (*B. melitensis* and *B. abortus*), 222 (88.1%) samples were positive for both *B. melitensis* and *B. abortus*. In the age group less than 18 years, 3.2% (41 samples) were positive for both *B. melitensis* and *B. abortus*. In the age group 18 to <30 years, 3.7% (47 samples) were positive for *B. melitensis* and *B. abortus*. In the age group 30 to <50 years, 7.1% (91 samples) were positive for both *B. melitensis* and *B. abortus*. In the age group 50 to <90 years, 3.3% (43 samples) were positive for both *B. melitensis* and *B. abortus*.

Table 4. Frequencies and percentages of single-strain infection and double-strain infection represented in age groups.

Parameters			B. melitensis	
			Negative	Positive
< 18	B. abortus	Negative	154 (12.0%)	7 (.5%)
		Positive	2 (.2%)	41 (3.2%)
From 18 to < 30		Negative	190 (14.8%)	2 (.2%)
		Positive	7 (.5%)	47 (3.7%)
From 30 to < 50		Negative	426 (33.1%)	5 (.4%)
		Positive	13 (1.0%)	91 (7.1%)
From 50 to < 90		Negative	245 (19.1%)	1 (.1%)
		Positive	8 (.6%)	43 (3.3%)
> 90		Negative	4 (.3%)	0 (.0%)
Total		B. abortus	Negative	1019 (98.5%)
	Positive		30 (11.9%)	222 (88.1%)

Discussion

This study is one of the first studies discussing the prevalence of brucellosis in Hawtat Sudair city. Hawtat Sudair city is part of the northern Riyadh province in Saudi Arabia covering an area of 700 km² with a total population of 28,954. It is based at the side of a very important international road linking Saudi Arabia to the northern provinces and countries. The city has only one governmental hospital, which is Hawtat Sudair General Hospital (HSGH). In this study, data of 1286 samples tested for *Brucella* spp. (*B. melitensis* and *B. abortus*) collected from the HSGH microbiology laboratory during the period from December 2102 to January 2017 was analyzed. Results reveal that overall preva-

lence of brucellosis in Hawtat Sudair city is 38.03% from the overall samples for *Brucella* spp. (*B. melitensis* and *B. abortus*) in HSGH during the period from December 2012 to January 2017. Although Saudi Arabia had implemented compulsory regulations for animal vaccination against *Brucella* infection, brucellosis still remains endemic in many areas in Saudi Arabia [9,14-15,19-20]. This is more likely to be caused by the lifestyle of many populations around Saudi Arabia where a combination of modern and traditional lifestyle is an integral part of the peoples' life [19]. Hawtat Sudair city is considered a rural area compared to big modernized cities like Riyadh in the Riyadh province, Saudi Arabia [9,14-15,19]. A huge number of families in Hawtat Sudair city tend to own their farms and barns where they keep animals such as sheep, cows and camels. Actually, it is a part of an important tradition to have such farms. People in these areas tend to consume unpasteurized animal milk directly from the female and use fewer precautions when slaughtering their animals for meat consumption. These practices are the main sources for *Brucella* infection infecting local families and farmers. In addition, brucellosis is considered as an occupational disease and the most common zoonotic disease that infect laboratory workers [21]. Therefore, it is likely that some of the cases we have may include laboratory workers in the hospital in addition to families, farmers, and travelers. In this study, most cases were in the age group of 30 to < 50 years. Several recent studies showed the prevalence of brucellosis in dif-

ferent regions in Saudi Arabia having similar age group [9,15,19]. These studies also confirmed that younger aged cases have lower incidence of brucellosis, which is consistent with observations made in neighboring countries such as Kuwait, Lebanon, Iran and Jordan [22,23]. These data are consistent with our study where we showed that cases having an age <30 years are less infected compared to ages 30 to < 50 years (Table 2 and 3, and Fig 1 and 2). This is most likely because people are coming into contact with infected animals (i.e. livestock) more often when they become adults. Moreover, according to several studies conducted in Saudi Arabia, males have higher cases of brucellosis compared to females [9,15,19]. Males are more likely to come into contact with infected livestock. This is because males in Saudi Arabia go out more, travel more, work in farms more compared to females, which makes them more vulnerable to infection especially when drinking unpasteurized milk.

In contrast, a study by Ageely (2016) reported that *B. melitensis* remains the principle cause of human brucellosis, with less frequent infections by *B. abortus* in Saudi Arabia, our study suggests that *B. abortus* have higher positive cases (30 cases; a single-strain infection) compared to *B. melitensis* (15 cases; as single-strain infection) (Table 4). In addition, our study found that there are more cases with double-strains infection (*B. melitensis* and *B. abortus*) compared to single strain infection in all age groups (Table 4). This is may be because of the lower specificity of the agglutination test. Therefore, a more specific and

sensitive molecular diagnostic test could be used to confirm these results such as PCR.

Conclusion

This study is one of the first studies discussing the prevalence of brucellosis in Hawtat Sudair city, Riyadh, Saudi Arabia. The results confirm the endemicity of brucellosis in the region. However, we do not think this study gives a clear estimation of the prevalence of brucellosis in a broader area such as the north part of Riyadh province. Future studies need to cover more hospitals in different cities in Riyadh province. More studies are needed to get detailed socio-demographic data for the brucellosis prevalence among families, farmers, travelers and laboratory workers. We recommend HSGH to improve their data records to cover more details about their patients and visitors for future statistical analysis. In addition, more rigorous regulations are needed for livestock vaccination and importation protocols. Health sectors in Saudi Arabia need to perform public awareness campaign to educate the community on how to deal with livestock to reduce the risks of infection. Furthermore, researchers need to get motivated to perform broader studies about the epidemiology, molecular pathogenicity, and molecular diagnostics and vaccination to eradicate the *Brucella* infection in the country.

Acknowledgement

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Conflict of interest statement

There is no conflict of interest to be declared.

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Original Article:

Long-Term Safety and Efficacy of Corneal Cross-Linking in thin Corneas with Keratoconus

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Abstract

Objective: To evaluate the long-term safety and efficacy of corneal cross-linking in keratoconus patients with thin corneas.

Methods: Forty eyes of 25 subjects having progressive keratoconus with thinnest corneal thickness (TCT) less than 400 μm were evaluated. Uncorrected distance visual acuity (UDVA), corrected distance visual acuity (CDVA), corneal topography, and endothelial cell loss were assessed at baseline and followed at six-month interval till the end of 1st year of follow up and then yearly till the fifth year, de-epithelization of cornea was performed, followed by ultrasound pachymetry to measure TCT. Hypoosmolar riboflavin (0.1%) solution was applied after every 2 minutes for 25 minutes. Ultraviolet A (UVA) irradiation was performed for 30 minutes along with riboflavin for every 2 minutes.

Results: Mean TCT was $381.5 \pm 13.2 \mu\text{m}$ (range: 344–396 μm) without corneal epithelium. Following hypotonic riboflavin instillation, mean TCT increased by $97.8 \pm 12.1 \mu\text{m}$ (range: 83–112 μm) for a mean thickness of $478.1 \pm 14.9 \mu\text{m}$ (range: 409–506 μm). The average follow-up period was 61.79 ± 6.19 months (range: 42–68 months). Corrected distance visual acuity, pachymetry values and posterior elevation showed no significant difference before and after CXL at 5 years follow-up. Corneal astigmatism and maximum keratometry reading (Kmax) were significantly reduced. Mean reduction of endothelial cell count was 1.5% at the last follow-up visit.

Conclusions: CXL with UVA and hypoosmolar riboflavin was effective in stabilizing keratoconus progression in patients with thin corneas however further studies are required to confirm our results.

Keywords: corneal cross-linking, keratoconus, riboflavin, thin cornea

المخلص

الهدف: تقييم سلامة وفعالية عملية تصليب القرنية المخروطية ذات الترقق على المدى الطويل.

منهجية الدراسة: تم تقييم أربعين عينا من ٢٥ شخصا والذين يعانون من القرنية المخروطية التقدمية حيث كانت أنحف ثخن قرنوي أقل من ٤٠٠ ميكرون. تم تقييم حدة البصر البعيد غير المصحح وكذلك حدة البصر البعيد المصحح وتضاريس القرنية وفقدان الخلايا البطانية في الزيارة الأولى وتلا ذلك في فترة ستة أشهر من المتابعة حتى نهاية السنة الأولى ومن ثم سنويا حتى السنة الخامسة، تم إزالة ظهارة القرنية، تلاها قياس الموجات فوق الصوتية لقياس الثخن القرنوي. تم استخدام قطرات ريبوفلافين ناقص التوتر (٠,١٪) بعد كل دقيقتين لمدة ٢٥ دقيقة ثم التشبيح بواسطة الأشعة فوق البنفسجية A لمدة ٣٠ دقيقة مع استخدام الريبوفلافين كل دقيقتين.

النتائج: كان متوسط أنحف ثخن قرنوي 381.5 ± 13.2 ميكرون (المدى: ٣٩٦-٣٤٤ ميكرون) دون ظهارة القرنية. بعد تقطير ريبوفلافين ناقص التوتر، كان هناك زيادة في الثخن القرنوي بمقدار 97.8 ± 12.1 ميكرون (المدى: ٨٣-١١٢ ميكرون) لمتوسط الثخن القرنوي 478.1 ± 14.9 ميكرون (المدى: ٤٠٩-٥٠٦ ميكرون). وكان متوسط فترة المتابعة 61.79 ± 6.19 شهرا (المدى: ٤٢-٦٨ شهرا). لم يظهر اي فرق كبير قبل وبعد تصليب القرنية لكل من حدة البصر المصحح، الثخن القرنوي والارتفاع الخلفي بعد ٥ سنوات من المتابعة. تم تقليل اللابورية قرنوية المنشأ وكذلك تقوس القرنية بشكل ملحوظ. وكان متوسط انخفاض عدد الخلايا البطانية 1.5% في آخر زيارة متابعة.

الخلاصة: تصليب القرنية بواسطة ريبوفلافين ناقص التوتر كان فعالا في تحقيق استقرار القرنية المخروطية في المرضى الذين يعانون من ترقق قرنوي ولكن هناك حاجة إلى مزيد من الدراسات لتأكيد نتائجنا.

كلمات مفتاحية: تصليب القرنية، القرنية المخروطية، الريبوفلافين، ترقق القرنية

INTRODUCTION

Keratoconus is a common bilateral, non-inflammatory, degenerative disorder of the cornea with an incidence of 1 in 2000 individuals in the general population.¹ The characteristic feature of this disease is progressive thinning and ectasia of the cornea² leading to corneal steepening, irregular astigmatism and reduction in visual acuity.³ Onset of keratoconus occurs typically at puberty, then progresses for next 10 to 20 years and finally tends to stabilize.³ Disease symptoms are highly variable depending on the severity and have no well-described signs at the early stage, whereas, in advanced stages, the vision undergoes significant distortion along with visual loss, severe pain, and corneal scarring.¹ The molecular mechanisms governing the pathogenesis of the disease is not yet clear. However, it seems that keratoconus is the eventual manifestation for several conditions, such as reduced number of collagen cross-links leading to decreased biomechanical stability, higher pepsin digestion than in normal corneas, slippage of collagen lamellae, and the loss of normal interwoven lamellar structure.⁵

Fortunately, the conventional treatment options for keratoconus which include, use of rigid contact lens, intracorneal ring segment implantation for early to moderate stages and lamellar keratoplasty or corneal transplantation for advanced stages have been encouraging⁶ since, they only improve the visual acuity, but cannot arrest disease progression.⁵

Recently, a novel, minimally invasive technique known as Corneal Collagen cross-

linking (CXL) with Ultraviolet A (UVA) has been introduced as a treatment option for progressive keratoconus.⁷ CXL improves corneal rigidity by increasing the biomechanical stability of the stromal tissues and also increases corneal resistance to enzymatic digestion, hence arresting disease progression.^{7,2} However, one major limitation of CXL is that it is not effective in thin corneas (< 400µm) due to a risk of corneal endothelial cell damage by UV rays. In fact, in many advanced cases, patients are often excluded from CXL as their corneal thickness is less than 400 µm. In order to overcome this problem, Hafezi et al,⁸ proposed an alternative protocol using UVA along with hypoosmolar riboflavin solution. In patients with thin cornea, riboflavin actually helps to swell corneal stroma and increases its thickness before CXL.⁸ In fact, riboflavin (Vitamin B2) performs two important functions, firstly, it acts as a photosensitizer, leading to the formation of new covalent bonds between collagen molecules, fibers, and microfibrils by photosensitized oxidation in combination with UVA,⁹ and secondly, it protects the deeper ocular structures, such as the corneal endothelium, lens, and retina by absorbing the UVA.⁵ This approach of CXL using hypotonic riboflavin actually aids in stabilization of keratoconus with no major complications. Nonetheless, little is known about the long-term safety and efficacy of the treatment.

The present study investigated the long-term safety and efficacy of CXL using UVA and hypoosmolar riboflavin solution for the treatment of kera-

toconus in patients with thin cornea.

Subjects and methods

Subjects

A total of 40 eyes of 25 subjects (18 males, 7 females) with an average age and disease duration of 29.21 ± 5.6 years and 42.1 ± 9.7 months respectively were enrolled in this study. Inclusion criteria involved documented progressive keratoconus, as confirmed by the evaluation of the anterior, posterior elevation maps and keratometry (Kmax) maps, as well as the corneal thickness maps at the thinnest point (obtained using the Pentacam tomography). The average follow-up was 61.79 ± 6.19 months (range: 42–68 months). Exclusion criteria were a history of herpes keratitis, corneal scarring, severe dry eyes, and any autoimmune disease. The protocol was reviewed and approved by Magrabi Aseer institutional Review Board. The study conducted adhered to the tenets of the Declaration of Helsinki. Written informed consent was obtained from all study participants, following a conversation about the nature and risks/benefits of participation.

Methods

Topical anesthesia Alcaine® 0.5% (proparacaine hydrochloride ophthalmic solution, Alcon, USA) eye drop was administered to control ocular pain and then 9 mm of epithelial tissue was mechanically removed using a Beaver blade. De-epithelization was followed by measuring thinnest corneal thickness (TCT) via ultrasound pachymetry (Corneo-Gage Plus, SonoGage, Inc., Cleveland, OH, USA) and instillation of hypo-osmolar

riboflavin (0.1%) solution to the cornea every 2 min for 30 min. The corneal thickness was checked continuously by ultrasound pachymetry and riboflavin was administered until the corneal thickness reached 400 μm . The center of the cornea was then exposed to UVA light of 370 nm wavelength and irradiated with an energy dosage of $3\text{mW}/\text{cm}^2$ for 30 minutes. During UVA irradiation period, hypo-osmolar riboflavin solution was applied every 2 min to maintain the necessary concentration of riboflavin and to protect cornea from drying up.⁷ Following the procedure, topical VIGAMOX® (0.5% Moxifloxacin HCl ophthalmic solution, Alcon Lab. Inc., Fort Worth, TX, USA) and Vexol® (1% Rimexolone Eye Drops, Alcon Laboratories, TX, USA) were administered in all patients until re-epithelialization of the cornea was completed. Rimexolone was prescribed for over four week's periods.

Examinations

Patients were followed at 6 six months interval till the end of the first year of follow up and then yearly till the fifth year. At each examination, BCDVA, corneal tomography (OCULUS-Pentacam®, Wetzlar, Germany), and corneal endothelial cell density (ECD; EM-3000 specular microscope, Tomey, Nagoya, Japan) of each subject were measured.

Evaluation

Paired *t*-test with SPSS software version 20 (SPSS Inc., Chicago, IL, USA) was used for statistical evaluation at baseline and at 6 months interval up to 1 year, and then yearly for 5 years after corneal CXL using the procedure. Statisti-

cal significance was defined as $P < 0.05$.

Results

In the present study, 40 eyes of 25 patients with progressive keratoconus were examined via corneal tomography, preoperatively and at 6 months interval up to 1 year, and then at 1-year interval up to 5 years after treatment. 15% of the patients (6 out of 40 eyes) showed mild corneal haze following CXL procedure, but rest of the patients showed clear corneas after CXL. About 12.5% cases (5 out of 40 eyes) showed development of dry eyes after the treatment.

Corneal thickness: The mean TCT of all eyes with epithelium was $432.5 \pm 15.7 \mu\text{m}$. Following corneal epithelial removal, all eyes had a TCT $< 400 \mu\text{m}$ and the mean value of TCT was $381.5 \pm 13.2 \mu\text{m}$ (range: 344–396 μm). After the application of hypotonic riboflavin solution, the mean TCT increased to $478.1 \pm 14.9 \mu\text{m}$ (range: 409–506 μm). At 6 months follow-up TCT reduced to 371.12 ± 14.2 (p value < 0.05) however it stabilized to 382.15 ± 12.9 at the last follow-up (p -value > 0.05). This finding agreed with the finding by Coskunseven et al. [12] Table 1 summarized all the preoperative and postoperative values.

Visual acuity: Mean CDVA value (decimal scale) at preoperative stage was 0.7 ± 1.92 and at postoperative stage was 0.7 ± 1.88 (all with $p > 0.05$) (Table 1). Hence, CDVA showed no significant change in values from pre-CXL to the follow-up visits. Moreover, none of the eyes lost any line of CDVA after the treatment. Additionally, UDVA also remained almost same at pre-operative (0.05

± 3.51), 6 months, 12 months, and at the last post-operative follow-ups (0.05 ± 3.65).

Corneal topography: Analysis of corneal topography data revealed that the mean Kmax value was reduced by 1.4 Diopters (D) from the pre-operative value. The pre-CXL Kmax was $62.71 \pm 4.68\text{D}$ and the post-CXL Kmax was $61.31 \pm 4.62\text{D}$, $p < 0.05$. The K average (Kave) was also decreased by a mean of 0.7 D from pre-operative to 5 years follow-up evaluation from 49.15 ± 2.61 to $48.45 \pm 2.69\text{D}$, $p < 0.05$.

Mean Anterior elevation at the thinnest location was significantly reduced to a value of $27.12 \pm 4.89\text{D}$ post-operatively from $38.12 \pm 4.65\text{D}$ pre-operatively. On the other hand, posterior elevation did not change considerably ranging between $73.48 \pm 12.51\text{D}$ pre-operatively to $72.59 \pm 13.29\text{D}$ postoperatively ($p > 0.05$). The mean value of corneal astigmatism showed a significant decrease from $5.49 \pm 3.16\text{D}$ before treatment to $4.19 \pm 3.22\text{D}$ ($p < 0.05$) at 5 years after treatment. Mean endothelial cell density (ECD) was not substantially lost before and after CXL treatment as evident from the values such as: $2789 \pm 154\text{ cells/mm}^2$ pre-CXL and $2748 \pm 171\text{ cells/mm}^2$ at 5 years post CXL.

Apart from corneal haze, slight dryness of eyes, and mild reduction of ECD, no other direct or primary complications of the procedure was reported.

Table 1 Mean preoperative and postoperative results

Parameter	Preoperative	6 months	12 months	Last follow-up
UCVA (Decimal scale)				
Mean±SD	0.05 ± 3.51	0.05 ± 3.78	0.05 ± 3.63	0.05 ± 3.65
P value		> 0.05	> 0.05	> 0.05
CDVA (Decimal scale)				
Mean ± SD	0.7 ± 1.92	0.7 ± 1.83	0.7 ± 1.9	0.7 ± 1.88
P value		> 0.05	> 0.05	> 0.05
K max (D)				
Mean±SD	62.71 ± 4.68	63.15 ± 3.19	62.28 ± 4.74	61.31± 4.62
P value		< 0.05	< 0.05	< 0.05
Corneal astigmatism				
Mean±SD	5.49 ± 3.16	4.14 ± 4.81	4.79 ± 3.48	4.19 ± 3.22
P value		> 0.05	> 0.05	> 0.05
Average Sim K (D)				
Mean±SD	49.15 ± 2.61	50.21 ± 3.73	49.87 ± 2.98	48.45± 2.69
P value		> 0.05	< 0.05	< 0.05
Anterior elevation				
Mean±SD	38.12 ± 4.65	31.54 ± 3.22	29.14± 4.11	27.12± 4.89
P value		> 0.05	0.05	> 0.05
Posterior elevation				
Mean±SD	73.48 ± 12.51	72.63 ± 13.29	73.85 ± 14.83	72.59 ± 13.94
P value		> 0.05	> 0.05	> 0.05
Thinnest corneal thickness (µm)				
Mean±SD	381.5 ± 13.2	371.12 ± 14.2	383.55± 14.7	382.15± 12.9
P value		< 0.05	> 0.05	> 0.05
ECD (cells/mm²)				
Mean±SD	± 2789 154	± 2677 162	± 2681 167	± 2748 171
P value		0.05>	0.05>	0.05>

Abbreviations:

UVA, Uncorrected visual acuity;
 CDVA, Corrected distance visual acuity;
 K max, Simulated maximum keratometry values;

Average Sim K, Average of simulated keratometry values;

ECD, Corneal endothelial count density

Discussion

Collagen CXL with UVA and riboflavin is a promising therapeutic method widely performed to strengthen the cornea of patients with progressive keratoconus and to stabilize the disease progression. Wollensak *et al.* found the reaction between riboflavin (a photomediator), oxygen and UVA light of wavelength 370 nm (absorption maximum of riboflavin) resulted in increased corneal stiffness of rabbit and porcine eyes.⁴ However, corneal epithelium is impermeable to riboflavin, hence epithelial debridement is normally performed to allow sufficient penetration of riboflavin to corneal stroma in standard ‘epithelium off’ CXL method.¹⁰ Baiocchi *et al* showed that in absence of riboflavin, around 30% of UVA light is absorbed by the lamellae of intact cornea.¹¹ On the contrary, in presence of riboflavin, approximately 95% of UVA is absorbed in the cornea, resulting in a 20-fold decrease of the original irradiance, which in turn minimizes the possibility of damage to the endothelium, lens and retina.^{12,7}

The present study showed a significant reduction in TCT at 6 months follow-up (371.12 ± 14.2). This finding agrees with that by Gu *et al.*² However the TCT values returned to the pre-operative values at the last follow-up. Besides, it was observed that treatment efficacy of CXL with riboflavin performed on eyes with thinner corneas (<400 µm following epithelial removal) was like the traditional CXL performed on eyes with thicker corneas.

Corneal topography (Kmax and Kave) is considered as one of the key outcome mea-

tures for CXL method.⁶ Changes in these measurements provide a more comprehensive analysis of the probable improvement in the shape and optical properties of the cornea after crosslinking. Generally, the topography indices are higher than normal in patients with keratectasia. Thus, a substantial reduction of any of the postoperative measurements after CXL may indicate improvement in the contour of the cornea and increased visual acuity.¹³ Several previous reports revealed a Kmax reduction of 1-2 D after 1-year post CXL such as, Henriquez et al reported a Kmax reduction of 2.66 D, Hersh et al reported a decrease of 1.70D, Chunyu et al detected a small change in both Kave (0.4 D) and Kmax (0.26 D) values after 18 months post -CXL.⁶ Our experimental results also showed a significant Kmax reduction of 1.4 D and Kave reduction of 0.70 D at 18 months post-CXL. This reduction of Kmax and Kave values could be due to the rearrangement of corneal lamellae and surrounding matrix. However, the duration of the turnover rate of stromal collagen fibers is several years,⁶ indicating the necessity of long term follow-up to determine whether repeated CXL treatment is required.

The current study examined the anterior and posterior elevation of cornea because they play an important role in determining keratoconus progression. Both front and back elevation at the thinnest point of the cornea was measured via Pentacam tomography. Anterior elevation showed a significant reduction, whereas the posterior elevation displayed a slight reduction after 5 years

post-CXL. Based on our observation, it can be suggested that assessment of elevation is a better way to reveal the long-term effects of CXL and improvements in corneal shape.³

Regarding the mean UDVA and CDVA values, our study could not detect any significant changes at pre and post-CXL treatment. Irrespective of the finding, the visual acuity was stable during the follow-up examinations. The same issue is seen with the study of Chunuya et al,⁶ where no significant change in UCVA was detected 18 months post-CXL. To display a meaningful correlation between topographic changes and post-operative visual acuity, further research is needed to detect baseline characteristics and outcome measures as potential indicators for visual acuity improvement after CXL.¹³ Keratoconus may often lead to corneal astigmatism, a common refractive abnormality that arises due to rotational asymmetry of corneal curvature. CXL is considered to be an emerging treatment for corneal ectasia. Our study demonstrated a decrease of mean corneal astigmatism by 1.3 D at 5 years follow-up post-CXL, indicating the importance of CXL-based corneal treatment for astigmatism correction.

Previous studies showed that corneal ECD was not compromised following either traditional CXL^{6,14,15,16} or contact-lens assisted CXL. However, we noticed 1.5 % reduction in mean ECD at 5 years follow up, which can be related to aging.

Development of corneal haze is one of the potential complications of CXL, affecting 10-90% of patients. Corneal haze

may affect CDVA, and hence, deteriorates the quality of vision.¹⁷ In the present study, although mild corneal haze was observed in 15% cases (6/40), yet the values of both CDVA and UCVA remain stable after CXL. Furthermore, the patients with corneal haze did not show any other complications and quality of vision was not found to be affected. Future studies should be done to detect the impact of haze development after CXL.

The main limitation of the present study is the relatively small sample size. Further studies with a larger number of patients should be done for better understanding of clinical outcomes of CXL. Additionally, increased sample size will help to detect whether any difference in complication rates exists between isotonic and hypotonic riboflavin solutions. In conclusion, it was observed in the present study that CXL technique with UVA and riboflavin is an effective treatment option for stabilizing the cornea thus arresting the progress of keratoconus in patients with thin corneas (mean thinnest corneal thickness less than 400 μm) as well as remarkably stabilize their visual acuity.

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Original Article:

Prevalence and Risk Factors of Hypercholesterolemia in Majmaah, Saudi Arabia

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Abstract

Cholesterol is one of the body substances present in the blood and important for the health. When the level of cholesterol exceeds the normal, it is called hypercholesterolemia and usually accompanied by high risk of developing coronary heart disease, strokes, and other health problems. Efforts were paid in the developed countries to control and prevent this problem and accordingly age adjusted mortality from coronary artery disease (CAD) is gradually falling, but it is still high in developing countries, and in the future probably become the most important health problem. The objectives of the study were to estimate the prevalence and risk factors of hypercholesterolemia among Saudi adults visiting Al Majmaah primary health care centers. The study was cross-sectional. The sample size was collected as 353. The data was collected by a structured, pre-coded and pre-tested questionnaire. In addition, we measured height and weight to calculate the body mass index. The total serum cholesterol level was measured for all participants. The overall prevalence of hypercholesterolemia (total cholesterol more than 200 mg/dl) was 45.3%. The prevalence of hypercholesterolemia increased with age reaching a maximum at the fifth decade. The logistic regression results concluded that, marital status (married patients) had significant relation ($p = 0.007$) and had the main effect on hypercholesterolemia among Saudi Adults in Majmaah. The study concluded that hypercholesterolemia prevalence among Saudi adults is high. The disease is associated with marital status; divorces and widowed showed high prevalence of the disease.

Key words: hypercholesterolemia; Al Majmaah; Saudi adults

المخلص

الكوليسترول هو أحد مواد الجسم الموجودة في الدم والمهمة للصحة. عندما يتجاوز مستوى الكوليسترول الحد الطبيعي تسمى الحالة ارتفاع الكوليسترول، وعادة ما يرافقه خطر كبير من الإصابة بأمراض الشرايين التاجية، والسكتات الدماغية، وغيرها من المشاكل الصحية. وقد بذلت جهود في البلدان المتقدمة من أجل السيطرة على هذه المشكلة ومنعها، وبالتالي فإن معدل الوفيات من امراض الشرايين التاجية حسب العمر تراجعت تدريجيا، ولكن معدل الوفيات لا يزال مرتفعا في البلدان النامية، وربما يصبح في المستقبل من أهم المشاكل الصحية. هدفت هذه الدراسة المقطعية الي تحديد مدي انتشار ارتفاع الكوليسترول، وعوامل الخطورة لدى البالغين السعوديين الذين يزورون مراكز الرعاية الصحية الأولية بالمجموعة. تم حساب حجم العينة ٣٥٣ مشاركا. تم جمع البيانات بواسطة استبيان تم اختياره مسبقا. وبالإضافة إلى ذلك فقد قمنا بقياس الطول والوزن لحساب مؤشر كتلة الجسم، وقياس إجمالي مستوى الكوليسترول في الدم. كان معدل انتشار الكوليسترول (مستوي الكوليسترول أكثر من ٢٠٠ ملغ / ديسيلتر) ٤٥,٣٪. لوحظ زيادة معدل انتشار الكوليسترول مع زيادة العمر ووصل المعدل إلى الحد الأقصى في العقد الخامس من العمر. خلصت الدراسة إلى أن معدل انتشار الكوليسترول بين البالغين السعوديين مرتفع كما أن الزواج له التأثير الرئيسي على ارتفاع الكوليسترول بين البالغين السعوديين في المجموعة ($p = 0.007$).

Introduction

Cholesterol is one of the fat like substances present in the blood and important for the health. When the level of cholesterol exceeds the normal levels in the blood, it is called hypercholesterolemia and usually accompanied by high risk of developing coronary heart disease, strokes, and other health problems. ⁽¹⁾ The above association is well established and proved by inducing atherosclerosis in animal experimentally, and well established epidemiologically in the presence of high prevalence of vascular disease due to hypercholesterolemia even in younger age group ⁽²⁾. In addition, intervention studies have proved that lowering blood cholesterol level with drugs reduces the incidence of coronary artery disease (CAD) ⁽³⁾. Coronary artery disease as one of the consequences of hypercholesterolemia is a major health problem and a leading cause of death in adults throughout the world. Efforts were made in the developed countries to control and prevent this problem and accordingly age adjusted mortality from CAD is gradually falling, but it is still high in developing countries, and in the future, would probably become the most important health problem. ⁽⁴⁾ Many studies have shown variations with respect to the distribution and prevalence of hypercholesterolemia in different parts of the world. The exact cut-off point to diagnose hypercholesterolemia varies between research groups. Most studies used cut off levels of more than 200mg/dL (>5.2 mmol/L) as borderline and more than 240 mg/dL (>6.2 mmol/L) as high. However, irrespec-

tive of the variation in the cut off level hypercholesterolemia is common in most modern populations. The prevalence of hypercholesterolemia in males aged from 35 to 74 years in Minnesota, United States was 54.9%, and in females aged 35 – 74 years was 46.5% (more than 200mg/dL)⁽⁵⁾. In Mexican adults more than 20 years of age was 22.8% (more than 200mg/dL) ⁽⁶⁾. In Punjab Indian adults aged > 30 years was 7% (more than 200mg/dL) ⁽⁷⁾. In Chinese individuals aged 35 – 74 years the prevalence was 9% (more than 240 mg/dL) ⁽⁸⁾. In a study of hypercholesterolemia in adult Mexican the prevalence of borderline hypercholesterolemia (TC between 5.2 and 6.2 mmol/l) was 22.8% and the prevalence of high risk hypercholesterolemia (TC > or = 6.20 mmol/l) was 10.6%. The study showed significant geographic differences in serum TC, with mean state values ranging from 4.43 +/- 1.05 mmol/l in the south to 5.48 +/- 1.36 mmol/l in the north. The large variation in mean TC values is probably due to diet. ⁽⁹⁾ In Saudi Arabia, a developed Middle Eastern country, there has been a significant increase in CAD, and admissions to hospital because of angina, and /or myocardial infarction. ⁽¹⁰⁾ In a cross-sectional national epidemiological randomized household survey in Saudi Arabia, the prevalence of hypercholesterolemia was 5.2 mmol/L. For Saudi subjects over the age of 15 years was 16% and 19% for male and female subjects, respectively, and there is regional variations present (In the west = 5.6, the central = 9, the south = 5.7, the east = 14.3, the north = 3.3) ⁽¹¹⁾. Another study in

Saudi Arabia done in 2013 showed that 8.5% of Saudis had hypercholesterolemia and another 19.6% had borderline hypercholesterolemia ⁽¹²⁾. Hypercholesterolemia is a preventable condition and is associated with many risk factors as well as consequences, so by knowing its prevalence and associated risk factors in this community will be as a database information for further researches, and solid base for any intervention and programs.

The objectives of this study was to estimate the prevalence and risk factors of hypercholesterolemia among Saudi adults visiting Al Majmaah primary health care centers

Materials and methods

Our study was a descriptive cross-sectional to determine the prevalence of hypercholesterolemia in Saudi adults in Majmaah area. The study was conducted in Al Majmaah city, which is located in Majmaah governorate in Riyadh region, Saudi Arabia. The population of Al Majmaah is about 45,000. While the population of the governorate, as a whole is approximately 97,000. Concerning the health system there are eleven health centers and one public hospital (King Khalid Hospital Al Majmaah). Five primary health centers (Al Majmaah, Hai Almatar, Al-faiha, Al Yarmok and Alfaisalya) were chosen randomly for the study. The Study population was all Saudi adults, males and females, between 20-70 years of age attending the selected primary health care Centers in Majmaah for any reason. The participants were chosen from the selected primary health care centers by systematic random sampling. The

interval between participants was decided according to the average number of center's visitors every day. The sample size was calculated as 353 participants and taken during September 2014 and February 2015. Data were collected through a structured, pre-coded and pre-tested questionnaire. In addition, we measured height and weight to calculate the body mass index according to the formula ($BMI = \text{weight (kg)}/\text{height (m)}^2$). The subject is considered underweight if his/her BMI was less than 18.5, normal if it was between 18.5 and 24.9, overweight if it was between 25 and 29.9 and obese if it was above 30. Total serum cholesterol level was measured in the laboratory of King Khalid Hospital Al Majmaah, using the machine Dimension[®] X pand, clinical chemistry system from Siemens. The cholesterol method used is an in-vitro diagnostic test intended for quantitative determination of total cholesterol in human serum. The test is enzymatically based (cholesterol esterase, cholesterol oxidase and peroxidase). The quality control for the analyte was done at two levels with the Biorad chemistry controls. The reference range for total cholesterol serum is considered normal if it is less than 200 mg/dl ($< 5.2 \text{ mmol/l}$), and high if above 200 mg/dl ($> 5.2 \text{ mmol/l}$). The data was entered and analyzed using SPSS 22.0. Mean \pm SD was given for quantitative variables. Frequencies and percentages were given for qualitative variables. Pearson Chi-Square and Fisher exact tests were applied to observe associations between qualitative variables. Logistic regression analysis was also applied

to observe the log odds. A p-value of < 0.05 was considered as statistically significant.

A written informed consent was obtained from each respondent before the interview and collection of blood samples. The research was approved by Majmaah University Research Ethics Committee.

Results

The mean total cholesterol level was 188.5 mg/dl (4.9 mmol) ± 1.11 , with a range between 7.7 mg/dl (0.2 mmol) and 426.9 mg/dl (11.1 mmol).

Table (1) showed that the overall prevalence of hypercholesterolemia (total cholesterol more than 200 mg/dl) was 45.3%. The prevalence of hypercholesterolemia among male and female subjects were 45.1% and 45.5% respectively ($p=0.943$) as shown in table (2). The prevalence of hypercholesterolemia increased with age reaching a maximum at the fifth decade, 20ys – 29ys, 30ys – 39ys, 40ys – 49ys, 50ys – 59ys, (29.0%, 35.7%, 48.0%, 49.0%,) respectively, and it was 40.5%, for the age groups 60 yrs and above ($p=0.116$). Concerning the level of education, illiterate subjects were having higher level of hypercholesterolemia (51.6%), where the prevalence in primary, intermediate, secondary, university and above were 45.3%, 47.1%, 35.7%, 43.6%, respectively ($p=0.442$). Almost 50% of the respondents with monthly income less than 500 SR had hypercholesterolemia. And the level of hypercholesterolemia was 48% in the group of income between 5000 – 10000. The prevalence of hypercholesterolemia among 10001 – 15000 income

group was 41.2%, and those who had monthly income above 15000, it was 25% ($p=0.517$). The presence of hypercholesterolemia was 45.9% in smokers while it was 40% in non-smokers. Widows were having the highest prevalence of hypercholesterolemia (65.2%), followed by Divorced (55.6%), Married (46.5%), and Single (27.0%) participants. The association between hypercholesterolemia and marital status was statistically significant ($p=0.014$). The association between hypercholesterolemia and body mass index was the highest among the participants who were underweight (50%), followed by overweight (46.2%), obese (45.9%) then lastly those who had normal BMI (39.5%). 26.9% of those who regularly exercised were found to have hypercholesterolemia ($p=0.588$), while 87.5 % of those eating fatty food were having hypercholesterolemia ($p=0.414$).

The logistic regression analysis concluded that, marital status (married patients) had significant positive association ($p = 0.007$) on hypercholesterolemia among Saudi Adults in Majmaah (table 3)

Table (1) Overall Prevalence of hypercholesterolemia

Level	No.	Percent
Normal	193	54.7
High	160	45.3
total	353	100.0

Table 2 Distribution of Saudi adults with hypercholesterolemia by selected risk factors (n=353)

Risk factor	Total no.	No. (%)	P value
Gender			
Male	164	74 (45.1%)	0.943
Female	189	86 (45.5%)	
Age			
20 – 29	55	16 (29.0%)	0.116
30 – 39	54	29 (35.7%)	
40 – 49	102	49 (48.0%)	
50 – 59	100	49 (49.0%)	
60 and more	42	17 (40.5%)	
Level of education			
Illiterate	93	48 (51.6%)	0.442
Primary	64	29 (45.3%)	
Intermediate	53	25 (47.1%)	
Secondary	56	20 (35.7%)	
University and above	87	38 (43.6%)	
Monthly income/ SR			
< 5000	165	77 (46.7%)	0.517
5000 - 10,000	100	48 (48.0%)	
10,001 - 15,000	80	33 (41.2%)	
> 15,000	8	2 (25.0%)	
Tobacco smoking			
Smokers	35	14 (40%)	0.775
Non smokers	318	146 (45.9%)	
Marital Status			
Single	48	13 (27.0%)	0.014*
Married	273	127 (46.5%)	
Divorced	9	5 (55.6%)	
Widow	23	15 (65.2%)	
BMI			
Underweight	10	5 (50%)	0.532
Normal	43	17 (39.5%)	
Over weight	93	43 (46.2%)	
Obese	207	95 (45.9%)	
Performance of regular physical activity (sport)			
Yes	90	43 (26.9%)	0.588
no	263	117 (73.1%)	
Eating fatty foods			
Yes	303	140 (87.5%)	0.414
no	50	20 (12.5%)	

shows significant association between marital status and hypercholesterolemia*

Table (3) Logistic Regression Analysis of hypercholesterolemia among Saudi adults in Majmaah

Variables	Adjusted Odds Ratio	P-Value	95% CI for Odds	
			Lower	Upper
Age	1.034	0.911	0.57	1.86
BMI	0.971	0.841	0.72	1.29
Gender	0.785	0.392	0.45	1.3
Education	0.925	0.465	0.75	1.14
Occupation	0.924	0.532	0.83	1.06
Monthly Income	0.909	0.486	0.69	1.19
Marital Status	1.787	0.007*	1.17	2.87
Smoking	1.302	0.516	0.58	2.91
Regular Exercise	0.821	0.476	0.49	1.38
Diabetes	1.312	0.876	0.80	2.14
Hypertension	1.371	0.276	0.77	2.32
Dyslipidemia	1.06	0.676	0.78	1.44
Eating Fatty food	1.86	0.221	0.31	1.38
Exercise	0.75	0.965	0.65	1.44

Discussion

The results in this study showed that the overall prevalence of hypercholesterolemia was (45.3%) and with no significant sex difference (males=45.1) (and females=45.5). It is lower than the study done in Minnesota in USA (males 54.9%, females 46.5%)⁽⁵⁾. Whereas it is higher than the Mexican study

(22.8%)⁽⁶⁾, in Punjab (7%)⁽⁷⁾, China (9%)⁽⁸⁾ and the Saudi survey done in 2013(28.1%)⁽¹²⁾. A recent survey done by the Department of Health in the United Kingdom suggested that the average plasma cholesterol concentration was 5.9 mmol/l, while it was 4.9 in our study¹³. The peak prevalence of hypercholesterolemia in the age group between 50 – 59 years is similar to the study done in Japan, in which they found that hypercholesterolemia is more in the age of 50-59 years in males and 60-69 years in females¹⁴. Our study showed that hypercholesterolemia increased with decreased body mass index unlike the Japanese study in which it increased with the increase of body mass index¹⁴. This may be due to the fewer number of underweight subjects⁽¹⁰⁾. The only significant finding was a higher incidence of hypercholesterolemia in widows and it can be explained as a consequence of overeating due to grief, which can be triggered by death of the partner.

Conclusion

Hypercholesterolemia prevalence among Saudi adults in this study is high. The disease is associated with marital status; divorces and widowed showed high prevalence. Raising awareness is recommended to reduce the prevalence of the disease.

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Case Study

Neuro Motor Development in a Girl with SERAC 1 Gene Dysfunction from Kingdom of Saudi Arabia.

A case study

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Abstract

Background & Purpose: The SERAC1 gene mutation is rare disorder related to deficits in mitochondrial metabolism. Neuromotor development was not studied in literature for this type of patients based on physical therapy perspectives. However, in this case report, we described the Neuromotor development in a child with SERAC1 mutation at 18 months of age in order to plan for better rehabilitation care in pediatrics physical therapy profession. **Case Description:** A girl child with SERAC1 mutation (18 months old) presented to the physical therapy clinic with delay in Neuromotor development. During physical therapy evaluation, hearing and vision are intact, Able to distinguish her parents voice and able to recognize them. Speech is impaired, Head control and sitting was perceived at six months of age, and became very dependent at 18 months of age. Grasping and reaching is not completely developed. **Outcomes:** The child was evaluated at the age of 12th and 18th month for normal development by using Alberta infant motor scale. The total score at 12 months was 17/58, and at 18th month was 13/58. We observed that the child development was less than 5th percentile of normal at both the measurements. We evaluated her neuromotor development by using Infant Neurological International Battery (INFANIB). The child was under abnormal category for neuro motor systems by having the total score 36/100. We used these two outcome measures as primary measure since they are the most common measures that used among pediatric physical therapists **Discussion:** This indicates that the abnormality in motor development was due to the nature of the disease, which is consistent with clinical manifestations presented in the literature. Both the scales have good reliability and validity. INFANIB scale has good predictive validity, by seeing definite abnormality at the 18th month we can assume that child may not

المخلص:

الهدف من الدراسة: الطفرة الجينية SERAC1 هو اضطراب نادر متعلق بقصور في وظيفة الميتوكوندريا داخل الخلية. حتى هذه اللحظة لم يُدرس التطور الحركي العصبي في الأبحاث الطبية السابقة لهذا النوع من المرض من منظور مهنة العلاج الطبيعي. في هذه الدراسة، قمنا بوصف التطور الحركي العصبي في طفلة مع طفرة SERAC1 في ١٨ شهرا من العمر من أجل تحسين الخطة العلاجية والرعاية التأهيلية للأطفال.

وصف الحالة: قدمت طفلة مع طفرة SERAC1 (١٨ شهرا من العمر) إلى عيادة العلاج الطبيعي مع تأخير واضح في الحركة والعضلات. أثناء التقييم المبني للعلاج الطبيعي، كانت وظائف السمع والرؤية سليمة، ولديها القدرة على تمييز صوت والديه وأيضا قدرة على التعرف عليهما. لا يوجد تواصل لفظي لديها، السيطرة على الرأس والجلوس كانت سليمة في أول ستة أشهر من العمر، وأصبحت غير قادرة على ذلك في عمر ١٨ شهرا. الوظائف الدقيقة لليد لم تصل لمرحلة التطور تماما.

النتائج: تم تقييم الطفلة في سن ١٢ و ١٨ شهرا للتطور الطبيعي باستخدام مقياس Alberta infant. وكانت النتيجة الإجمالية في ١٢ شهرا ١٧/٥٨، وكانت النتيجة في الشهر الثامن عشر ١٣/٥٨. لاحظنا أن نمو الطفلة كانت أقل من ٥ في المئة من الطبيعي بالمقارنة مع أقرانها. وأيضا قمنا بتقييم تطورها العصبي باستخدام مقياس (INFANIB) وكانت النتيجة الكلية ٣٦/١٠٠. لقد استخدمنا هذين المقياسين في دراستنا كمقياس أساسي لأنهما من أكثر المقاييس شيوعا بين مختصو العلاج الطبيعي للأطفال

المناقشة: بعد الاطلاع على النتائج وجدنا هناك تدهور في الحالة الطبية للطفلة وذلك يرجع إلى طبيعة المرض، وهو ما يتفق مع الدراسات السريرية السابقة. هناك حاجة لعمل دراسات مستقبلية لاستكشاف فعالية التأهيل الطبي (بما في ذلك العلاج الطبيعي، وعلاج النطق والتخاطب) في تحسين المهارات الوظيفية أو المحافظة لمنع أي تدهور قد يحصل مستقبلا. وبالإضافة إلى ذلك، هناك حاجة إلى مزيد من الاختبارات السريرية اللازمة مثل اختبارات السمع لضمان نتائج أفضل أثناء برنامج التأهيل الطبي.

الكلمات الرئيسية: INFANIB، طب الأطفال، التأهيل الطبي، التطور الحركي العصبي

have normal development in future also. Future studies are required to explore the effectiveness of intensive rehabilitation therapy (including physical therapy, occupational therapy, and speech pathology services) in improving neuromotor development also to prevent any neuromotor regression for this type of disease. In addition, further investigations are required such as hearing test for better rehabilitation outcomes.

Keywords: Infanib, Pediatrics, Rehabilitation, Neuromotor Development.

Introduction

Serine active site containing 1 is a gene protein found in humans and it is encoded as SERAC 1 gene. [1] The SERAC1 plays a key role in phosphatidylglycerol remodeling which is essential for intracellular cholesterol trafficking and mitochondrial function. [2] Abnormality in SERAC 1 gene leads MEGDEL (3-methylglutamic aciduria with deafness, encephalopathy and Leigh-like) syndrome. [3] The SERAC1 gene mutation is rare disorder related to deficits in mitochondrial metabolism. [4]

The children with SERAC 1 gene dysfunction had shown following clinical features like hypotonia and hypoglycemia at neonatal stage, in infancy, there was failure to thrive, feeding difficulties, recurrent infections and developmental delay. After the first year the clinical features are severe progressive sensory neural deficit, hearing loss, spasticity, extra pyramidal signs like dystonic movements, episodes of respiratory insufficiency and developmental regression. [5-7] Lab analysis of these children had shown mitochondrial hepatopathy, lactic acidosis, elevated serum transaminase levels, elevated serum γ -glutamyl transpeptidase, hyper ammonia and elevated serum

α -fetoprotein. [7] MRI shows brain atrophy, leigh like findings, small corpus striatum and progressive dysfunction of the basal ganglia. [7]

Case description:

The case described here is a girl child with age 2 years and 6 months. She was born in the United States of America, but she is of Saudi nationality and currently residing in the Kingdom of Saudi Arabia. The parents of the child have step first degree consanguinity the full pedigree was mentioned in (Figure.1). The informed consent form was obtained and fully explained to her guardian.

The child was full term born through normal vaginal delivery to a G₁P₁L₁ mother. The birth weight of the child was 2.6 kilograms, birth length was 46.9 centimeters and head circumference was 32.5 centimeters. APGAR score was 9 at the first minute and 10 at fifth minute. First 24 hours' child was on normal breast feeding after that child developed metabolic crisis and respiratory distress with rapidness and difficulty in breathing, the food intake and urine output were decreased, increase in drowsiness, no eye contact and no sucking. On lab examination child had hypoglycemia with sugar levels at 37 mg/dl, elevated ammonia at 271 μ mo/l and elevated lactate at 13.5 mmol/l. As an emergency the

child was shifted to Neonatal Intensive Care Unit (NICU). During this time child Complete Blood Count (CBC) was normal no signs of bone marrow suppression were found. Next three weeks' child was in the NICU on oxygen support and underwent one session of dialysis to decrease the ammonia levels. After three weeks she was discharged during this time she was on intravenous hydration, carnitine, bolus of ammonul, arginine and glucose infusion. Four weeks after the birth the child underwent whole exome sequencing tests for detecting genetic abnormality. At 4 weeks her development was 3.1 kg in birth weight (2nd percentile), body length 50 centimeters (4th percentile), head circumference was 36.7 centimeters (37th percentile), muscle tone was normal and there was no clonus. At 3 months of age lab examination showed lactate at 5.8 mmol/dl, serum ammonia 72 umol/l, alkaline phosphate 1386 u/l and elevated liver enzymes that is Alanine Aminotransferase (ALT) at 76.7 u/l and Aspartate Aminotransferase (AST) at 97.5 u/l. At 6 months of age she was diagnosed with deleterious mutations in SERAC 1 gene. She was diagnosed with 3-methylglutaconic aciduria with deafness, encephalopathy and Leigh-like syndrome (MIM: 614739) Confirmed Sanger sequencing identity's mother and father as heterozygous. Examination of urine revealed significant elevation of 3 – methylglutaconic acid. Before the evaluation, the child was hospitalized only once with lactic acidosis and hyper ammonia.

During the current general evaluation, hearing and vision are intact, Able to distin-

guish her parents' voice and able to recognize them. Speech is impaired, head control and sitting was perceived at six months of age, but it is deteriorating and become very dependent by 18 months of age. Grasping and reaching is not completely developed. There is only mass grasp. She shows fluctuating tone with athetoid kind of movements.

The child was evaluated at the age of 12th and 18th month for normal development by using an Alberta infant motor scale. [8] The total score at 12 months was 17/58, and at 18th month was 13/58. We observed that the child development was less than 5th percentile of normal at both the measurements and there is deterioration in normal motor development. At 18 months we evaluated her Neuro-motor development by using the Infant Neurological International Battery (INFANIB). [9,10] The child was under the abnormal category for Neuro motor systems by having the total score 36/100. At the age of 2 years and 3 months the Gross Motor Function Measure (GMFM 66) was done. The total score was 6.24 %, which is very poor for that age. Out of the 5 sub components of GMFM child was able to perform some activities in the first two components only that is lying-rolling and sitting.

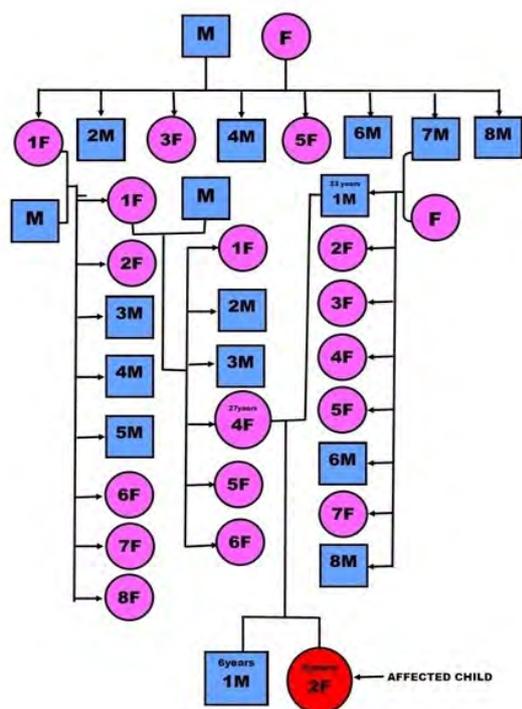


Figure legend

Figure -1: Full Pedigree of the affected child
Note for figure one: M means male and F mean female

Discussion

Based on case description, it indicates that the abnormality in motor development was due to the nature of the disease, which is consistent with clinical manifestations presented in the literature. Similar cases were reported in the past, [1-4,12] but they did not describe about the developmental aspects of the child in a quantitative manner. All the scales used to measure the development have good reliability and validity. [13-20] By seeing definite abnormality at the 18th month and 2 years we can assume that child may not have normal development in future also.

There are limited studies in literature regarding this kind of disorder. Thus, cohort studies are required to make a concrete clinical picture about the complete development of these children. Future studies also are required to explore the effectiveness of intensive rehabilitation therapy including physical therapy, occupational therapy, and speech pathology services in improving neuromotor development also to prevent any neuromotor regression for this type of disease and to provide preventive and management measures for this type of genetic disease. Physical therapist working with pediatrics patients need full picture regarding neuromotor development in order to assess and manage similar conditions.

Conclusion

This girl child with SERAC 1 gene dysfunction had shown severe abnormality in motor development by three standard scales. She even showed deterioration in the motor development on Alberta Infant Motor Scale.

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Review Article

Physical Therapy Intervention in Post Stroke Shoulder Subluxation: A Narrative Review

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Abstract

Objective:

The purpose of this narrative review is to summarize the recent advances in Glenohumeral subluxation (GHS) treatment approaches.

Background:

Glenohumeral subluxation (GHS) subluxation is found 81% of the individuals following stroke, a preventable secondary complication often accompanied with poor upper limb function. GHS is also considered as an important risk factor for shoulder pain and other problems. GHS is a complex phenomenon with very little understanding of its pathomechanics.

Method:

The literature was obtained by searching in computerized database. Evidence was obtained from articles published in peer-reviewed journal and published in English language.

Discussion and Conclusion:

Ultrasound measurements are considered the best method of quantifying GHS. Clinical evaluation such as finger breadth method and sulcus sign can be useful and quick clinical assessment tool. Novel methods such as Functional electrical stimulation and tapping method are effective in an acute stage of hemiplegia and arm slings have been shown a negative impact on rehabilitation of GHS, However, it shall be used for a shorter period of time.

Key Words

Stroke rehabilitation, Glenohumeral subluxation, physiotherapy intervention.

المخلص:

الاهداف:

الغرض من هذا الاستعراض السردي هو تلخيص التطورات الأخيرة في نهج العلاج تحت خلع غلينو هومرال.

الخلفية:

تم العثور على خلع غلينوميرال الجزئي في 81% من الأفراد الذين أصيبوا بالسكتة الدماغية، ومن المضاعفات الثانوية المرافقة والتي يمكن الوقاية منها في الغالب هي ضعف وظيفة الطرف العلوي. ويعتبر خلع مفصل الكتف أيضاً عاملاً خطورة مهم لآلام الكتف وغيرها من المشاكل، كما هو ظاهرة معقدة مع القليل جداً من فهم الميكانيكا الباثولوجية الخاصة به.

الطريقة:

تم الحصول على الخلفية العلمية من خلال البحث في قاعدة البيانات المحوسبة. تم الحصول على الأدلة من المقالات المنشورة في مجلات عالمية مراجعة ونشرت باللغة الإنجليزية.

المناقشة والاستنتاج:

تعتبر قياسات الموجات فوق الصوتية أفضل طريقة لقياس خلع مفصل الكتف.

التشخيص السريري مثل طريقة الفحص التقويمي يمكن أن تكون أداة مفيدة وسريعة للتقييم السريري، بينما أثبتت أساليب وظيفية جديدة مثل التحفيز الكهربائي فعاليتها في مرحلة حادة من الشلل النصفي للذراع كانت ذات أثر سلبي على إعادة تأهيل خلع مفصل الكتف، ومع ذلك، فإنه يجب أن تستخدم لفترة أقصر من الزمن.

الكلمات الدالة:

إعادة تأهيل السكتة الدماغية، خلع مفصل الكتف، تدخل العلاج الطبيعي.

Introduction

The Shoulder Joint is highly mobile but its mobility comes with the cost of its stability⁽¹⁾. The Glenohumeral joint is the major joint of the shoulder complex. It is a ball and socket variety of synovial joint formed by the articulation of glenoid cavity medially and head of humerus laterally.⁽²⁾ Laxity in the articular capsule and a large humeral head facilitates wide degree of freedom of movement.⁽³⁾ Glenoid fossa of scapula covers less than one third of the head of humerus leaving it incongruent. Therefore, its stability mainly depends on integrity of static restraints by joint capsule and ligaments and balanced activity of dynamic restraints (rotator cuff, deltoid)⁽⁴⁾ leading to lower levels of activity and a diminution in autonomy. Current physical therapies (PT)⁽⁵⁾

Static stability of the glenohumeral joint depends on joint capsule, shape of articular surfaces and glenoid labrum.⁽⁶⁾ While as, Dynamic stability of shoulder complex is derived from three major muscle groups.⁽⁷⁾ The scapulohumeral group consists of rotator cuff muscles (subscapularis, infraspinatus, teres minor, and subscapularis). The axioscapular group consists of muscles that act on the scapula, they are, rhomboids, trapezius, serratus anterior, and levator scapula. The axiohumeral group formed by the muscles that originate on the thorax and insert on the humerus they are latissimus dorsi and pectoralis major muscles.⁽⁸⁾

The compression forces generated by the rotator cuff muscles during dynamic activity improves stability by approximating

the head of humerus against glenoid fossa.

⁽⁹⁾ Upward rotation of the scapula produced by steering activity of trapezius and serratus anterior increases the congruency of the articular surfaces during overhead activity.⁽¹⁰⁾ Supraspinatus initiates the shoulder abduction and also checks the superior translation of the head of humerus, thereby preventing impingement.⁽¹¹⁾ Paralysis of muscle activity and Hypotonicity during the initial phase of stroke, predominantly to the supraspinatus and deltoid, overstretches the weak inferior capsule and ligaments by the weight of the dependent arm resulting in pain.⁽¹²⁾

Instability of the shoulder joint is further worsen due to impairment of muscular and capsuloligamentous structures following stroke⁽¹³⁾ consequently resulting in shoulder subluxation among 17 to 81 percent of patients.⁽¹⁴⁾ Its also known as Glenohumeral subluxation (GHS). Inferior subluxation of the shoulder joint is the most frequently encountered impairment than anterior posterior, medial and lateral subluxation.⁽¹⁵⁾ Incidence of GHS is most commonly seen in patients with flaccid hemiplegia and usually develops within first 3 weeks following stroke.⁽¹⁶⁾ Lack of self-care, poor positioning and left hemiplegia are associated with higher risk of developing GHS.⁽¹⁷⁾ Flaccidity and inactivity of the supporting muscles, leaves a shoulder joint vulnerable to subluxation and pain.⁽¹⁸⁾ Electromyography data revealed the posterior fibers of deltoid and supra-spinatus muscles provide dynamic stability to the shoulder joint. These muscles restrain inferior trans-

lation of humerus thereby, maintaining the correct alignment of Glenohumeral joint.⁽¹⁹⁾

Shoulder pain is often associated with GHS but research has proven that the amount of pain doesn't correlate with the degree of subluxation.⁽²⁰⁾ Ultrasound studies have confirmed the involvement of soft tissue around shoulder joint such as joint effusion and tenodesis of long head of biceps brachii and supra-spinatus.⁽²¹⁾ Available data suggests no direct relationship between GHS and Shoulder pain (SP) but GHS may predispose to many painful conditions.⁽²²⁾ Clinically, the Glenohumeral subluxation is diagnosed by placing the finger between inferior aspect of the acromion and the superior aspect of the humeral head.⁽²³⁾ Glenohumeral subluxation is confirmed in cases where the gap is more than one finger. Sulcus sign is another clinical tool to detect ligament laxity and inferior instability of shoulder by applying a gentle inferior traction on the humerus.⁽²⁴⁾ In addition, appearance of visible groove under the acromion is the positive indication of GHS.⁽²⁵⁾

There are three simple methods to qualify the amount of GHS. Palpation is the method by which an examiner palpates the space between acromion process and head of the humerus.⁽²⁶⁾ Finger breadth method is also used frequently, herein, the examiner places the fingers in the space between acromion process and head of the humerus.⁽²⁷⁾ Brohanon and Andrews⁽²⁸⁾ recommended to use the thumb as a tool to measure the amount of subluxation. Anthropometric evaluation using Caliper or a tape is also used to measure

the distance between two reference points. Proximal distal point is acromion process and distal is lateral epicondyle or head of the humerus.⁽²⁹⁾ Lastly thermoplastic Jig is used to measure the distance between acromion process and head of the humerus. The device is L shaped made up of thermoplastic material, sliding marker, tape and a thumbscrew.⁽³⁰⁾

GHS changes the biomechanical alignment between the glenoid cavity and head of humerus. Hypotonicity of the shoulder muscular following stroke leads to the palpable gap between the acromion process and the head of humerus.⁽³¹⁾ Significant number of patients show symptoms of shoulder hand syndrome characterized by pain, edema and restricted freedom of movement of shoulder joint.⁽³²⁾ Shoulder hand syndrome is also characterized by increased skin temperature, change in skin color.⁽³³⁾ Although the mechanism of SHS is not fully understood, various helpful measures have been proposed to prevent it,⁽³⁴⁾ including special orthotic devices.⁽³⁵⁾ In one of the Cochrane review,⁽³⁶⁾ sufficient evidence is not present to prove the contribution of such devices to improve or prevent shoulder joint subluxation. Interventions used by physiotherapists at various stages of stroke ranges from electrotherapeutic modalities like functional electrical stimulation, to mechanical support from slings and special taping methods.⁽³⁷⁾⁽³⁸⁾ The literature review, revealed number of RCT studies published comparing various methods of taping techniques and electrical stimulation.⁽³⁹⁾ This review is intended to reveal the best

evidence at present in the current literature.

Search Strategy

Database was searched electronically from 1990 up to June 2017 to identify relevant trials for this narrative review. MEDLINE®, EMBASE® and Saudi Digital Library(SDL) was searched for relevant literature using combinations of the key words “shoulder,” “subluxation,” “pain,” “stroke,” and “hemiplegia.” This research provided 69 articles in MEDLINE, 10 articles in EMBASE and 43 articles in SDL. Grey areas like reference lists and bibliographies of related journal articles and books for additional trials. This additional research provided 21 articles (6 abstracts, 3 books or chapters of books, and 12 articles not indexed or published before 1990). We limited our search for articles published in English language and articles published in peer reviewed journal.

Review of literature:

Intervention Available Robotic Therapy

Many authors have recommended the use of robotic technology in upper limb stroke rehabilitation.⁽⁴⁰⁾⁽⁴¹⁾⁽⁴²⁾ Dijkers et al⁽⁴³⁾ was one of the few researchers to utilize simple robotic therapy. He emphasized on repetition and record of movement, however author didn't evaluate the quality of movement and amount of patient participation.

Simulation environmental for arm therapy (SEAT)⁽⁴⁴⁾ developed at VA Palo Alto Rehabilitation R&D center and Stanford University by Johnson et al in 1999, works on the principle of mirrored-image. The subjects performed bimanual tasks like rotating

a steering wheel, which was equipped with sensors to provide assistance and resistance torque. The system was also equipped with a low resolution screen to provide traffic scenes.

The SEAT method includes 3 diverse therapy types: normal, active and passive. Normal type evaluates the participation of both the upper limbs on the steering wheel in terms of force and coordination. Active type encourages the use of paretic side while relaxing the non-paretic side lastly passive type assists the paretic side guided by non-paretic limb.

Based on the concept of mirror imaging Mirror-image Motion Enabler (MMIME)⁽⁴⁵⁾ was constructed at the VA Palo Alto rehabilitation and R&D center. Initially Puma 260 robot⁽⁴⁶⁾ was developed with force torque sensor attached to the arm support. Later it was replaced by more advanced Puma-560 robot.⁽⁴⁷⁾ The MMIME method moves the paretic arm by mimicking the pattern of movement in the non-paretic side. The system manipulates the amount of assistance as soon as system detects the efforts made by the subject. Many authors⁽⁴⁸⁾⁽⁴⁹⁾⁽⁵⁰⁾ concluded that the robotic therapy has no negative effects and also it's safe and effective in neuro rehabilitation.

Slings

Slings to support shoulder joint are mostly used in acute phase of stroke rehabilitation. The basic purpose of these slings are to support the soft tissue of shoulder joint against pull of gravity or reduce GHS and pain.

There are a wide variety of slings available. Most commonly prescribed and researched slings include the Bobath roll

sling⁽⁵¹⁾, Harris single-strap sling⁽⁵²⁾ and Humeral cuff sling⁽⁵³⁾. The Harris sling is a single-strap traditional sling worn around the neck which supports the elbow and wrist keeping the shoulder joint in adduction and internal rotation. The Bobath roll sling utilizes a foam roll kept under the axilla to keep the arm in adduction and external rotation (anti-spastic pattern). Many researches have reported that the Bobath sling is ineffective⁽⁵⁴⁾⁽⁵⁵⁾ in preventing inferior subluxation, moreover creates a harmful lateral displacement of humerus. The Roylan Humeral cuff sling⁽⁵⁶⁾ consists of a cuff around the proximal humerus for correction of glenohumeral alignment. The main advantage of this sling is that it allows freedom of movement. A recent Cochrane review⁽⁵⁷⁾ reported that none of the slings prove to be effective in preventing GHS rather they restrict the functional activity of upper limb. However, the slings can be used for a short period of time during ambulation by counteracting against the traction on joint by weight of the arm and gravitational pull. A systemic review revealed that an orthosis which comprises of humeral support are less effective as compared to orthosis with forearm support. It was concluded that wearing the orthosis which supports the shoulder through elbow, is effective in reducing vertical subluxation. There are some researches⁽⁵⁸⁾⁽⁵⁹⁾ which suggests that wearing the orthosis for four weeks would reduce the level of shoulder pain.

Lap boards and arm troughs

Lap boards and arm troughs are mostly utilized while the patient is seated. The

main aim of these instruments is proper positioning of the arm. An arm trough is an adjustable plastic box covered with foam to support the paralytic arm by raising the hand above elbow. It is fixed on the arm rest of a wheel chair on affected side whereas lap boards are flat broad surface that can be attached to any arms of wheel chair. Both of these aids have shown to assist⁽⁶⁰⁾ in correcting shoulder subluxation and produce little contracture and tonal variation that are usually associated with slings. There are a few disadvantages⁽⁶¹⁾ associated with these devices as they tend to overcorrect the subluxation and are only suitable to patients who are wheelchair bound.

Shoulder strapping

Shoulder strapping involves application of a wide variety of adhesive tape over the skin of the shoulder joint. They provide little stretch in the direction of the muscle fibers mainly posterior fibers of deltoid and supraspinatus in order to reduce shoulder subluxation. There is research evidence⁽³⁹⁾ that the correct taping technique could delay the development of HSP by 14 days. The beneficial effect of strapping over slings is that, it allows the freedom of shoulder movement. Kinesiology taping⁽⁶²⁾ seems to be promising method of shoulder strapping but little evidence is available to prove its efficacy. Overall, the strapping method is not a useful method in the management of shoulder subluxation. There are other disadvantages⁽⁶³⁾ associated with strapping such as skin irritation and vascular compromise.

Functional Electrical Stimulation

Functional Electrical Stimulation (FES) is the application of electrical current to stimulate the motor nerves and muscles fibers causing functional muscle contraction. FES used in cases of GHS is primarily used to reduce subluxation by correcting the glenohumeral alignment.⁽⁶⁴⁾ Electrodes are placed over the posterior fibers of deltoid and supraspinatus, as these muscles act as dynamic stabilizers during traction of the humerus in normal subjects. Generally the treatment last 6 hours a day, 5 to 6 days a week and for 6 weeks. Normally the intensity and duration of electrical stimulation is such that the muscle is in the state of tetanized muscle contraction. Ratio of contract: relax is modulated to avoid fatigue. There are research proven benefits of FES, such as reduction in subluxation⁽⁶⁵⁾, decrease in level of pain, and improvement in functional range of motion.⁽⁶⁶⁾ FES can also be used prophylactically, as it is believed to help prevent stretch damage to the joint capsule.⁽⁶⁷⁾

Linn et al⁽⁶⁸⁾ reported that the use of electrical stimulation (ES) resulted in no significant difference in level of pain but a visible improvement in Passive humeral lateral rotation (PHLR).Improvement in PHLR is strongly associated with reduction in shoulder subluxation. Subjects gained pain free range following ES might be due to improvement in muscle strength and cerebral plasticity following afferent nerve stimulation.

Hemiplegic shoulder pain is effectively treated with percutaneous neuromuscular electrical stimulation (NMES)⁽⁶⁹⁾ and intraarticular

corticosteroid injections.⁽⁷⁰⁾ Although corticosteroid injections produce immediate satisfactory results but its use inevitably cause post injection flare and ruptured tendon.⁽⁷¹⁾

Percutaneous NMES in a procedure which involves insertion of electrodes subcutaneously and is associated with a risk of electrode-related infections. Surface electrodes are more readily used in clinics to stimulate muscles and nerves of the affected area. Transcutaneous electrical nerve stimulation⁽⁷²⁾ is a widely used intervention to reduce pain in post-stroke upper limb dysfunction. Normally TENS is used for pain relief at the sensory level, without causing muscle contraction.

Handling and positioning techniques

Proper Positioning of paretic upper limb plays an important role in the treatment of GHS. Pillows are placed to position the paretic upper limb in neutral position in lying, sitting. It is believed to prevent muscle contractures, wasting and prevent undue stretch injury during acute phase of stroke. A study by SF Tyson and C Chissim⁽⁷³⁾ reported a handling technique to properly manipulate the hemiplegic shoulder. They compared two different handling techniques to move a hemiplegic shoulder, i.e. axilla hold and distal hold. They suggested that supporting the paretic shoulder at axilla while maintaining the external rotation will result in greater degree of pain free range of shoulder movement. It is believed that axillary hold would restore shoulder locking mechanism and lost scapula-humeral rhythm, thereby avoiding traction injuries and soft tissue entrapment. Scapular mobilization prior

to Passive range of motion in vital to prevent sub-acromion injury. During the shoulder must not be abducted beyond 90 degree unless it's accompanied with upward rotation of scapula and external rotated of humeral head.

Extracorporeal shock wave therapy

Extracorporeal shock wave therapy (ESWT)⁽⁷⁴⁾ is a non-invasive method of treating shoulder pain post stroke. ESWT a series of sonic waves, with a peak pressure up to 100 MPa, abrupt stress rise (<10ns), and a very short duration of pulse (10 μ s). During ESWT, sonic shock waves are emitted by a generator to a target area by an applicator tip. Depth of penetration ranges from 0-30 cm from the skin surface.

Brain-computer interface (BCI)

Brain-computer interface (BCI)⁽⁷⁵⁾ is an advance system of neurorehabilitation through neuro-feedback. The BCI captures the neuronal signals from brain by using electroencephalogram, magnetoencephalogram and converts the information into meaningful motor response. The information obtained from neuronal activity of brain is amplified and fed to biofeedback equipment's like FES or robotic assist devices. Consequently such interface overcomes the limitation of FES system by achieving conscious participation of the subject. BCI controlled FES system is used as neuro-rehabilitation treatment for training the upper limb impairment after stroke. This system enables the participants to directly control the activity of upper limb motor system through voluntary brain commands. Few researches⁽⁷⁶⁾⁽⁷⁷⁾ have re-

ported the significant improvement in shoulder flexion and abduction in stroke patients.

Acupuncture

Acupuncture is one of the old traditional treatment for various conditions, chronic pain, musculoskeletal problem, and neurological ailments. Randomized control trails⁽⁷⁸⁾ have reported positive effects of acupuncture in the treatment of shoulder subluxation. A recent systematic review⁽⁷⁹⁾ ⁽⁸⁰⁾ revealed the effect of acupuncture in the treatment of post stroke shoulder pain.

Summary

GHS is the most common complication associated with the flaccid paralysis post stroke. Subluxation of the shoulder predisposes to painful shoulder although no direct link has been found. Following stroke, the subluxed shoulder joint cause's functional limitations and affects quality of life. Current treatment is limited in number and feasibility of use. These include shoulder slings, tapping techniques, arm troughs, lap boards and FES. There are other options like surgery, kinesiology tapping, but the evidence supporting these are not so conclusive. Lastly, ultrasound assessment has been found to accurately measure shoulder subluxation, and FES is the best choice in shoulder subluxation preventive as well as curative.

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Review article:

Use of FDG-PET/CT for Biological Target Volume Definition in Head and Neck Cancer

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ABSTRACT

Most of patients with head and neck cancers (HNC) need curative radiotherapy either as radical treatment or in the postoperative adjuvant setting. Accurate target definition is paramount to ensure a good outcome of radiotherapy. Pretreatment Computed Tomography (CT) is regularly performed for radiation therapy planning, which both guides dose calculation and aids accurately contouring the tumor volume. Nevertheless, when using CT, the low resolution of soft-tissue and the dental artifacts may render the primary tumor identification difficult. The interobserver inconsistency on the definition of the radiation target volume is additionally a generally perceived issue. With the increase of the frequency of HNC treatment by Intensity-modulated radiotherapy (IMRT), the accurate target volume delineation performed by using Fluorodeoxy-D-glucose positron emission tomography combined to CT (FDG-PET/CT) had become even more significant. Nevertheless, the ideal technique for precisely deciding the exact margins and form of the biologic tumor volume (BTV) remains challenging. FDG-PET/CT can define BTVs either for escalation of dose or alternative treatment strategies. Debatable issues still exist on the role of FDG PET/CT during radiotherapy treatment. Moreover, some new PET tracers, other than FDG, have been investigated for imaging specific biologic tumor characteristics in HNC. The purpose of this narrative review is to discuss the use of FDG-PET/CT for BTV definition before and during delivery of radiotherapy for HNC with attention to PET tracers other than FDG.

Key words: FDG-PET/CT, biologic target volume, head and neck cancer, radiotherapy planning.

المخلص:

يحتاج معظم المرضى الذين يعانون من سرطان الرأس والرقبة العلاج الإشعاعي إما كعلاج جذري أو كعلاج مساعد بعد العمليات الجراحية. إن تعريف الهدف الدقيق في العلاج الإشعاعي هو أمر بالغ الأهمية لضمان نتائج جيدة من العلاج. يتم إجراء التصوير المقطعي قبل العلاج بانتظام وذلك من أجل تخطيط العلاج الإشعاعي، حيث يساعد في حساب الجرعة الإشعاعية ويسهم بدقة حساب حجم الورم. ومع ذلك، فعند استخدام التصوير المقطعي، فانخفاض الدقة التصويرية للأنسجة الرخوة والإضافات المعدنية للأسنان تجعل من الصعب تحديد الورم الأساسي. كما أن عدم الاتساق بين المقيمين في تعريف حجم الهدف الإشعاعي هو مسألة معروفة عموماً.

مع زيادة وتيرة علاج سرطانات الرأس والرقبة عن طريق العلاج الإشعاعي معدل كثافة (IMRT)، فتعيين حجم هدف العلاج الإشعاعي بدقة باستخدام التصوير المقطعي المدمج مع التصوير البوزيتروني باستخدام نظائر الفلوروديوكسي-دي-الجلوكوز أصبح أكثر أهمية، ومع ذلك، فإن الأسلوب المثالي لتحديد هوامش والشكل الدقيق لحجم الورم البيولوجي لا يزال تحدياً قائماً.

يمكن للتصوير المقطعي المدمج مع التصوير البوزيتروني باستخدام نظائر الفلوروديوكسي-دي-الجلوكوز أن يحدد حجم الورم البيولوجي إما لغرض تصعيد الجرعة الإشعاعية أو لإيجاد استراتيجيات العلاج البديلة. لا تزال هناك قضايا قابلة للنقاش حول دور التصوير المقطعي المدمج مع التصوير البوزيتروني خلال العلاج الإشعاعي. وعلاوة على ذلك، يتم التحقق من بعض نظائر التتبع الجديدة، خلاف الفلوروديوكسي-دي-الجلوكوز، لتصوير خصائص الورم البيولوجية في أورام الرأس والرقبة.

والغرض من هذا الاستعراض هو مناقشة استخدام التصوير المقطعي المدمج مع التصوير البوزيتروني باستخدام نظائر الفلوروديوكسي-دي-الجلوكوز لتحديد حجم الورم البيولوجي قبل وأثناء العلاج الإشعاعي لأورام الرأس والرقبة مع إلقاء الضوء على نظائر التتبع بخلاف الفلوروديوكسي-دي-الجلوكوز.

Introduction

Head and neck cancer (HNC) is the sixth most common type of cancer, representing about 6% of all cases and accounting for an estimated 650,000 new cancer cases and 350,000 cancer deaths worldwide each year (1-3). Patients needing curative radiotherapy, either as radical therapy or in postsurgical adjuvant setting, constitute 74% of the all patients with HNCs. The results of a phase III trial illustrate that there is an overall decrease of 20% in survival rate among patients who did not adhere to recognized organizational standards during their radiation therapy protocols (4). Thus, the adherence to accepted radiation therapy protocols affects their intended positive outcomes (5).

Imprecision in tumor target definition is recognized as a common source of radiation therapy error (6). Intensity-modulated radiotherapy (IMRT) use is on the rise during HNC as it allows for the delivery of high radiation doses with steep dose gradients sparing critically important adjacent tissues, (7,8). Accurate target delineation is essential for ensuring a good outcome of IMRT. Imaging plays a central role in defining the targets for radiation therapy, which is routinely planned on the basis of a single pretreatment Computed Tomography (CT) scan, thus providing the required electron density maps for dose calculation and accurate geometric contouring (9).

CT data contribute to radiotherapy planning based upon the definition of a number of target volumes defined by the International Commission on Radiation Units

and Measurements (ICRU) Report 62 (10). Grossly palpable or visible disease identified and delineated on axial CT images, is defined as a Gross Tumor Volume (GTV). It is spatially expanded depending upon natural history of disease, patterns of spread, and probability of microscopic disease being present in apparently normal surrounding tissues. The GTV is spatially expanded further to create the planning target volume (PTV), to account for setup errors related to patient and organ motions. The boundary between GTV and PTV is variable and depends on site, technique and institutional practice.

Moreover, the radiation oncologist needs to define target volumes surrounding normal structures as organs-at-risk (OARs) on axial CT images. However, the low resolution of soft-tissue and dental artifacts may complicate the identification of primary tumor when using CT. Interobserver inconsistency of radiation target volume definition is a widely known issue. In laryngeal cancer for example, target definition using only CT leads to significant inter- and intraobserver variations in delineation of the GTV (11).

Grouping both imaging modalities, Positron Emission Tomography (PET) and CT, together in one scanner machine allows the addition of functional data into anatomical images. Fluorodeoxy-D-glucose PET combined to CT (FDG-PET/CT) has become an important diagnostic tool for HNC evaluation, and is applied in various clinical settings, ranging from the detection and staging to tumor response assessment and

post-therapy follow-up^(9,12). With the simultaneous introduction of IMRT and the advances in radiation therapy techniques, the accurate target volume delineation performed by using FDG-PET/CT has become a major area of interest. However, the optimal method for accurately determining the exact margins and shape of the BTV remains challenging.

With greater access to PET / CT imaging modality, radiation oncologist has begun to consider a modification of the conventional notion of standardized administration dose for PTV. On the other hand, the idea of biological focusing on and dose mapping has turned attractive.

FDG, a glucose analog, is the most commonly used radiotracer. There are potential favorable benefits of utilizing FDG for target volume outlining. It might aid to diminish the interobserver inconsistency in GTV, help in reducing the measure of GTV, and aid in perceiving the tumor range or the lymph nodes missed by CT or MRI, and confine the distinctive GTV elements conceivably needing extra radiation dosage. Be that as it may, the utilization of FDG-PET/CT likewise bears a few inconveniences: the constrained spatial determination, and the absence of an institutionalized technique for signal segmentation, and false-positive perceived caused by inflammation. A variety of novel alternative tracers to image specific biologic tumor characteristics are under investigation⁽¹³⁾.

The correct definition and the detailed specifications of BTV remains a pending query. Since the introduce of the PET/

CT scanners target delineation in radiation therapy planning using FDG-PET/CT scans is still controversial. The purpose of this review is to discuss the use of FDG PET/CT for BTV definition before and during delivery of radiotherapy for HNC with attention to PET tracers other than FDG. Consequently,

For that purposes and after presenting the adopted research methodology, we will evaluate the two topics of (a) Target volume definition and (b) Novel PET/CT tracers. They include the consecutive subsections of : Thresholding methods for target outlining, Clinical implications, Dose escalation with PET/CT based GTV and Adaptive dose planning based on mid-therapy PET/CT, for (a); and Targeting hypoxia and Imaging proliferation, for (b).

Methodology

In order to fulfill the requirements of this narrative review, aiming to establish clinical significance of the possibility of contouring biological target volume using [18]FDG-PET/CT before and during radiotherapy treatment, especially for HNC patients, we carried out a thorough research of the bibliography in Pubmed, Google Scholar and Web of Science databases. We included unique articles disseminated during the last decade to date. The inquiry methodology utilized two mixes of Watchwords: (a) “FDG-PET/CT” AND “head and neck cancer” and (b) “Biological Target Volume Definition” AND “head and neck cancer”, and an aggregate of 155, 7 and 303 articles were found, from previously cited databases.

We evaluated every one of the titles and modified works(excluding redundant articles), surveys, publications, letters to the editorial manager, case reports, works including low statistical sampling (number of patients with cancer), non-clinical examinations and additionally include potential for PET/MRI multimodality.

A sum of 70 articles were incorporated and classified by sections and subsections as follows: Thresholding methods for target outlining ⁽²⁰⁾, Clinical implications ⁽¹²⁾, Dose escalation with PET/CT based GTV ⁽⁹⁾, Adaptive dose planning based on mid-therapy PET/CT ⁽¹⁴⁾, Novel PET/CT Tracers ⁽¹⁾, Targeting hypoxia ⁽¹⁹⁾ and Imaging proliferation ⁽¹⁶⁾.

Target volume definition

Thresholding methods for target outlining

At the level of target definition and in addition to the decision of appropriate treatment techniques, the fusion of functional imaging data into the radiation planning procedure is understood to open a pathway into new era of radiation oncology based on molecular imaging.

Integrating functional imaging into radiation therapy planning provides a specific level of functional articulation bringing the prospect for quantitative analysis of functional imaging, yielding an upper hand over anatomical imaging modalities (CT, MRI) ^(14,15). There are different means to contouring the volume of the target within PET/CT images, different methods have been reported, ranging from a manual qualitative visual method to automated quantitative or semi-quantita-

tive thresholding methods. It is challenging to identify lesion edges in noisy PET data. One of the primary regions of ambiguity is the characterization of the target 'edge'. Distinctive strategies have been established for that reason. From which we refer to the following: (1) Visual analysis, which is mainly administrator reliant and is prone to window-level settings and interpretation contrasts ⁽¹⁶⁻¹⁸⁾. (2) Iso-contouring in light of a set standardized uptake value (SUV). (3) Set limit of max tumor signal intensity (40 or 50%) ^(19,20).

A noteworthy downside of utilizing the SUV is that it is mainly affected by contrast recovery and noise characteristics that shift with reconstructive conventions and choice of scanners. Thusly, different strategies have been introduced, for example, the iterative background subtracted relative-limit utilizing watershed algorithm and hierarchical clustering in which the ideal relative-edge relies upon the tumor size not the signal-to-background ratio (SBR) (SBR) ^(21,22) and the variable threshold in view of flexible SBR ⁽²³⁾.

One an examination on 78 patients, planning methods were evaluated and it was observed that volume and shape of GTV was impacted by the segmentation technique of choice (figure 1) ⁽²⁴⁾. Applying the visual strategy, it was discovered that volumes are near CT-characterized GTV while every single automated volume were reduced. In the same report fixed SUV strategy was not successful to classify the GTV and more than fifth of PET-based GTV were off the clinical/CT-based GTV, however it is uncertain

if this symbolizes a false positive as a result of peri-tumoral inflammation. Furthermore, another examination demonstrates that SUV (SUVmax) and SBR techniques delivered a comparable GTV volume more practically identical to tumor volumes than CT or MRI. Nevertheless, none of the three techniques was successful to recognize superficial tumor expansion because of an absence of correct spatial determination ⁽²³⁾. While, gradient-based segmentation algorithm appeared to be more exact than the SBR, none of these systems is broadly accessible off institutes where they were originally produced ⁽²¹⁾.

When comparing functional volumes delineated by specific SUV cutoff and gradient percentage of the SUVmax, **Moule et al.** ⁽²⁵⁾ have discovered that the technique was not able to distinguish amid the tumor and background uptake above 36 Gy and the outlined volumes was relative to the dose conveyed. **Schinagl et al.** ⁽²⁶⁾ on a study on 12 patients with head and neck cancer reported that the segmentation tools using the primary tumor as reference correlated poorly with pathology. PETSUV was unsatisfactory in 35% of the patients due to merging of the contours of adjacent nodes. They recommended an automated segmentation method for purposes of reproducibility and inter-institutional comparison. **Perez-Romasanta et al.** ⁽²⁷⁾ reported on a cohort of 19 patients (39 lesions) with a histological diagnosis of head and neck cancer who would undergo definitive concurrent radio-chemotherapy or radical radiotherapy with intensity-modulated

radiotherapy technique (IMRT). Contouring on PET images was accomplished through standardized uptake value (SUV)-threshold definition. The threshold value was adapted to R(S/B). They concluded the methods that rely mainly on SUV(max) for thresholding, as the RS/B method, are very sensitive to partial volume effects and may provide unreliable results when applied on small lesions.

Visual interpretation by skilled experts remain the most accurate delineation technique, and there is no agreement regarding the optimal contouring method. Due to the lack of proper validated automatic segmentation tools, the visual definition (delineation) of the tumor target remains the most useful approach which is based on expert visual interpretations by radiologists and nuclear medicine physicians and on knowledge of the likely patterns of disease infiltration within strict SUV scale limits and with particular windowing protocols ⁽²⁸⁾.

On the wake of the rapid expansion of multimodalities and hybrid imaging, a question arise of whether the GTV should be defined based on single imaging modality or on several modalities and was addressed by some studies; in one such investigation, 41 patients with oropharyngeal carcinoma , GTVs were defined on the basis of findings at separate CT, MR imaging, FDG PET, and physical examination (GTVREF) and then compared to those from a combination of CT and MR imaging (GTVCTMR) and CT and FDG PET (GTVCTPET) ⁽²⁸⁾. The GTVREF was significantly larger than GTVCT-

PET and GTVCTMR for primary tumors and a poor concordance was observed. The qualitative analysis demonstrated that the underestimation of mucosal disease when contouring mainly caused such discrepancy.

The lack of concordance found between various imaging modalities in this and other studies (28-30,24) suggests that using all imaging modalities along with physical examination was the safest approach when defining a target.

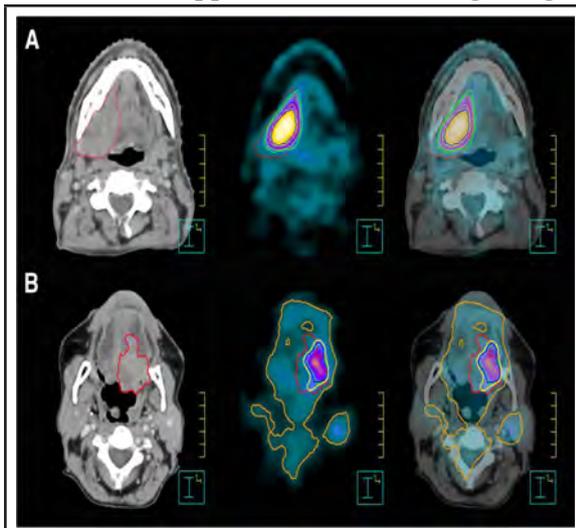


Figure (1):CT (left), ^{18}F -FDG PET (center), and combined ^{18}F -FDG PET/CT (right) patient with T4N2M0 carcinoma of oral cavity/ base of tongue, for A/B. Red color corresponds to GTV delineated on CT (absolute volumes equal to $47.5\text{ cm}^3 / 16.9\text{ cm}^3$ for A/B); green color corresponds to PET-based GTVs got by visual observation (absolute volumes equal to $43.8\text{ cm}^3 / 6.9\text{ cm}^3$ for A/B); orange color corresponds to GTVs acquired by applying isocontour of SUV of 2.5 (absolute volumes equal 32.6 cm^3 for A; this technique was unsuccessful in B as a result of consideration of substantial ranges with typical background); yellow and dark blue colors correspond to GTV with fixed threshold of 40% and 50%, respectively, of maximum signal intensity (absolute volumes equal to $20.1\text{ cm}^3 / 15.5\text{ cm}^3$ and $14.9\text{ cm}^3 / 7.1\text{ cm}^3$ for A/B); light blue color corresponds to GTV with versatile threshold in light of signal-to-background proportion (absolute volumes equal $15.7\text{ cm}^3 / 6.8\text{ cm}^3$ for A/B). (24).

Clinical implications

There have been various investigations demonstrating the impact of PET/CT on the definition of GTV and PTV. From those, we refer to an earlier study, noting the conceivable change in the GTV when utilizing the FDG-PET data for the treatment planning, by **Ciernik et al.** (19). In the study, the team explored 39 cases with solid tumors, imaged with CT and FDG-PET with an incorporated PET/CT scanner. Treatment planning were based on combined images from both imaging modalities. CT data were used at first for volume outlining; PET data were incorporated at a later stage as an overlay, later, to outline the target volume. Two independent specialists both noticed the expansion of GTV by at least 25%, as a result of PET imaging in 17% of head and neck tumor cases (2/12). Generally, 56% (22/39) of cases showed that utilizing metabolic imaging can cause a substantial change in GTV delineation. Furthermore, the study pointed that PET might be valuable to choose candidates with genuine restricted tumors and that PET/CT uncovered far off metastases for 16% of cases, hence changing the treatment arrangement from curative to palliative.

Nishioka et al. (16) investigated the advantages of joining the FDG-PET data into treatment planning by considering 21 candidates having head and neck carcinoma and they concluded that there were no visible change caused by image co-registration for 89% of cases, as far as GTV volumes for primary tumors. Clearer CTV and GTV identification on the co-registered images prompt

better normal tissue preservation. In particular parotid gland was preserved in 79% of patients whose upper neck areas were tumor-free. Besides, no attempt was carried on the study to change the size of primary tumor by thresholding methods. **Chatterjee et al.**,⁽³¹⁾ explored the differences in GTV and CTV definitions for the primary and nodal volumes when FDG PET/CT was used as compared with contrast enhanced CT (CECT) in 20 patients with oropharyngeal cancer. PET/CT gross tumor volumes were smaller than CECT volumes (mean \pm standard deviation: 25.16 cm(3) \pm 35.8 versus 36.56 cm(3) \pm 44.14; $P < 0.015$) for the primary tumor. There were no significant differences in gross tumor volume for T1/T2 disease, although differences in gross tumor volumes for advanced disease (T3/T4) were significant. The nodal target volumes (mean \pm standard deviation: CECT versus PET/CT 32.48 cm(3) \pm 36.63 versus 32.21 cm(3) \pm 37.09; $P > 0.86$) were not statistically different.

Wang et al.⁽³²⁾ and **Paulino et al.**⁽²⁰⁾ have examined the utilization of PET/CT guided IMRT for the treatment of HNC. The advantage of utilizing IMRT is that it enables a high dosage of radiation to be conveyed to the PTV while limiting the exposure of neighboring vital tissues. In the study of Wang et al., on 28 patients initial CT based staging changed in 57 % as a result of PET/CT. In 14 of 16 studied cases, they found that the volume analysis using PET/CT differ fundamentally in relation to those outlined from the CT alone, for which CT alone was not sufficient

to distinguish primary tumors for 8 patients. Moreover, 16 of 28 patients who were followed for over half a year did not have any evidence of recurrence. An aggregate of 40 patients with squamous cell carcinoma emerging in the head and neck have been investigated by **Paulino et al.** utilizing the IMRT method. They found that about 25% of candidates were subjected to PET/CT-GTV under-dose when the CT-GTV was utilized for IMRT protocol. In any case, these findings are not definite, as it is well known that GTV outlining in the head and neck can be troublesome in light of the fact that specific normal tissues can favor FDG (tonsils, base of tongue, thyroid and parotid glands). Another study by **Arslan et al.**⁽³³⁾, reported on 37 HNC patients treated with definitive radiotherapy. GTV determined by CT (GTVCT-Total) was increased in 32 cases (86.5%) when compared to total GTV determined by PET/CT (GTVPET/CT-Total). The GTV of the primary tumor determined by PET/CT (GTVPET/CT) was larger in 3 cases and smaller in 34 cases compared to that determined by CT (GTVCT). The GTV of lymph nodes determined by PET/CT (GTVLN-PET/CT) was larger in 20 cases (54%) and smaller in 12 cases (32.5%) when compared to GTV values determined by CT (GTVLNCT).

From these discussed historic cohort studies, so far on contrasting PET versus CT based GTVs, the correct impact of the modification of the target volume consequences is not well understood. In addition, inadequate number of prospective studies observed. Up to this point, many studies^(24,34,35) concluded that

the normal routine with regards to contrasting the GTV_CT with the GTV_PET isn't direct and special attention should be addressed with the speculative representations of the outcomes. The intrinsic variances between CT and PET imaging and the poor association between the images of the two modalities articulated in terms of a large statistical variation in the GTV ratios, can be attributed to such complexity. However, there are two clinical features of FDG-based PET incorporation into radiotherapy treatment planning that might be noted. At the level of the addition and/or omission of the proximal nodes into CTV for head-and-neck cancer cases, PET imaging gives confined indicative data whereas nodes identification by PET are being delineated from the CT informational index. PET imaging can likewise move radiotherapy treatment from curative to palliative should the functional imaging uncovers metastasis. Till now, there are insufficient dosimetric analyses to investigate contrasting dose volume of carried radiotherapy utilizing CT and PET-based GTV. Clinical and phantom based examinations, did not confirm the most fit approach of consolidating PET information into the radiation treatment procedures, as pointed out by Devic and Kolarova et al. ^(14,15, 36).

Dose escalation with PET/CT based GTV

Several clinical studies were performed to evaluate the feasibility of using dose escalation to a PET-based GTV contouring and the effectiveness of PET for radiation therapy planning in general ⁽³⁷⁻⁴⁰⁾. Dose gradations can be assigned to an area outlined using PET

or, otherwise, on the basis of voxel intensity according to "dose painting by numbers" ⁽⁴¹⁾.

Dose painting by numbers, assumes that a target can be defined by voxels with intensity values, but not necessary indicating whether voxels are inside or outside the target. The feasibility study of applying the dose escalation to an FDG PET-avid GTV with dose painting by numbers instead of GTV contouring was carried out elsewhere ⁽⁴²⁾. Their examination reasoned that PET-characterized BTVs are an appealing focus for dosage escalation, because of the imperfect result for the greater part of patients with HNC. Where, the needed radiotherapy dose to exceed the radio-resistance in target volume is unspecified. Radiobiological simulations may foresee such dosages; however, existing treatment calculations in the head and neck are as of now approaching tolerance dose. Of notice are two disseminated clinical studies assessing the result of 18F-FDG-PET-based treatment employing dose escalation method. Madani et al. ⁽⁴³⁾ revealed a stage 1 trial dose escalation plan of 25 and 30 Gy conveyed along 10 fractions followed by 22 fractions of 2.16 Gy utilizing IMRT, for an aggregate dosage of 72.5 or 77.5 Gy. They contemplated 23 and 18 candidates selected at dosage level 1 and 2, respectively. For four of nine examined patients, the site of relapse was inside the 18F-FDG-PET-contoured area (figure 2), despite the fact that dosages were accomplished and toxicity were experienced. In a later report, a similar research team has distributed the outcome of a phase 1 trial of DPBN conveying a mean dose

of 80.9 Gy to the high dosage CTV, for seven examined cases, and a mean dosage of 85.9 Gy to the GTV, for 14 considered cases, at 32 fractions.⁽⁴²⁾The initial 10 fractions included a voxel intensity based (DPBN) IMRT plan utilizing a pattern of ¹⁸F-FDG-PET scan, for every patient. Using a similar imaging method (¹⁸F-FDG-PET) for fractions 11-20 and the rest of the fractions were carried out by applying a uniform dose IMRT, they perceived that the radiation exposed volume of normal tissue and target was decreased, especially while escalating dose to GTV. Madani et al.⁽³⁹⁾ had not reported any grade 4 toxicity taking note that just 9 of 21 patients, got corresponding chemotherapy, follow-up have indicated mucosal ulcers as the dosage restricting toxicity. For a period of 4 to 10 months following the treatment, six examined cases had mucosal ulcers where five of them were seen at dose level II (mean aggregate dose of 85.9 Gy to the GTV). Therefore establishing dose level I (mean aggregate dose of 80.9 Gy to the high CTV) as the upper tolerance dose in the study and the significance of longer-term aftercare and follow-up in these investigations.

Optimization in term of balancing dose escalation (fraction dose, total dose) effectiveness versus patient safety (toxicity) and the added advantage of PET/CT tumor volume delineation should be addressed further in clinical research.

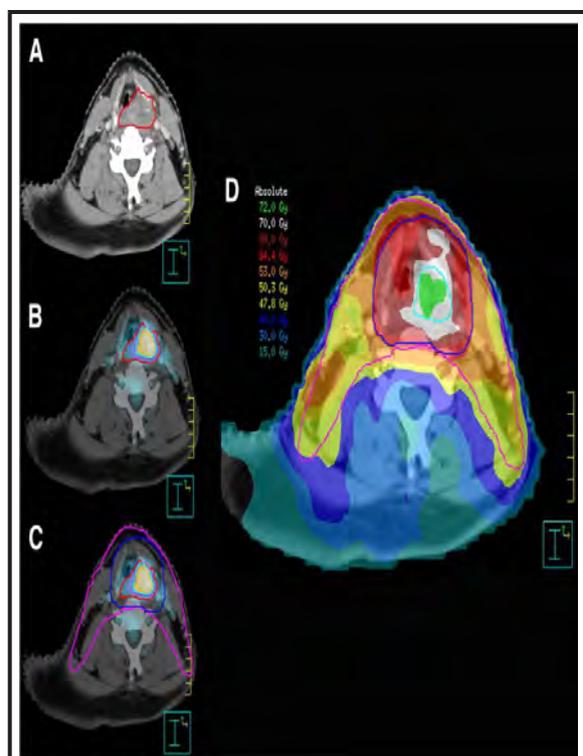


Figure (2): Patient with T3N2M0 hypopharyngeal carcinoma imaged with CT (A), compared to ¹⁸F-FDG PET combination images (B and C) and the corresponding measured dose (D). Red/light blue color refers to GTV portrayed on CT, GTV_{CT} , and ¹⁸F-FDG PET utilizing adaptive threshold based on signal-to-background ratio, GTV_{SBR} , (absolute volume of 39.0/13.1 cm³). Moreover shown are target volume to 50.3, 68.0 and 72.0 Gy for pink, dark and light blue colors, respectively. Sub volume of GTV_{CT} has received a dose of 72.0 Gy due to added integrated IMRT boost of 4.0 Gy.⁽⁴³⁾

Adaptive dose planning based on mid-therapy PET/CT

The compromise between disease control and toxicity in head and neck cancer in both chemotherapy and radiation therapy is subtle. Cure rates remain unsatisfactory, while intensity and toxicity of treatment have been described as “pushed to what must be the limits of human tolerance”^(44,45). In attempts to optimize the therapeutic ratio for individual patients, personalizing treatment is gaining

interest. The alteration of radiation delivery, during the therapy course, based on changes in the normal and tumor tissues, can be considered as a mean to achieve such personalized treatment. CT scan is typically utilized –pretreatment- for radiation therapy planning to delineate the target volume and any organs at risk. Treatment usually proceeds without taking into account the anatomic changes arising during the course of fractionated dose delivery. **Geets et al** ⁽⁴⁶⁾ observed a reduction of 51% and 48% in the clinical and in the planned target volumes, respectively, after a partial radiation therapy treatment course of 45Gy. In a later study of patients with laryngopharyngeal cancer receiving chemo-radiation therapy ⁽⁴⁷⁾, PET-based and CT-based primary tumor GTVs were found to decrease at a mean rate of 3.2% and 3.9% per treatment day, respectively, while nodal GTVs decreased at a rate of 2.2% per treatment day. In addition, spatial shifts were noted in the GTV. Furthermore, geometric shifts in the position of the primary tumor during treatment differed between PET and CT-defined GTVs. Thus, it is suggested that anatomic (CT) and the functional (PET) imaging modalities provide complementary information during treatment (figure 3).

Adaptive radiation therapy delivers an advantage by means of improving the therapeutic ratio i.e. minimizing the overall dose to normal tissues and focusing therapeutic dose at tumor tissues, and presents a clinical challenge. Of great interest is the characterization of therapy regimen alteration relied to tumor based on changes observed on im-

ages. The usefulness of integrated biologic and functional imaging techniques is concretized by tumor sub volumes identification (eg, radiation-resistant hypoxic regions) as candidates for dose escalation ⁽⁴⁸⁾. The non-uniform radiation delivery can be guided by biologic characterization of tumor and neighboring tissues at functional imaging. **Geets et al.** ⁽⁴⁶⁾, in a study examining 10 patients encountering pharyngolaryngeal SCC and treated with CRT and subjected to various imaging modalities (MRI, CT and ¹⁸F-FDG-PET during the course of treatment (at baseline and after mean recommended doses of 14, 25, 35, and 45 Gy)), demonstrated that the early reaction observation over the treatment can aid the modification or the adjustment of the overall procedure. Utilizing a technique based on the gradient to outline GTVs on ¹⁸F-FDG-PET, throughout radiotherapy regimen. GTVs were considerably diminished, yet stay less than those characterized with MRI and CT ($P < 0.001$) for all cases. In contrast to pre-treatment CT based volume contouring a gradual decrease of the irradiated volume by 15% to 40% was observed.. In addition, they observed that just high dose volumes ($\geq V90$) were affected by this adaptive approach with additional sparing of organs at risk (OAR). **Hentschel et al.** ⁽⁴⁹⁾ investigated serial ¹⁸F-FDG-PET scans at three times during CRT on 37 patients contrasting changes in SUV with baseline. They noted that a 50 % drop in SUVmax after 10 to 20 Gy radiation dose delivery, for the studied case, was predictive of two years OS (88% versus 38%, $P = 0.02$),

“and a below median volume of disease defined on baseline PET was also predictive of two year OS (83% versus 34%, $P= 0.02$).”

Key challenges present in the use of functional imaging to guide adaptive radiotherapy treatment. Proper selection of imaging technique is an issue with few data to support one choice of one modality over the other, reproducibility of imaging characteristics critical for modifying dose delivery is another issue, **Bittner et al.** ⁽⁵⁰⁾ and **Lin et al.** ⁽⁵¹⁾ demonstrated significant difference in hypoxic sub-volumes identified on successive ¹⁸F-fluoromisonidazole (FMISO) PET scans obtained before treatment. Moreover, the optimal timing for radiology imaging evaluation during the course of treatment is unknown. Decreasing tumor uptake and increasing the nonspecific background activity, limit the utility of obtained PET images in the course of fractionated radiation therapy ^(13,42,46,47). Also, the impact of concurrent chemotherapy on changes during treatment process is uncertain and the optimal tumor contours method is not well-understood. On the other hand, the decrease of tumor to background uptakes ratio makes it difficult to use automated tools related to the threshold SUV. The maximal SUV of tumor imaged with FDG-PET, decrease progressively and the volume defined by the threshold SUV is unchanged during the radiation treatment course, as found by **Moule et al.** ⁽⁵²⁾. The possibility of moving beyond the simple delivery of homogeneous dose to an anatomically defined treatment volume, becomes possible thanks to the inclu-

sion of functional imaging into the treatment planning process. Thus, the adaptive planning of the radiotherapy treatment protocols based on functional imaging is a relatively new area of investigation, and it remains in the realm of research. Nevertheless, we cannot imagine that radiation therapy will continue to be delivered exclusively on the basis of a single pre-treatment imaging assessment of the tumor.

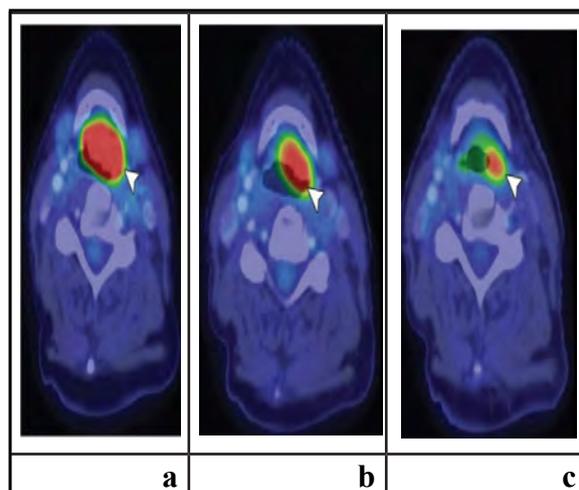


Figure (3): Adaptive therapy planning in a 68-year-old man with a supraglottic SCC (T2N2bM0) treated with chemoradiation therapy (70 Gy in 35 fractions over 7 weeks, two cycles of cisplatin 100 mg/m² per day in weeks 1 and 5). (a) Axial fused PET/CT image obtained before the start of therapy shows marked metabolic activity (SUVmax, 22.2) in the tumor (arrowhead). (b) Axial fused PET/CT image obtained after 11 fractions of radiation therapy shows a reduction in tumor size and metabolic activity (SUVmax, 9.7). (c) Axial fused PET/CT image, obtained after 21 fractions of radiation therapy, shows continued reduction in tumor size and metabolic activity (SUVmax, 7.9)(9).

Novel Pet/Ct Tracers

FDG is not a tumor-specific tracer and accumulation in benign lesions, such as

regions of inflammation, causes false-positive results with consecutively low specificity. Therefore, novel alternative tracers with higher specificity are under investigation for the non-invasive imaging of cellular processes such as hypoxia and proliferation (45).

Targeting hypoxia

As concluded in the work of (53), hypoxia is an established indicator of poor prognosis for patients with head and neck cancers. It leads to radiation resistance in tumor cells. **Hall et al.**, (54) found that the needed cell-killing dose, in hypoxic conditions, reach the three time value of those in normoxic conditions. Hypoxia imaging provides relevant information for treatment planning in HNC. It enables dose escalation in hypoxic tumor tissue while sparing non hypoxic surrounding tissue (figure 4). This contributes to a reduction of post radiation side effects and consecutive improvement of the quality of life in these patients in spite of intensified radiation dose. Yet the main requirement of hypoxia imaging remains dose adjustment for IMRT. The assessment of tumor hypoxia can be carried out by a number of invasive techniques. They include the polarographic oxygen electrodes and the immunohistochemical staining of pathologic specimens. Additionally, from the many existing number of PET tracers, allowing the noninvasive visualization of hypoxia, we cite the mostly investigated one, FMISO, that has been used for the assessment of HNC (55-58). It has been used for hypoxic GTV definition, in the form of 18F-FMISO, during a study aiming to demonstrate

the potential to dose-escalate to sub volumes (59,60). Moreover, **Lee et al.** (61) delivered a dose of 70Gy to the gross tumor volume (GTV; the range of 18F-FMISO uptake inside the 18F-FDG-PET/CT GTV) and a dose of 84 Gy to the hypoxic GTV, for ten cases without surpassing ordinary tissue tolerance. They found that the hypoxic GTV dose of 105Gy was feasible for one of two patients sparing normal tissue. On the other hand, **Thorwarth et al.** (59) studied 13 candidates and analyzed the dosage painting by numbers (DPBN) in contrast to IMRT plan keeping up iso-toxicity, observing an increase of tumor control probability from 0.552 to 0.702 by dose escalation to a contoured 18F-FMISO hypoxic volume. The sequential time variability constraint of the 18F-FMISO imaging makes difficult clinical studies with dose escalation to 18F-FMISO-defined volumes

Moreover, **Nehmeh et al.** (62) have shown that a voxel by voxel investigation of putative hypoxic regions, for patients undertaken two benchmark 18F-FMISO scans along 3 separated days, uncovered a solid association over the two time points in under 50% of patients. Delivering a higher target-to-background signal ratio, the hypoxia-specific PET agent Fluorine 18 fluoroazomycinarnoside (FAZA) clears the blood more rapidly than FMISO (63,64). Moreover, **Grönroos et al.** (65) showed theoretically that the Fluorine 18 fluoroerythronitroimidazole (FETNIM) is a more potent indicator of hypoxia than FMISO, owing to its greater hydrophilia and better pharmacokinetics. To define the optimal

time point for the integration of hypoxia ^{18}F -FAZA-PET/CT information into radiotherapy treatment planning to benefit from hypoxia modification or dose escalation treatment, **Bollineni et al.** ⁽⁶⁶⁾ reported that instead of using the FAZA-BL scan as the basis for the dose escalation, FAZA at the second week of chemo-radiotherapy is most suitable and might provide a more reliable basis for the integration of ^{18}F -FAZA-PET/CT information into radiotherapy treatment planning for hypoxia-directed dose escalation strategies. Appearing to be promising hypoxia-specific radiotracers, FAZA and FETNIM required in depth investigation, especially in direct comparison with FMISO. On the other hand, using numerous Cu isotopes ($^{60}/^{61}/^{62}/^{64}$) as a form of Cu-diacyetyl-bis(N4-methylthiosemicarbazone) (Cu-ATSM) can be considered as a PET tracer for imaging hypoxia. The ^{64}Cu isotope was considered as a non-invasive marker of tumor hypoxia due to its ideal physical properties and great formation yield ⁽⁶⁷⁾. For hypoxic and normoxic cells, the $[\text{Cu}(\text{II})\text{-ATSM}]$ complex is diminished by intracellular thiols bringing about an unsteady complex $[\text{Cu}(\text{I})\text{-ATSM}]$, which is in turn re-oxidized to a more stable state $[\text{Cu}(\text{II})\text{-ATSM}]$ that diffuses out of cells in normoxic cells. While, in hypoxic cells it separates gradually and irreversibly caught by intracellular copper chaperone proteins. In rat models, Lewis et al. ⁽⁶⁸⁾ have shown the association between ^{60}Cu -ATSM and tumor pO_2 and **Chao et al.** ⁽⁶⁹⁾ have demonstrated that the dissemination of ^{60}Cu -ATSM inside the GTV of patients with HNC was heterogeneous and

planned delivery of 80 Gy into 35 fractions to the ATSM-avid tumor sub-volume and the delivery of 70 Gy into 35 intervals to the GTV without compromising normal tissue dose tolerance. **Grassi et al.** ⁽⁷⁰⁾, reported in HNC patients, F-FDG and Cu-ATSM provided similar results about delineation of BTV.

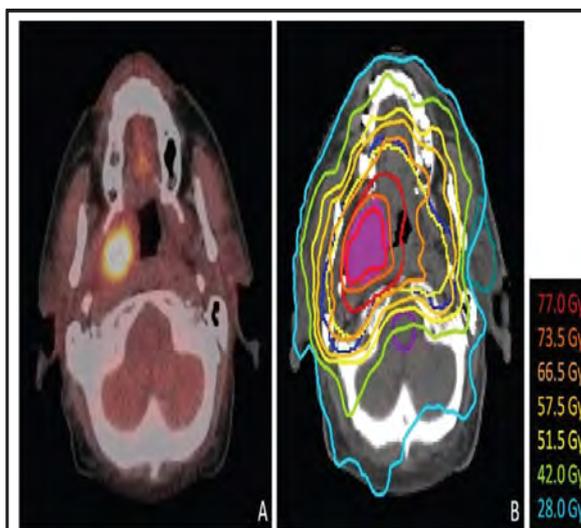


Figure (4): A. ^{18}F -FMISO PET/CT acquired 4h pi. A hypoxic volume was delineated based on this image by applying a 40% threshold relative to the maximum SUV. This contour was then registered to the RT planning CT and prescribed with 110% of the conventional dose (77 Gy). B. Corresponding slice of the RT planning CT with the FMISO PET based hypoxic target volume overlaid in pink. Resulting IMRT dose distribution of a homogeneous dose escalation by 10% is shown. Regions of interest: PTV70 (red), PTV60 (yellow), PTV54 (blue), left parotid gland (dark green), brain stem (purple). (71).

In summary, no appropriate hypoxia-agent for PET can be favored most, each agent has its advantages and disadvantages and may be better suited for evaluating particular tumor types than others, allowing for extra studies to be investigated for such purpose.

Imaging proliferation

Both chemotherapy and radio-therapy treatment can cause the rate of cellular proliferation in responding tumors and consequently the tumor size to decrease⁽⁷²⁾, on the other hand continued and accelerated cell reproduction is an indication of treatment failure⁽⁷³⁾. Developing imaging strategies is crucial to identify tumor cell repopulation for early response assessment and to delineate these areas as targets for dose escalation. Unlike FDG, the FLT-PET is the most widely used to assess cellular proliferation^(74,75) and allows the detection of cellular division as it is taken only the actively dividing and not surrounding inflammatory cells. FLT uptake can be used for early monitoring of cellular response to radiation treatment in HNC tumors^(73,76).

Studies had shown that FLT can provide an advantage of assessing early tumor response to therapy in HNC patients with good reproducibility of SUV measurements and with changes in uptake observed prior to changes in tumor volume⁽⁷⁶⁻⁷⁸⁾.

As illustrated by **Troost et al.**⁽⁷⁶⁾, it is technically feasible to delineate areas with high cell proliferation for dose escalation. However, the use of FLT is not histologically validated. **Linecker et al**⁽⁷⁹⁾ concluded that the FLT uptake and the Ki-67 index are not correlated, after a study of 19 patients with head and neck SCCs. Due to its uptake by the germinal centers of reactive lymph nodes, leading to a low positive predictive value, the FLT cannot yield a clear differentiation between benign and malignant abnormal cervical lymph node

⁽⁸⁰⁾. The ultimate need of further research is obvious concerning the establishment of the FLT in the assessment of early treatment response and the adaptive radiation therapy planning.

Furthermore, the accelerated repopulation along the radiotherapy for HNC can unfavorably influence result. Besides, the advancement of PET tracers for DNA synthesis imaging may provide better specificity than ¹⁸F-FDG-PET which is additionally taken up by peri-tumoral inflammatory cells. The tracer 3'-Deoxy-3'-¹⁸F-fluorothymidine (¹⁸F-FLT) mirrors the activity of thymidine kinase 1, a key enzyme in DNA synthesis and is taken up by dividing tumor cells however not by terminally separated resistant reaction cells⁽⁸¹⁾. **Troost et al.**⁽⁵⁹⁾ examined 10 patients with HNC (two of them have gotten corresponding chemotherapy) and investigated the role of such tracer in early reaction evaluation to radiotherapy, as shown in figure 5. They imaged patients utilizing ¹⁸F-FLT-PET/CT, before and along the second and fourth weeks of the radiotherapy course, where in the fourth week they noted a substantial lessening in CT-based GTV, contouring not perceived at earlier phase of the treatment and major changes in SUV_{mean} and SUV_{max} on ¹⁸F-FLT images as early as one-week post radiotherapy and a further decrease before the fourth week of treatment.. Utilizing a subjective fixed SUV_{max} limit of 80%, permitting the tumor sub-volume to be outlined in the first and second ¹⁸F-FLT PET scan, the feasibility of dosage escalation was illustrated. Whereas, the expected repopulation hap-

pening after a month of radiation treatment were not reflected on the uptake of ^{18}F -FLT PET along the radiation delivery for patients with HNC. Moreover, the feasibility study of Fuzzy Locally Adaptive Bayesian algorithm (FLAB) as the ideal segmentation strategy for the proliferative volume for repeated FLT PET/CT along chemo-radiotherapy, for patients with HNC, was carried out by **Arens et al.** ⁽⁸²⁾. Also, there are some studies demonstrating the uptake reduction of ^{18}F -FLT PET relative to the radiation delivery duration, for Squamous Cell Carcinoma (SCC) of the esophagus case study. **Yue et al.** ⁽⁸³⁾ on the other hand, noted a raise in the uptake of ^{18}F -FLT PET after treatment breaks mirroring the acceleration of the repopulation process.

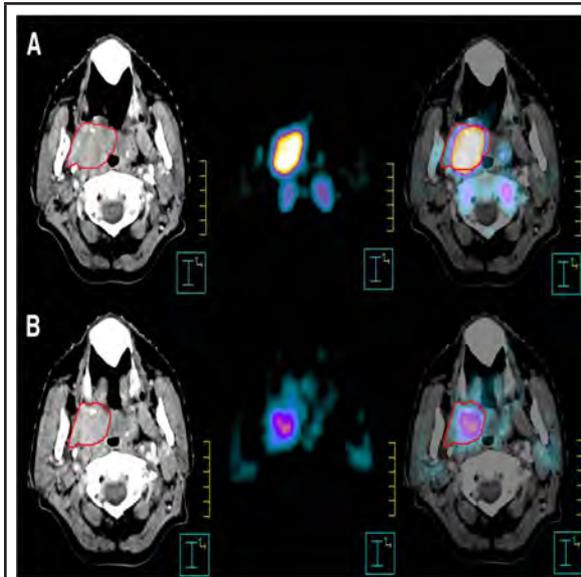


Figure (5):CT (left), ^{18}F -FLT PET (center), and combined ^{18}F -FLT PET and CT (right) patient with T3N0M0 oropharyngeal carcinoma before and after 8 fractions of 2 Gy radiation treatment for (A) and (B), respectively. Red color corresponds to GTV based on CT imaging modality. As observed, there is an considerable decrease in ^{18}F -FLT PET signal intensity compared to the small reduction of GTV on CT.(76).

As hypoxic tumor volume eventually decreases during the course of treatment, further studies are needed to investigate best practice to integrate methods of adapting treatment regimen delivery. Proliferation imaging play a vital role in monitoring specific tumor reactions, and hence the effectiveness of the therapy procedure, post radiation therapy mostly when treating below tumoricidal threshold dose.

Conclusion

FDG use is rapidly increasing as tracer in PET functional imaging due to both its high sensitivity and specificity in cancer imaging, emerging new tracers might in the near future play a bigger role in cancer management but not likely replace FDG soon. Limitation in regulations and lengthy clinical trials along economic feasibility is still a hindrance in the path of adopting such novel tracers clinically. Clinical examination together with CT remains the optimal standard for target volume definition in the planning of radiotherapy for HNC. PET/CT provides unique and complementary information about target volume which may increase the precision of radiotherapy planning. To what extent this improves the treatment outcomes for patient with HNC is unclear and will require further research.

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GUIDELINES FOR MANUSCRIPT PREPARATION

A. TYPES OF MANUSCRIPTS

I. ORIGINAL MANUSCRIPTS

Manuscripts submitted in this category are expected to be concise, well organized, and clearly written. The maximum length is 5000 words, including the abstract, references, tables, and figure legends. The maximum length is 5000 words, including the abstract, references, tables, and figure legends.

- The structured abstract must not exceed 250 words.
- The title must not exceed 130 characters.
- A maximum of 4 tables and 4 figures is allowed.
- References should not exceed a maximum of 100.
- The abstract must be organized as follows:
 - Background & Aims
 - Methods
 - Results
 - Conclusions
- Do not use abbreviations, footnotes or references in the abstract.
- An electronic word count of the abstract must be included.
- Three to ten key words at the end of the abstract must be provided.

The manuscript must be arranged as follows:

- Title page
- Abstract
- Introduction
- Materials and methods (or Patients and methods)
- Results
- Discussion
- Acknowledgements
- References
- Tables
- Figure legends
- Figures

Acceptance of original manuscripts will be based upon originality and importance of the investigation. These manuscripts are reviewed by the Editors and, in the majority of cases, by two experts in the field. Manuscripts requiring extensive revision will be at a disadvantage for publication and will be rejected. Authors shall be responsible for the quality of language and style and are strongly advised against submitting a manuscript which is not written in grammatically correct English. The Editors reserve the right to reject poorly written manuscripts even if their scientific content is qualitatively suitable for publication. Manuscripts are submitted with the understanding that they are original contributions and do not contain data that have been published elsewhere or are under consideration by another journal.

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Review articles on selected clinical and basic topics of interest for the readers of the Majmaah Journal of Health Science will be solicited by the Editors. Review articles are expected to be clear, concise and updated.

- The maximum length is 5000 words, excluding the summary, references, tables, and figures.
- References should not exceed a maximum of 150.
- The inclusion of a maximum of 4 high-quality tables and 4 colored figures to summarize critical points is highly desirable.
- Review articles must be accompanied by a title page and a summary.

- Reviews should include at least one Key Point Box, with a maximum of 5 bullet points, that briefly summarizes the content of the review.

Review articles are reviewed by the Editors and may be sent to outside expert reviewers before a final decision for publication is made. Revisions may be required.

III. EDITORIALS

This section consists of invited brief editorial comments on articles published in the Majmaah Journal of Health Science

The length of an editorial should not exceed 1500 words, excluding references.

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- References should not exceed a maximum of 20.
- A title page must be provided.

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Case reports would be only accepted if they represent an outstanding contribution to the Etiology, pathogenesis or treatment of a specific condition.

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The length of a Letter to the Editor should not exceed 800 words.

- A maximum of 1 table or 1 figure is allowed.
- References should not exceed a maximum of 10.
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International commentaries will be solicited by the Editors only.

- Commentary articles should not exceed a maximum of 800 words, excluding tables or figures.
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- References should not exceed a maximum of 10.
- A title page must be provided.

B. MANUSCRIPT SUBMISSION

ORGANIZATION OF THE MANUSCRIPT

- The submitted manuscript must be typed double-spaced throughout and numbered (including references, tables and figure legends). Preferably using a "standard" font (we prefer Times/Arial 12).
- For mathematical symbols, Greek letters, and other special characters, use normal text. The references must be in accordance with the Vancouver reference style (see References).
- Approved nomenclature for gene and protein names and symbols should be used, including appropriate use of italics (all gene symbols and loci, should be in italics) and capitalization as it applies for each organism's standard nomenclature format, in text, tables, and figures.
- Full gene names are generally not in italics and Greek symbols are not used. Proteins should not be italicized.
- Improperly prepared manuscripts will not be entered into the peer review process and will be sent back to the author for correction.

TITLE PAGE MUST CONTAIN:

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- Number of figures and tables.
- List of abbreviations in the order of appearance.
- Conflict of interest.
- Financial support.

Animal trials: Manuscripts reporting experiments using animals must include a statement giving assurance that all animals received human care and that study protocols comply with the institution's guidelines. Statistical methods used should be outlined.

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REFERENCES

References must be in accordance with the Journal of Hepatology reference style. References are ordered as they appear in the text and citation numbers for references are placed between "brackets" ("[]") in the text as well as in the reference list.

Authors should be listed surname first, followed by the initials of given names (e.g. Bolognesi M). If there are more than six authors, the names of the first six authors followed by et al. should appear.

Titles of all cited articles are required. Titles of articles cited in reference list should be in upright, not italic text; the first word of the title is capitalized, the title written exactly as it appears in the work cited, ending with a full stop. Journal titles are abbreviated according to common usage, followed by Journal years, semicolon (;) before volume and colon (:) before full page range (see examples below).

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An example of how references should look within the text:

"HVPG was measured by hepatic vein catheterization using a balloon catheter according to a procedure described elsewhere [14, 15] and used as an index of portal hypertension [16]."

An example of how the reference list should look:

[14] Merkel C, Bolognesi M, Bellon S, Zuin R, Noventa F, Finucci G, et al. Prognostic usefulness of hepatic vein catheterization in patients with cirrhosis and esophageal varices. *Gastroenterology* 1992;102:973-979.

[15] Groszmann RJ, Wongcharatrawee S. The hepatic venous pressure gradient: anything worth doing should be done right. *Hepatology* 2004;39:280-282.

FIGURES

A maximum of 4 figures is allowed

(This can be modified if needed by Editorial board).

- Figures will be often, but not always, re-designed by graphic designers. By signing and transferring the Copyright Agreement to MJHS, the author gives permission to the graphic designers to alter the visual aspect of any figures, tables, or graphs. The scientific content of figures will not be altered. Please provide this information with your covering letter.
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- Illustrator compatible EPS files with RGB color management (*.eps),
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- Include tables in the submitted manuscript as a separate section.

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- Figure legends should be listed one after the other, as part of the text document, separate from the figure files.
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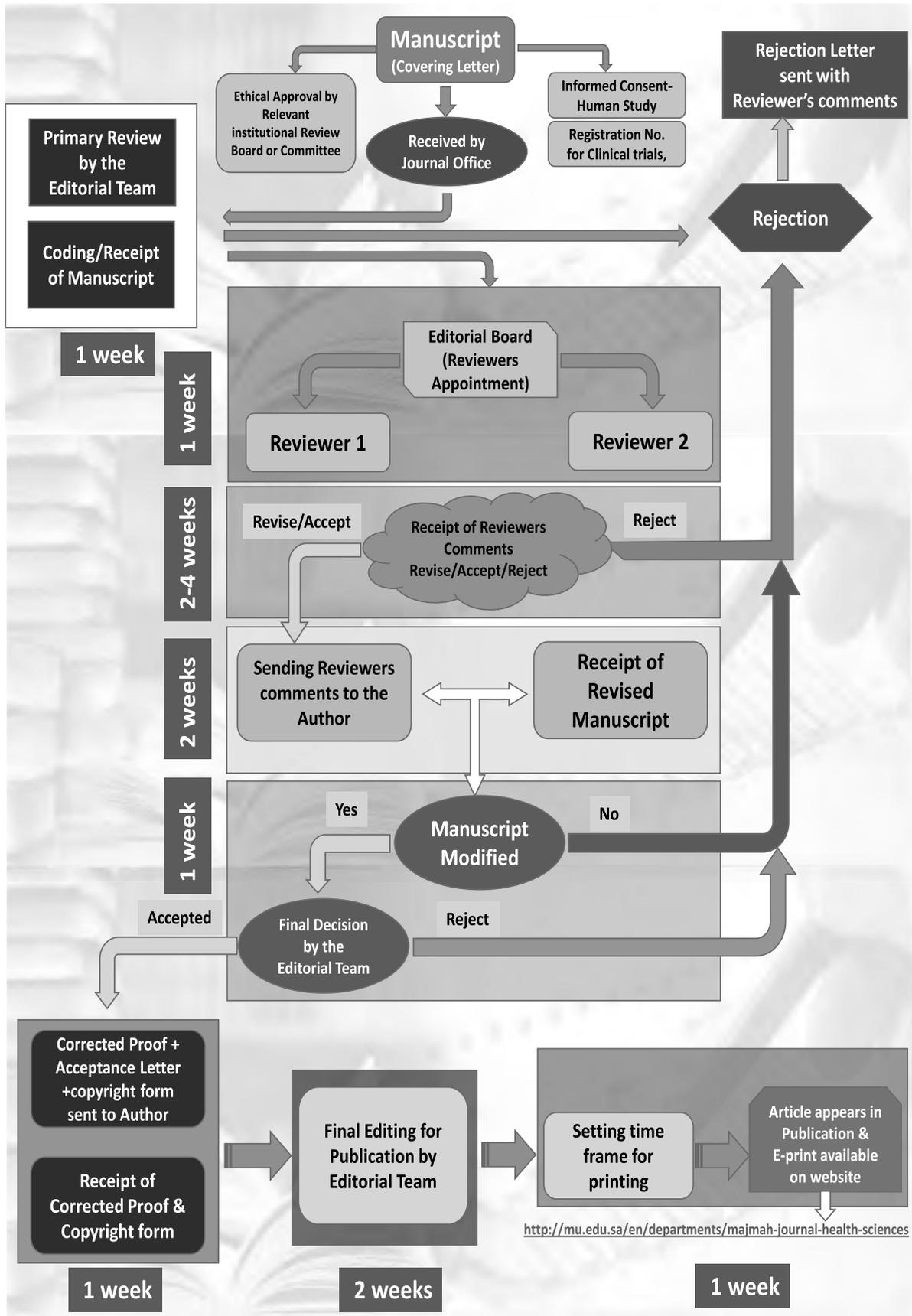
The manuscripts should include a complete and detailed description of what was done. This includes a description of the design, measurement and collection of data, the study objective and major hypotheses, type and source of subjects, inclusion and exclusion criteria and measures of outcome, number of subjects studied and why this number was chosen. Any deviation from the study protocol should be stated. The baseline characteristics of any compared groups should be described in detail and -if necessary -adjusted for in the analysis of the outcome.

For randomized clinical trials the following should also be clearly documented: treatments, sample size estimation, method of random allocation and measures taken for maintaining its concealment including blinding, numbers treated, followed-up, being withdrawn, dropping out, and having side effects (numbers and type). The statistical methods used should be relevant and clearly stated. Special or complex statistical methods should be explained and referenced.

Complex analyses should be performed with the assistance of a qualified statistician. Unqualified use of such analyses is strongly discouraged. The underlying assumptions of the statistical methods used should be tested to ensure that the assumptions are fulfilled.

For small data sets and if variable distributions are non-normal, distribution free (non-parametric) statistical methods should be used. The actual p values - whether significant or not - should always be presented (not NS). Confidence intervals convey more information than p values and should be presented whenever possible. Continuous variables can always be summarized using the median and range which are therefore preferred. Only in the infrequent case of a Normal distribution are the mean and standard deviation (SD) useful. Complex analyses (including Cox and logistic regression analysis) should be presented in sufficient detail: i.e. variable scoring, regression coefficients, standard errors and any constants. Odds-ratios or relative risks are not sufficient documentation of such analyses. The handling of any missing values in the data should be clearly specified. The number of statistical tests performed should be kept at a minimum to reduce spurious positive results. Explorative (hypothesis generating) analyses without confirmation using independent data are discouraged. Figures showing individual observations e.g. scatter plots are encouraged. Histograms may also be useful. Tables should indicate the number of observations on which each result is being based





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