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ORIGINAL SCIENTIFIC ARTICLE

Case Report

Adult onset still's disease in a 60 year old male patient with fever of unknown origin and chronic diarrhea

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# EDITORIAL TEAM OF THE UQU MEDICAL JOURNAL

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## Case report

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UQU Medical Journal

*Original Article*

# Glycaemic control markers fasting plasma glucose, glycated haemoglobin and fructosamine and their inter-relationship in non-diabetic and type 2 diabetes Saudi community

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## استخدام المؤشرات البيوكيميائية للدالة على كفاءة تنظيم سكري الدم في مرض السكر (نوع 2)

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### الملخص العربي

**الأهداف:**استخدام قيم تركيز الهيموجلوبين المرتبط بالسكر و الفركتوزأمين والجلوكوزفي البلازما (حالة الصيام) كمؤشر للدلالة على كفاءة تنظيم سكر الدم في مرضى السكر ( نوع 2) ودراسة الارتباط البيوكيميائي بين هذه المؤشرات الثلاث في مرضى السكر (نوع2) ومقارنتها بالأشخاص الأصحاء في المجتمع السعودي المكي.

**الطريقة:** عينة الدراسة تم إختيارهم عشوائياً من المجتمع المكي إناثاً وذكوراً أصحاء (359) ومرضى سكر ( النوع 2 ) (246) تم تعيين الجلوكوز والفركتوزأمين والهيموجاوبين المرتبط بالسكر في عينات البلازما باستخدام COBAS plus 400 – INTEGRA والتحليل الإحصائي باستخدام WINKS SDA 2007 .

**النتائج:**لم نتمكن من إيجاد ارتباط بين جلوكوز البلازما (حالة الصيام) في اليوم الأول وقيم الفركتوزأمين أو الهيموجلوبين المرتبط بالسكر بعد 42 يوماً في مجموعة عينة الدراسة (( الأصحاء A )).

هنالك ارتفاع في تركيز الجلوكوز والفركتوزأمين والهيموجلوبين المرتبط بالسكر في البلازما في مرضى السكر نوع 2 عن الأصحاء . تركيز جلوكوز البلازما في حالة الصيام يتناسب طردياً مع مستوى الهيموجلوبين المرتبط بالسكر وكذلك الفركتوزأمين في مرضى السكر نوع 2 , هذه العلاقات لم يتم التوصل إليها في حالة الأصحاء. تشير النتائج إلى إمكانية استخدام هذه المؤشرات الثلاث في تشخيص ومتابعة مرضى السكر من نوع ( 2 ).

**الخاتمة :** قيم تركيز الجلوكوز والهيموجلوبين المرتبط بالسكر والفركتوز في الدم (حالة الصيام) لمرضى السكر ( 2 ) أعلى من قيم الأصحاء, وهنالك إرتباط بين هذه المؤشرات ويمكن استخدامها في تشخيص ومتابعة مرضى السكر ( نوع 2 )

## ABSTRACT

**Objective:** To establish the reference ranges of fasting plasma glucose, HbA1c% and fructosamine, and the relationship among those glycaemic control markers in the non-diabetic and compared with type 2 diabetes Saudi population of Makkah city.

**Materials and Methods:** The study was conducted among 574 Saudi residents of Makkah, with 393 male and 181 female inhabitants. There was no history of diabetes in 328 individuals and the remaining 246 individuals were known to have type 2 diabetes mellitus. All participants were volunteers and randomly selected from the population of Makkah with aged ranged from 17 to 89 years. Type 2 diabetes subjects were selected according their previous diagnosis and clinical and biochemical finding. Pearson correlation is used to investigate the correlation among the glycaemic control markers.

**Results:** In type 2 diabetes fasting plasma glucose, HbA1c, and fructosamine levels were significantly higher 2, 2, and 1.5 fold than non-diabetic population. No correlation was observed among the estimated parameters in non-diabetic group whereas the in diabetic patients, the correlations were significant; r: 0.58, 0.66 and 0.71 for FPG vs. HbA1c, FPG vs. fructosamine, and HbA1c vs. fructosamine respectively, ($p \leq 0.001$).

***Keywords*:** Fasting plasma glucose, Fructosamine, Diabetes, Glycemic control, Glycated heamoglobin.

## INTRODUCTION

Measurements of glycated haemoglobin ( HbA1c) and fructosamine reflect the average of blood glucose concentrations over the preceding 6-12 weeks[1,2] and 2-3weeks[3,4] respectively. Both HbA1c and fructosamine determinations are used widely to assess the long-term[5,6,7] and short-term[8,9] glycaemia respectively, and to screen, diagnose and monitor glycaemic control in diabetes mellitus. The variations in HbA1c quantification and different reference ranges between different laboratories are attributed to diverse technical methods applied for the determination and the poor standardization[10] thus limiting the value as well as interpretation of the results.

Haemoglobinopathies, haemoglobin variants and hypertriglyceridaemia interfere with the estimation of HbA1c, where the value may be unreliable and inconsistent with a patient's clinical finding[11]. In such circumstances estimating fructosamine seems to be the method of choice for monitoring short-term glycaemia, [8,9,12,13] however with the limitation that <3.0 is not very low albumin concentration < 3.0 $g.l^{-1}$ may result in falsely low fructosamine value.

The aim of this study is to establish glycated haemoglobin and fructosamine along with fasting plasma glucose values as a measure of glycaemic control and to evaluate the relationship between these analyses in non-diabetic subjects and patients with type 2 diabetes in local Saudi community. This study was carried out in the absence of local and national reference ranges and lack of national standardization schemes for HbA1c and fructosamine determination. The use of locally derived values rather than national initiatives or international published values is beneficial and advisable since it is recommended that each laboratory should investigate the transferability of the expected values to their own patient's population and if necessary determine its own reference ranges.

A crucial element of modern below-knee amputation technique has been the more or less universal adoption of long posterior myoplastic flap,[10,11] as popularized by Burgess et al.[12] The healing of this flap is crucially dependent upon the blood supply. Considerable differences are noted in the various descriptions of how the posterior flap in below-knee amputation should be reconstructed.[10] One of these is whether to include or remove the soleus muscle that forms the main bulk of muscles in the posterior compartment of the leg at this level.[11]

The aim of the present work was to study the blood supply of the skin of the upper posterior aspect of the leg and the soleus muscle and to explore the anatomical basis of the possibility of excision of the soleus muscle from the posterior flap in below-knee amputations.

## MATERIAL AND METHODS

Study population: This cross-sectional population study consisted of 605 volunteers categorized into three groups as under:

**Group A**: 31 healthy adults (17 male and 14 female, age ranged from 19-28 years) with no known history of diabetes mellitus. The group included in order to assess the relationship between HbA1c % or the concentration of fasting plasma fructosamine with single fasting plasma glucose value of the preceding 42 days.

We hypothesize that HbA1c and fructosamine values would not reflect the fasting blood glucose concentration of the same sample for the preceding 6 weeks.

**Group B:** 328 apparently healthy individuals (193 male and 135 female, between 17 to 89 years) with no previous history of diabetes mellitus.

**Group C:** 246 type 2 diabetes mellitus patients (200 male and 46 female, between 17 to 78 years) on oral hypoglycaemic medication.

Measurements of fasting plasma glucose, fructosamine and HbA1c were determined on the same sample in non-diabetic subjects (group B) and type 2 diabetes mellitus participants group C were expressed as mean ±SD. The values were used for reporting reference ranges for the studied population and for the assessment of the correlations among the glycaemic control parameters using regression analysis.

**Setting**: All participants were Saudi residents in Makkah, Saudi Arabia.

**Laboratory assays**

All biochemical analyses were determined at Medical Research Laboratory of Umm Al-Qura University using COBAS INTEGRA 400 plus, Roche. Blood was drawn by venipuncture from individuals fasted 8-12 hr, with Li-heparin as anticoagulant. Glucose concentration was determined in plasma by hexokinase method, the coefficient of variation (c.v.) within run 1.9 % and 1.4% at the means of 81.40 and 234.85 $mg.dl^{-1}$ and between run 2.1% and 1.7% at the means of 81.83 and 234.00 $mg.dl^{-1}$ respectively.

Haemoglobin A1c (HbA1c) was determined in whole blood by immunoturbidimetric method with final result expressed as a percent HbA1c (HbA1c%). The c.v. within run 1.3% and 2.1% at the means of 5.3 and 10.9 and between run are 1.6 % and 1.9% at the means of 5.3 and 11 respectively. Fructosamine was assayed colorimetrically in plasma free from haemolysis. The c.v. within run 2.4% and 2.8 % at concentrations 284 and 543 $\mu mol.l^{-1}$, and between run 2.3% and 3.1% at 282 and 537 $\mu mol.l^{-1}$ respectively.

Cholesterol was determined by enzymatic colorimetric method, HDL-cholesterol, LDL-cholesterol were measured with homogeneous enzymatic assay. Triglyceride was measured by enzymatic, colorimetric method. Urea and albumin were measured by kinetic test. Glutamate dehydrogenase, and colorimetric assay with endpoint method respectively.

**Statistical analysis**

All statistical analysis were performed using TexaSoft WINKS SDA software, Statistical data Analysis, 6.0.8, PROFESSIONAL, Edition 6, cedar hill, Texas, 2007. The statistical significance was evaluated by Student's t-test, and all p values were two-tailed test.
Linear regression, Pearson correlation analysis were used to assess the correlation among parameters.

# RESULTS

**Table1**: shows the fasting plasma glucose (FPG), fructosamine concentrations, and HbA1c%, values for day zero and day 42 in group A. According to table, values for all measured parameters are within the reference range, for non-diabetic subjects. There is no statistical difference between the 1st and 2nd measurements of each parameter. The actual minimum and maximum values are 49-98 ($mg.dl^{-1}$), 4.5-5.9 (%), and 183-264 ($\mu mol.l^{-1}$) for glucose, HbA1c% and fructosamine respectively. Linear regression analysis shows no correlation between HbA1c% and the values of fasting plasma glucose of the preceding 42 day. The same finding for fructosamine, and no correlation was found between HbA1c and fructosamine values. The only correlations were reported in Table 1 between 1st and 2nd determinations of glucose, HbA1c and fructosamine.

**Table 1: The relationship between HbA1c(%), fructosamine, and the fasting plasma glucose of the preceding 42 days in healthy subjects.**

| | Day zero estimate | Day 42 estimate | r ( $p \leq 0.001$ ) |
|---|---|---|---|
| FPG ( $mg.dl^{-1}$) | 75.65 ± 9.49 | 73.94 ± 10.07 | 0.67 |
| HbA1c (%) | 5.00 ± 0.31 | 5.07 ± 0.27 | 0.84 |
| Fructosamine ($\mu mol.l^{-1}$) | 227.97 ± 17.22 | 228.00 ± 18.42 | 0.85 |

Table 1: Values are mean of 31 observations ± SD.
r : Pearson's correlation coefficient

**Group B:** Since no statistically significant differences were found for the estimated parameters between males and females in the non-diabetic (group B), and diabetic (group C), the data were all combined and presented as mean of each group in Table 2.
The confidence intervals about the mean 99% were 75.33-78.91 ($mg.dl^{-1}$), 5.05-5.23 (%), and 217-223 ($\mu mol.l^{-1}$) for fasting plasma glucose, HbA1c%, and fructosamine respectively for group B, and all means for the presented parameters in Table 2 for non-diabetic subjects fall within the reference values reported by the manufacturer. The usual practice of describing a reference range is as a mean **±2** SD**,** were for the studied non-diabetic population, as follow:
Fasting plasma glucose ($mg.dl^{-1}$) 52-102, HbA1c(%) 3.86-6.42, and fructosamine ($\mu mol.l^{-1}$) 178-262. The HbA1c% or fructosamine values do not correlate with fasting plasma glucose levels, also no significant correlation between HbA1c% and fructosamine values in non-diabetic population, the findings are consistent with those observed in group A.
Lipid profile (Total cholesterol, HDL-cholesterol, LDL- cholesterol, and triglycerides), urea, and albumin values are consistent with healthy individuals, in group B, whereas the values of the parameters in group C type 2 diabetes are statistically different from group B non-diabetic individuals, p-values are shown in the Table 2.

**Table 2. Population characteristics and correlation among glycaemic control parameters in non-diabetic and type 2 diabetes**

Values are the mean of the number of observations in parentheses ±SD.

| | Non-diabetic (328) | Type 2 diabetes (246) | P-2 tailed |
|---|---|---|---|
| Age (years) | 32.8 ±13.4 | 48.6 ±12.9 | |
| range | 17-89 | 17-78 | |
| FPG ($mg.dl^{-1}$) | 77.12 ±12.6 | 153.25 ±79 | ≤0.001 |
| HbA1c (%) | 5.14 ±0.64 | 9.85 ±3.7 | ≤0.001 |
| Fructosamine ($\mu mol.l^{-1}$) | 220 ±21 | 335 ±107 | ≤0.001 |
| Total Cholesterol ($mg.dl^{-1}$) | 171 ±32 | 179 ±42 | ≤0.008 |
| HDL-Cholesterol ($mg.dl^{-1}$) | 48 ±23 | 42 ±11 | ≤0.001 |
| LDL- Cholesterol ($mg.dl^{-1}$) | 106 ±28 | 114 ±34 | ≤0.004 |
| Triglycerides ($mg.dl^{-1}$) | 103 ±58 | 174 ±43 | ≤0.001 |
| Urea ($mg.dl^{-1}$) | 26 ±8 | 33 ±14 | ≤0.001 |
| Albumin ($mg.dl^{-1}$) | 4.3 ±0.5 | 4.2 ±0.4 | ≤0.005 |
| r : pearson correlation | | | Combined values (574) |
| HbA1c vs FPG | 0.07 | 0.58 | 0.73* |
| Fructosamine vs FPG | 0.04 | 0.66 | 0.76* |
| HbA1c vs Fructosamine | 0.17 | 0.71 | 0.81* |

*** combined values (non-diabetic & type 2 diabetes population).**

**Group C:** As shown in the Table 2 the mean values of fasting plasma glucose, HbA1c% and fructosamine of the diabetic subjects are higher by 2.2 and 1.5 fold than the values of non-diabetic population respectively. The

$p \leq 0.001$. HbA1c values correlates well with FPG and fructosamine, and fructosamine correlates with FPG, $p \leq 0.001$. The r values for the correlation ships among the glycaemic parameters were shown in table 2, and the linear regression equations which illustrate these relationships in type 2 diabetes are:

$FPG\ (mg.dl^{-1}) = 32.7497 + (12.228\times\ HbA1c\%)$
$FPG\ (mg.dl^{-1}) = -8.6885 + (0.4837\times\ fructosamine\ (\mu mol.l^{-1}))$
$Fructosamine\ (\mu mol.l^{-1}) = 135.5614 + (20.2173\times\ HbA1c\%)$

# DISCUSSION

Means and reference tested ranges of glycaemic control measures in healthy non-diabetic individuals (group A) are as follows:

The mean of FPG is about 77 $mg.dl^{-1}$, and the reference range is 52-102 $mg.dl^{-1}$. When the values of FPG were placed in to six categories, of 10 $mg.dl^{-1}$ intervals, and the corresponding mean values of HbA1c and fructosamine were tested using one-way analysis of variance, the average mean values across the categories of group A were not statistically different and indicate that all six categories are from a homogeneous population.

The mean of HbA1c is about 5.1 %, and the reference range is 3.9 - 6.4 %. When the values of HbA1c were placed in to 4 categories of 1% intervals and the corresponding mean values of FPG, and fructosamine were tested using one-way analysis of variance, the average mean values across the categories of the group were not statistically different, and indicate that all four categories are from a homogeneous population.

The mean of fructosamine is about 220 $\mu mol.l^{-1}$ and the reference range is 178 - 262 $\mu mol.l^{-1}$. When the values of fructosamine were placed in to 3 categories of 40 $\mu mol.l^{-1}$, intervals and the corresponding mean values of FPG and HbA1c were tested using one-way analysis of variance, the average mean values between the categories were not statistically different, and indicate that all categories are from a homogeneous population.

About 99% of the studied population (group B) fell within the reported reference ranges of FPG, HbA1c%, and fructosamine. Other estimated plasma chemistries (Total cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides, urea, and albumin) were within the normal ranges.

The relationships between the glycaemic parameters are as follows: In healthy subjects with no known history of diabetes mellitus although the fasting plasma glucose concentration was almost stable over a difference of 42 days( from day zero to day 42) with good correlation $r = 0.67$, $p \leq 0.001$, fasting plasma glucose do not represent the mean or average of blood glucose concentrations during the course of 42 days, a single fasting plasma glucose represents the glucose level at the time of sample withdrawal only, and reflects the physiological glycaemic control. The statistically significance ($p \leq 0.001$) correlation between matched values of glucose, HbA1c and fructosamine indicate the stability of these parameters (glycaemic control) during the course of the investigation. The absence of correlation between the values of HbA1c% or fructosamine with the preceding 42 days values of fasting plasma glucose does not contradict that HbA1c and fructosamine levels, reflecting the average of plasma of glucose the preceding 6-12 and 2-3 weeks.[1,2,3,4] FGP level which represents just one point (lowest) of about seven points measurements were used to estimate the mean of plasma glucose[14]. The higher value of Pearson's correlation coefficient for HbA1c% and fructosamine in comparison to glucose may indicate the stability of these parameters and less variation than FPG estimate, hence more reliable indicators for measuring past short- and long-term glycaemic control during the course of treating diabetes mellitus or even looking for the past (2-12) weeks glycaemic control in healthy subjects.

No correlation was found among the estimated glycaemic parameters in non-diabetic population (group B), and in group A. FPG does not represent the prevailing mean plasma glucose concentration, whereas in diabetic subjects (group C), FPG well correlated with

HbA1c and fructosamine measurements, and HbA1c well correlated with fructosamine. The loss of the correlation in non-diabetic population could be due to narrow physiological ranges of FPG, HbA1c and fructosamine, since all data points clustered around the mean of the population, and fall at the bottom of the regression line, so incomplete and invalid data sets limit to derive the correlation. This represents the stable physiological state rather than the pathological state of diabetes, whereas strong correlation among the broad distribution ranges of glycaemic parameters. Moreover combined data of non-diabetic and diabetic population showed a stronger correlation, and the predicted values are lower than those predicted by using diabetic population data.

The correlation of fructosamine with FPG and HbA1c in diabetic and combined (diabetic and non-diabetic) population were reported.[15,16] A poor, moderate and strong correlation between FPG and HbA1c in non-diabetic, diabetic + non- diabetic and diabetic population, were observed respectively.[17] Our results however support stronger correlation in combined data population. Also a strong correlation between HbA1c and preprandial glucose in type 2 diabetes, was observed.[18]

From linear regression analysis, we report that for each 1% in HbA1c represents about 12mg.dl$^{-1}$ FPG or 20 µmol.l$^{-1}$ fructosamine, and 20µmol.l$^{-1}$ fructosamine increase corresponds to about 10 µmol.l$^{-1}$ FPG in type 2 diabetes population.

The correlation between HbA1c and mean plasma glucose is reported in longitudinal and cross-sectional studies in type 1 and 2 diabetes as well as general population, and showed variable predicted estimates of mean plasma glucose, 1% rise in HbA1c represents 18 to 36 mg.dl$^{-1}$ rise in average plasma glucose.[14,19,20,21,22] The glycation of haemoglobin is influenced by erythrocyte life-span, haemolobinopathies, glucose transmembrane gradient, age, and race,[24,24,25] under such condition FPG and fructosamine are valid as glycaemic control markers.

In diabetic subjects FPG, HbA1c, and fructosamine values are significantly higher than non-diabetic, this indicates the persistent of hyperglycaemia in diabetic population, and estimating mean plasma glucose is impractical for patients and physician, so FPG along with HbA1c and fructosamine are valid parameters to monitor glycaemic control and provide important feedback to physician and patient. Discordance among these parameters suggests revising patient's blood disorder, diet and exercise behavior, or even medication regimen.

Although the size of studied population is comparable with other published work, it could limit the study. The volunteers past health history, clinical picture, and plasma chemistries are normal, but not performing OGTT to exclude undiagnosed diabetes could have limitation.

## CONCLUSIONS

Fasting plasma glucose, HbA1c, and fructosamine values are significantly higher in type 2 diabetes than non-diabetic population. Linear regression analysis demonstrated that FPG, HbA1c, and fructosamine are valid markers for glycaemic control in type 2 diabetes and non-diabetic population.

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# SLIP ,TRIP AND FALLS INJURIES DURING MUSLIMS PILGRIMAGE

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## النمط الوباءي لإصابات زلات القدم والانزلاقات والسقوط أثناء موسم الحج

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### الملخص العربي

**الأهداف:** لمعرفة طراز إصابات الانزلاق والسقوط وزلات القدم عند حجاج بيت الله الحرم سيزيد الإلمام والاهتمام بالمشكلة مما يساعد على وضع الدراسات لتقليلها.

**المرضى وطرق الدراسة:** دراسة مقطعية عرضية شملت 253 مريض بقسم الجراحة بمستشفى النور التخصصي تم فحصهم بالطوارىء أثناء الفترة من 2006 وحتى 2009م بنسبة (1:2) الرجال للنساء و 14.6% أطفال أقل من 10 سنوات.

**النتائج :** كل المصابين الذين تم فحصهم بالطوارىء بإصابات زلة القدم والانزلاق والسقوط تم حصرهم بغض النظر عن العمر وقد أظهرت النتائج أن مثل هذه الإصابات ليست كما كان الانطباع كلها بالبسيطة أو المتوسطة ولكنها قد تكون خطيرة، علماً بأن نموذج وطراز الإصابات يختلف قليلاً عن الإصابات الكبيرة وتحدث مثل هذه الإصابات بصورة واضحة وكبيرة لتجمعات الحجاج مع لفت النظر لأن نقاط الازدحام قد قل في الجمرات إلا أنه زاد بمناطق محطات القطار الجديدة والذي لم يؤثر على نموذج الإصابة.

**الخلاصة:1** ـ هذه أول دراسة لمثل هذه الإصابات والتي بينت حقيقة أن إصابات الانزلاق والسقوط وزلات القدم تحدث بكثرة مع زيادة فرصة الوفاة وحدوث المضاعفات.
**2**ـ ستكون هذه الدراسة معين لوضع تصورات ومشروعات صحية لتقليل الإصابات وتحسين مشاريع الصحة للحجيج ومناطق التجمعات أثناء موسم الحج.

## ABSTRACT

**Objective:** To identify the pattern and magnitude of slip, trip and falls injuries among pilgrims to improve the awareness and propose the measures to reduce them.

**Patients and Methods:** This is a cross-sectional study of all patients seen in the emergency department of Alnoor Specialist Hospital, Makkah, during the Hajj period of 2006-2009. Data was collected on a designed porforma. A total of 253 patients, male to female ratio (2:1). Thirty-seven (14.6%) were children below 10 years.

**Results:** All patients were presented to emergency department ( ED) with history of slip, trip and falls injuries. With no exception, all patient seen in this study have had some skeletal injuries, regardless of age and no mortality. In this study, children below 10 years have the same pattern of injuries of adults with higher magnitude. Only one patient of abdominal injury required laparotomy. No chest injuries was reported in this study. This study is a reflection of status of minor trauma due to slip, trip and falls and raising the attention of the magnitude of the problem especially when the train transport will start.

**Conclusion:** Slip, trip and falls injuries are very common during the Hajj and no age is immune, children are exposed to these types of injury with higher chance of morbidity. It is preventable if the pilgrims follow the instructions and regulations of Saudi Arabia. This first report on the pattern of injuries caused by slip, trip and falls during the hajj, it is minor trauma with major impact. This study will be of help to health care planners and officials and it is required for all significant mass gathering to minimize risks and maximize safety.


***Keywords*:** Slip , trip and falls injuries, Muslim pilgrims, Hajj. Mass gathering.

## INTRODUCTION

Hajj is the fifth of the five pillars of Islam. Any healthy Muslim adult is obliged to perform Hajj once in his/her life if he/she is financially and physically capable.
Approximately, 2 to 3 million pilgrims perform Hajj every year from around the globe, one-third of them come from within Saudi Arabia (citizens and lawful residents) and two thirds come from other countries. The hajj has become the epicenter of mass migration of millions of Muslims of enormous ethnic diversity and no other mass gathering can compare, either in scale or in regularity.

The injuries due to slip, trip and falls are relatively common, due to number of factors unique to Hajj. These include; overcrowding, considerable physical exertion, travel often undertaken by foot and walking through or near dense traffic, necessary to fulfill the hajj rites. More and above, we are expecting new points of crowding when the new train transport start on this Hajj time, where the pilgrims will find themselves in large crowds and at a more risk of getting these types of injuries.
This is the first report comes out from Alnoor Specialist Hospital, the biggest tertiary hospital, In Makkah, among other three hospitals belonging to Ministry of Health where free medical care services are provided to all pilgrims.

## PATIENT AND METHODS

The study was a cross sectional one to all patients presented to emergency department (ED) of Alnoor Specialist Hospital, Makkah, with history of slip, trip, and falls (STF) injuries. The study lasted 15 days period in four successive years (2006-2009) were included in the study. A total of 253 patients included in this study, their age ranged from one month to ninety years. One hundred thirty-five (53.4%) of whom were pilgrims from outside Saudi Arabia and 118 patients (46.6%), from inside the Saudi Arabia, 70 of whom (27.6%) were Saudi and 48 (19%) were residents. There were 80 (31.6%) females and 173 (68.4%) males with the male to female ratio of 2:1. Among them were 37 (14.6%) children below 10 years of age.

Data was collected on a designed porforma and assessed age, sex, nationality, pilgrims from inside or outside and the diagnosis. Patients with superficial laceration who did not need active management were excluded from the study.

## RESULTS

A total of 253 patients from inside and outside the Saudi Arabia with their demographic characteristics (Table 1), presented with history of slip, trip and falls injuries were seen in Emergency Department (ED) of Alnoor Specialist Hospital, Makkah. They were Two-hundred sixteen (85.6%) adults, and 37 patients (14.6%) children. The range of age of all patients from one month to ninety years table 1 & 2. The causes of injuries in children were either trip of their parents or pushed in crowds. Two-thirds of injured children 25 (67.6) in this study were diagnosed to have cerebral concussion with or without fracture skull (table 3). This study showed that slip, trip and falls were responsible for high morbidity among the children.

**Table 1: Demographic characteristics of all patients**

| Characteristics | Numbers & ( %) |
|---|---|
| Sex: | |
| Male: | 173 (68.4 %) |
| Female: | 80 (31.6 %) |
| Hajj (pilgrims status): | |
| Saudi | 70 (27.6% ) |
| Lawful residents | 48 (19.0 % ) |
| Other countries | 135 (53.4 % ) |
| Age group: | |
| 0 -10 | 37 (14.6 5) |
| 11-20 | 6 ( 2.37 ) |
| 21-30 | 20 (7.9 %) |
| 31-40 | 24 (9.48 %) |
| 41-50 | 29 (11.46 %) |
| 51-60 | 55 (21.74 %) |
| 61-70 | 53 (20.9 %) |
| 71-80 | 22 (8.69 %) |
| 81-90 | 6 (2.37 %) |

**Table 2. Age distribution of the children patients.**

| Age of the patient | Number of patients |
|---|---|
| One month | 2 |
| 6 months | 2 |
| 8 months | 2 |
| 9 months | 1 |
| 1 year | 2 |
| 2 years | 3 |
| 3 years | 10 |
| 4 years | 2 |
| 5years | 4 |
| 6 years | 3 |
| 7 years | 2 |
| 8 years | 3 |
| 10 years | 1 |

**Table 3. The injuries of the 37 children are shown.**

| The diagnosis | Number of cases & % |
|---|---|
| Cerebral concussion | 17 (45.94%) |
| Fracture skull | 8 ( 21.6%) |
| Supracondylar fracture humorous | 7 ( 18.9%) |
| Fracture of right radius | 1 (2.7%) |
| Fracture pelvis | 1 (2.7%) |
| Fracture cervical spine | 1 (2.7%) |
| Fracture shaft right femur | 1 (2.7%) |
| Injury to right hand | 1 (2.7%) |
| Total | 37 (100%) |

The common injury in the patients more than 10 years old was fracture femur, 99 patients (39%). Fifty-three patients had fractures in the shaft, 32 patients had fractures in the neck of the femur and 14 patients had trochanteric fractures. The next common injury was cerebral concussion, 31 patients (12%) Table 4.

**Table 4. The common injuries in the study are shown in**

| The injury | The number of the patients | The percentage |
|---|---|---|
| Fracture femur( shaft, neck and trochantr) | 99 | 39 % |
| Cerebral concussion | 31 | 12 % |
| Fracture ankle joint | 23 | 9 % |
| Coles' fracture | 15 | 5.9 % |
| Fracture skull | 11 | 4.3 % |
| Fracture humorous(shaft&supracondylar) | 14 | 5.5 % |
| Fracture tibia(shaft &medial maleolus) | 10 | 4.1 % |
| Fracture pelvis &lumber spine | 7 | 2.8 % |
| Fracture radius | 7 | 2.8 % |
| Fracture patella | 6 | 2.4 % |
| Shoulder dislocation | 5 | 2 % |
| Fracture acetabulum | 5 | 2 % |
| Miscellaneous (abdominal & soft tissues injuries ) | 20 | 8.2 % |
| Total | 253 | 100% |

One patient was admitted with fracture base skull and required intubation and Intensive Care Unit (ICU) admission and one patient admitted with intra-abdominal bleeding required laparotomy. All patients required admission to the hospital, with no mortality. The follow up was short because all patients were coming for pilgrimage. The patient on discharge was given full medical report including the diagnosis, the management done for him and instructions of follow up.

In spite of limitations this study, it is only a reflection of status of minor trauma due to slip, trip and falls.

## DISCUSSION

This is the first emerged report from Al-Noor Specialist Hospital, biggest hospital in Makkah, during Hajj specifically on slip, trip and falls injuries, while all previous studies covered trauma in general. All publications revealed that trauma was the major cause of morbidity and mortality at the Hajj[1], and the most common surgical presentations were orthopedic and neurosurgical.[1,2,3] Almost all pilgrims experience some form of trauma and considerable number of them are due to slip, trip and falls, where the stampedes are more likely at the hajj because of the extraordinary pressure of numbers in a limited, if large, space.

In this study more than 92% of all patients with no exception of age diagnosed as skeletal fractures with or without cranial injuries and up to 7.9% resulted for variety of other injuries. The limbs fractures alone accounted for almost three quarters (74.2%) The most serious consequences of fall in elderly are fractures of hip, humorous, wrist and pelvis.[4,5,6] In this study the most common serious injuries of falls are fractures femur 99 (39%), and then cerebral concussion 42 (16.3%) with fracture skull. It shows a significant injuries resulting from slip, trip and falls during Muslim pilgrims because pilgrims travel either by foot, walking through or near a dense traffic, worth to mention that no chest injuries reported and no mortality.

Slips, trips and falls (STFs) injuries are frequent events in childhood and the craniofacial injuries are the most common trauma.[7] The large majority of injuries, which occurred in children under the age of 6 years take place at home and mainly due to lake of save home environment.[8]

In United Arab Emirates they found the common cause of trauma in the age group less than 5 years is fall (41.1%).[9,10] In this study, the majority of adult patients seen in the emergency department (ED) were older than 50 years 136 (53.7%) who sustained fracture femur and cerebral injuries going with the same pattern of other studies of Hajj trauma.[1,3,4]

Of note in this study highlighted clearly the high susceptibility of category of children below 10 years of age 37 (14.6 %) of the patient and almost experienced all types of skeletal injuries including the cerebral concussion (Table III) due to STFs, injuries, all of them required admission. Slip, trip and falls injuries are common in United State and Western countries especially in elderly.

The annual incidence of falls is approximately 30% in person over the age of 65 years.[11] In the study the incidence of fell in patients over the age of 60 years is (31.5%.) almost the same

percentage. In this study, no single patient presented with chest injuries and only one abdominal injury need surgery due to (STFs).

This study revealed obviously the children as a new risk group among the pilgrims and the pilgrims needs to be forewarned of the risk of companion the children in Hajj. Ongoing surveillance and data analysis is necessary to better understand health risks and strengthen evidence base for health policy and prevention in dealing with enormous complex and challenging mass gatherings.

Many of these issues and findings coinciding with other studies of Hajj trauma which can be eased by the Islamic laws specially when realize that there are hazards accompanying children. Other measures to reduce the risk of slipping, tripping or falling during Muslim pilgrimage, we have to slow down on walking, avoid walking through or near dense traffic, limit the load and should not obstruct the vision, make sure you have adequate "tread" (proper footwear), keep their mind focused on what they are doing and using trains or buses for transportation.[12,13]

## CONCLUSION

Slip, trip and falls injuries during Muslim pilgrimage are very common but preventable or can be dramatically reduced if the pilgrims complied by Hajj laws and with the concessions granted by Islam which Hajj is for adult Muslims who are physically and financially able and capable to perform Hajj.

This study revealed information on the pattern of injuries caused by slip, trip and falls during the hajj. It is hoped that this information will be of help to health care planners and officials to provide optimal and cost effective health care services in attempt to minimize the risks and maximized the safety to pilgrims in Hajj. Pilgrims must follow the instructions of safety and rules of Hajj.

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# Testicular tumor at King Faisal Specialist Hospital and Research Centre - Jeddah, Kingdom of Saudi Arabia

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## الاورام الخصوية في مستشفى الملك فيصل التخصصي ومركز الأبحاث، جدة، المملكة العربية السعودية

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### الملخص العربي

**المقدمة:** الاورام الخصوية من الاورام الشائعه بين الرجال ما بين سن (20-35) - 94% من هذه الاورام ناشئة من الخلايا الجنسية (المنتشيه) وهي تنقسم الى 30% اورام منويه ,وليست ذات عدوانية وطبيعة نموها بطيئة ولاتنتشر سريعا و 70% غير منويه دائما ما تحدث مبكرا وتشمل الاورام المسخية و اورام الكيس المحي والسرطانات المضغيه و الميشامية.

**الاهداف:** تهدف هذه الدراسة لتحديد انماط الاورام الخصوية مع معرفه حصيلة علاجها.

**الطريقة:**اجريت هذه الدراسة الاسترجاعية في مستشفى الملك فيصل التخصصي بجدة المملكة العربية السعودية وذلك خلال الفترة من العام 2000_2009 وقد شملت الدراسة 25 مريض تم جمع معلوماتهم السريرية بأستمارة معدة مسبقا شملت الاعراض والظواهر المرضية مع الطرق العلاجية ونتائجها وقد تم تحليل المعلومات بالطريقة الاحصائية spss.

**النتائج :** شملت الدراسة ما مجموعه (25) مريض ووصل متوسط العمر فيهم 29.7 +/- 10.2 منهم 13 في المرحلة الاولى للسرطان و6 بالمرحلة الثانية و6 بالمرحلة الثالثة – من مَن شملتهم الدراسة 14 منهم مصابين بالاورام الخصوية غير المنوية و10 بالاورام الخصوية المنوية وواحد باورام خلايا ليدج . كل المرضى تم علاجهم جراحياً منهم 14 خضعوا للعلاج الكيماوي بعد الجراحة و 4 احتاجوا علاج اشعاعي و3 منهم تم استئصال الغدد الليمفاوية خلف البريتون و4 لم نتمكن من متابعتهم وقد تراوحت فترة المتابعة لما بعد العلاج بين 5 -91 شهراً بمتوسط 35 شهراً ومن الذين تمت متابعتهم خلال هذه الفترة وصلت نسبة الحيا ه منهم 95 %.

**الخلاصة :** ان الاورام الخصوية من أخطر سرطانات الذكور الا انها جيدة الانذارية اذا ما تم علاجها صحيحاً . الدراسات متعددة المراكز ضرورية و مهمة لايجاد ومعرفة اطر وخصائص هذه الاورام كما يجب ان تكون هذه الدراسات موجه لتطوير استراتيجات تشخيص وعلاج الاورام الخصوية في هذا البلد.

**الكلمات الرئيسية:** الاورام الخصوية - السريرية – العلاج- المملكة السعودية.

## ABSTRACT

Testicular cancer is the most common cancer in males between 20 and 35 years of age. Worldwide, testicular cancer has the highest incidence in Europe. Germ cell tumors account for about 94% of testicular cancers. These cancers are separated into two groups, seminomas (30%) and nonseminomas (70%). Seminomas are less aggressive, tend to grow slowly, and usually do not metastasize. Nonseminomas include four types: yolk sac tumors, teratomas, embryonal carcinomas, and choriocarcinomas. They often occur earlier in life and grow and spread more quickly than seminomas. This article addresses the demographics, histology and treatment of testicular tumors in our institute, Jeddah, Saudi Arabia.

**Objectives:** To determine the pattern of testicular tumor and management out come.

**Methods:** This is a cross-sectional study was conducted at King faisal Specialist Hospital and Research Centre ,Jeddah,KSA. We reviewed, retrospectively, the files of all patients treated, at our institution, for testicular cancer from 2000 till 2009. The information regarding: clinical presentation, histopathological pattern, stage at presentation, modality of treatment, and complications of treatment were collected and statistically analyzed.

**Results:** A total of Twenty-five patients were reviewd. Average age was 29.7 (+/- 10.2 SD). Of the 25 patients, 13 patients presented with stage I, 6 patients with stage II and 6 patients with stage III disease. Fourteen patients had Nonseminoma (NS), 10 had Seminoma (S) and 1 had Leydig cell tumor. Post radical orchidectomy, 14 patients required chemotherapy, 4 patients received radiation therapy, 3 patients underwent RPLND and 3 patients were on surveillance. Of the last 3, one NS patient required RPLND 6 months later and one S patient required chemotherapy after one year. The average follow up was 35 months, ranges between 5 and 91 months. Four patients were lost during follow up. Among the rest the overall survival is 95%.

**Conclusion:** Testicular tumor is a serious disease of male with good prognosis if treated properly. Multicenter study is strongly required to better understand the behavior of this cancer. This should optimize our strategy of detecting and managing this disease in our country.

**Key Words:** *: Testicular tumor, clinical, management, Saudi Arabia.*

## INTRODUCTION

Testicular cancer is the most common cancer in males between 20 and 35 years of age. Germ cell tumors account for about 94% of testicular cancers. The majority of testicular tumors originate from the germ cell, which is the principal cell type of the testis. An increasing incidence of testicular tumors, particularly in men of European origin, has been noted over the second half of the 20th century.[1] In Saudi Arabia, around 40 new cases of testicular cancer are reported annually. Although it is the most common malignancy in young male, it represents only about 1.3% of all male malignancies in the country. Such rarity has made a study of a large series difficult. Detailed epidemiological and clinical information is required to optimize the diagnostic and treatment modalities of this disease.

Worldwide testicular cancer is a rare cancer. Although in the western hemisphere it is accounting for only about 1% of all male cancers, it is the leading cause of cancer in men between the ages of 15 and 35 years, with an average age at diagnosis of 34. The annual incidence of 4 cases per 100,000 men is rising and has nearly doubled in the past 40 years.[2]

Although it accounts for 1.1-1.3% of all malignancy in the Kingdom of Saudi Arabia (KSA), testicular tumor is the most common solid tumor among young males. There are 38-44 new cases reported annually or about 0.4 case per 100,000. This is 10 times less than the west.[3,4] Testicular cancer is considered nowadays one of the most curable solid neoplasms. More than 90 percent of patients with newly diagnosed germ-cell tumors are cured, and delay in diagnosis correlates with a higher stage at presentation for treatment. The dramatic improvement in survival resulting from the combination of effective diagnostic, surgical technique, and multidrug chemotherapeutic regimens.[5]

In recent years, little is known or published about the demography, clinical characteristics, and prognosis of testicular tumors in KSA. Over the past few decades, there were many changes in the medical care facilities as well as patient awareness and education.[6,7,8]

## OBJECTIVES

To determine the pattern of testicular tumor and management out come

## MATERIAL AND METHODS

The study is a retrospective review of the medical records of patient with established diagnosis of testicular tumor who were treated at King Faisal Specialist Hospital and Research Centre, Jeddah (KFSHRC-Jed.), Saudi Arabia between 2000 and 2009. We collected the file numbers from the operative lists and the oncology data unit at KFSHRC-J. Our review includes the clinical feature, histological type, stage, modality of treatment used and follow up.

## RESULTS

Twenty-five patients were found in our records. Mean age was 29.7 (+/- 10.2 SD), ranging between 19 and 60. The tumors were two times more in the right side than the left. About half of the patients presented with painful swelling (Table1). Thirteen patients presented with stage I, 6 patients with stage II and 6 patients with stage III disease. Of the 25 patients, 14 (56%) had Nonseminoma (NS), 10 (40%) had Seminoma (S) and 1 (4%) had Leydig cell tumor. In regards to germ cell tumor (GCT) the NS group presented at younger age than S group (Table 1 & 2).

**Table 1: Clinical Features at presentation**

| | All testicular tumors | S | NS |
|---|---|---|---|
| Mean Age (SD) | 29.7 (+/- 10.2) | 36.7 (+/- 12.5) | 25 (+/- 4.6) |
| History of UDT | 1 (4%) | 1 (10%) | - |
| Site | | | |
| Right | 17 (68%) | 5 (50%) | 11 (79%) |
| Left | 8 (32%) | 5 (50%) | 3 (21%) |
| Scrotal Swelling | 23 (92%) | 8 (80%) | 14 (100%) |
| Pain | 12 (48%) | 5 (50%) | 6 (43%) |
| Mets. at presentation | | | |
| Lung | 5 (20%) | - | 3 (21%) |
| Inguinal L.N | | 1 (10%) | - |
| Brain | | - | 1 ( 7%) |

(S=Seminoma, NS=Nonseminoma, Mets= metastasis, LN= lymph node, SD= standard deviation)

**Table 2: Age - group distribution according to histological type.**

| Age group | All testicular tumors | S | NS |
|---|---|---|---|
| < 21 | 3 | 0 | 3 |
| 21 – 30 | 16 | 5 | 10 |
| 31 – 40 | 4 | 3 | 1 |
| 41 – 50 | 1 | 1 | 0 |
| 51 - 60 | 3 | 3 | 0 |
| > 60 | 0 | 0 | 0 |

(S=Seminoma, NS=Nonseminoma)

Post radical orchidectomy, 14 patients required chemotherapy, 4 received radiation therapy (RT), 3 patients underwent retroperitoneal lymph node dissection (RPLND) and 3 patients were on surveillance. Around two third responded to the chemotherapy. Nevertheless, about

one third of them developed both neutropenia and pulmonary toxicity. All of complications were in the NS group. Of both S and NS patients, a small number received RT with 50% response rate and no reported complications (Table 3).

**Table 3: The patient's follow up, treatment and prognosis.**

| | S | NS |
|---|---|---|
| No. of pt. Total | 10 | 14 |
| Lost F/U | 3 | 1 |
| F/U | | |
| Range (month) | 9 -57 | 5 – 91 |
| Mean (SD) | 30.4(16.4) | 24.3(22.2) |
| Mets. | | |
| Lung | | 2 |
| Liver | 1 | 1 |
| Nonregional L.N | | 2 |
| Death | 0 | 1 |
| Treatment | | |
| Surveillance | 2/10 (20%) | 1/14 (7%) |
| Chemotherapy | 3/10 (30%) | 11/14 (78%) |
| Respond | 2/3 (67%) | 7/11 (64%) |
| Relapse | 0/2 (0%) | 1/7 (14%) |
| Complications Neutropenia, Pulmonary | 0 | 5/11 (45%) |
| Radiotherapy | 3 (30%) | 1/14 (7%) |
| Respond | 1/3(33%) | 1/1(100%) |
| Complication . | 0 | 0 |
| RPLND | 0 | 3/14 (21%) |

(S=Seminoma, NS=Nonseminoma, F/U= follow up, Mets= metastasis, RPLND= retro peritoneal lymph node dissection, SD= standard deviation)

Of the 3 patients who were on surveillance,[2] were of the S group. One S patient required chemotherapy after one year. The other NS patient required RPLND after 6 months. The average follow up of all patients was 35 months, ranges between 5 and 91 months. Six patients developed distant metastasis, mostly among NS group. Four patients were lost during follow up. Among the rest the overall survival was 95% (Table 3).

More than quarter of the causes of presenting abdominal pain of the patients in this study were intestinal obstruction 66 (26.6%) more than half of them were Africans 38 (54.3%), which included complicated hernias and adhesions. Acute appendicitis 52 (20.8%) of the total patients, most of them were perforated. The other causes were cholecystitis 28(11.2%),

perforated peptic ulcer 24(9.6%), pancreatitis 16 (6.4%), ischemic bowel 8 (3.2%). Non-surgical cause was seen in 56 patient (23.2%). 34 (14.4%) 0f the them were labeled as non specific abdominal pain and 22 (8.8%) as renal cause. All non surgical patients were made by clinical resolution of the symptoms or diagnostic laboratory results Tables II & III, In this study no acute abdominal gynaecological.pain were reported.

## DISCUSSION

Acute In comparison to old data seen in KSA,[9] patients in our study had different demography, presented at younger ages, had less history of undescended testis, complained more of discomfort and diagnosed at earlier stages (Table 1,3). The difference in documenting painful mass is probably owing to more detailed history or data collection. International data revealed that scrotal pain with or without a mass occurs in up to 50% of testicular cancer presentations.[10] We encountered higher NS:S ratio in comparison to the old data in KSA as well as to international studies.[11,14] No obvious explanation to this variation. Availability of chemotherapy in our referral centre is a possible reason.

As in most tertiary care centers worldwide, our treatment decision after orchiectomy depends on staging (table 3). Lower stage seminomas are treated with surveillance or RT post orchiectomy.[15] Nonseminomas may require RPLND and chemotherapy. Higher categories are typically treated with chemotherapy, with or without further surgery.

Because of the young age at diagnosis, long survival, and potential carcinogenicity of RT, postorchiectomy surveillance of Stage I seminoma is an attractive alternative. In a series of 93 patients who underwent surveillance for a similar stage, the 5-year actuarial relapse-free survival rate was 78%. Relapse was more common in those with known adverse prognostic factors (rete invasion or size greater than 4 cm). The actuarial 5-year relapse free rate was 86%, 71%, and 50% for patients with no risk factor, one risk factor, or both risk factors, respectively. The disease-specific survival rate at 5 years was 96% [14] among our S patients 2 patients underwent surveillance while 3 received RT, and 1 responded to RT.

With appropriate treatment, survival rates from GCT are excellent,[15] In the current era of effective chemotherapy, most (but not all) patients can be salvaged despite delays in diagnosis and, consequently, more advanced disease.[9,16] GCT have been considered a curable malignancy since the introduction of cisplati. More than half (56%) of our patients received chemotherapy with good response (66%) (table3), but more than a third (36%) reported significant complication. It is known that patients with markedly elevated tumor marker levels or extrapulmonary metastasis are classified into the poor-prognosis group, for whom 5-year overall survival is 48–61%. A total of 16% of our patients, mainly in the NS, presented with metastasis (table 1), which is within the international range (11-30%).[17] Even though, the overall survival of our study population was 95%, which is in concurrence with international figures. According to the National Cancer Institute, the overall 5-year survival rate from testicular cancer was 95.3% between 1999 and 2006. If the cancer was confined to the testis at the time of diagnosis, the survival rate was 99.2% and dropped only slightly to 96% with regional extension. For patients with distant metastases, the survival rate was 71.5 %.
All efforts should be spent to detect testicular cancer at an earlier stage. This can minimize morbidity of treatment. Akin to case finding is the concept of testicular self-examination (TSE) and increasing awareness of this disease among young men. Numerous recent studies

have demonstrated that young men generally are ignorant regarding testicular cancer and TSE.[9]

The most relevant patient-dependent prognostic factor in testicular cancer is early presentation. Symptomatic delay has a proven negative impact on disease stage, treatment outcome, and mortality. Poor public awareness of the disease and a lack of TSE are presumed reasons for symptomatic delay and late presentation. There has been considerable effort to examine possible reasons for delayed presentations and to heighten public awareness of testicular cancer and encourage TSE.[18]

Testicular tumor is a serious disease of male with good prognosis if treated properly. Multicenter study is strongly required to better understand the behavior of this cancer. This should optimize our strategy of detecting and managing this disease in our country.

## CONCLUSION

Testicular tumor is a serious disease of male with good prognosis if treated properly. Multicenter study is strongly required to better understand the behavior of this cancer. Our result matching with other centre world-wide. This should optimize our strategy of detecting and managing this disease in our country.

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UQU Medical Journal

*Original Article*

# Isolation of *Candida spp.* and *E. coli* as the most frequently isolated causative agents of women urinary tract infection in Makkah Al-Mukaramah

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## عزل فصيلة الكانديدا و الايشريشيا كولي كأكثر الفصائل المسببة لعدوى الجهاز البولي التي تصيب النساء في مكة المكرمة

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قسم الكائنات الدقيقة بكلية الطب وقسم طب المختبرات بكلية العلوم الصحية* – جامعة أم القرى – مكة المكرمة – المملكة العربية السعودية. ص. ب. : 7607

**الملخص العربي**

**المقدمة:** تعتبر عدوى الجهاز البولي واحدة من أكثر الأمراض شيوعا التي تصيب جسم الإنسان بشكل عام وتعتبر من اخطر المشاكل التي تصيب النساء الحوامل بشكل خاص. وتعزى زيادة حدوث هذا النوع من العدوى بالتغيرات الفسيولوجية المتعلقة بفترة الحمل عند النساء.

**الاهدف:** الدراسة الحالية كان لتشخيص ومعرفة مدى انتشار هذه العدوى والميكروبات المسببة لها في النساء الحوامل والغير حوامل اللواتي يراجعن عيادة النساء والولادة في مستشفى حراء العام.

**الطريقة:** اشتملت الدراسة على مجموع 300 حالة من النساء في عمر (18-60 عاما) قسمت كما يلي (200 امرأة حامل و 100 امرأة غير حامل) وذلك بواسطة استخدام استبان ممنهج احتوى أسئلة عن المعلومات الشخصية، التاريخ المرضي، العوامل المؤثرة في الدراسة. استخدمت في الدراسة عينات بول لعمل التحاليل المجهرية والزراعة البكتيرية. تعرف عدوى الجهاز البولي بوجود بكتريا في البول بمعدل أكثر او يساوي 100,000 وحدة تكوين مستعمرة بكتيرية/مل من البول مع او بدون خلايا قيحية. عينات الدم الكامل استخدمت لتحديد صورة الدم الكامل للحالات المدروسة لمعرفة العدوى الشاملة للجسم البشري.

**النتائج :** أظهرت الدراسة نسبة 6,5 % و 10% مصابة بعدوى الجهاز البولي في النساء الحوامل وغير الحوامل بالتتالي. 2,5 % من النساء الحوامل صنفوا على أنهم مصابين بعدوى الجهاز البولي مع وجود أعراض مرضية, بينما 4% منهم مصابين من غير وجود أعراض مرضية. في حالات النساء الغير الحوامل سجلت4% و6% مصابين بالعدوى مع وجود أعراض مرضية وعدم وجود أعراض مرضية بالتتالي. فصيلة الكانديدا والايشريشيا كولي كانت أكثر الفصائل الميكروبية المعزولة في الدراسة بنسب 39,1% و 17,4% بالتتالي.اختبار الحساسية للمضادات الحيوية اظهر ان الاجمنتين والاميكاسين وببراسيلين هم الأقل مقاومة (7,1%) بينما النيتروفيورنتين والامبسيلين هما الأكثر مقاومة (42.9%).

**الخلاصة:** بصورة غير متوقعة وجد أن مدى انتشار عدوى الجهاز البولي اكبر بين النساء الغير الحوامل من النساء الحوامل. أظهرت الدراسة كذلك إن الكانديدا كانت هي أكثر الفصائل ظهورا في حالات عدوي الجهاز البولي (39,1%) تليها الايشريشياكولي بنسبة 17,4%, وجد كذلك ان الاجمنتين والاميكاسين والبيبرسيلسن كانوا الأكثر تأثيرا في علاج البكتيريا المسببة لعدوى الجهاز البولي.

## ABSTRACT

Urinary Tract Infection (UTI) is one of the most common infections in the body. In pregnant women, UTI represents a serious health problem. The increasing frequency of UTI among pregnant women is attributed to the physiological changes that associate pregnancy.

**The aim**: the current study was aim to investigate the prevalence and causative agents of UTIs among pregnant and non pregnant women attending OPD clinics at Hera'a Hospital.

**Methods & Materials:** A total of 300 women with age range of 18–60 years (200 pregnant and 100 non pregnant women) were subjected to the study. Personal data, medical history, and risk factors-related data were collected by using of structured questionnaire. Sterile urine samples for urine analysis, and urine culture were used. UTI was defined as the presence of significant bacteriuria ≥ 100, 000 CFU/mL of urine with or without pus cells. Whole blood samples for CBC were also collected from studied cases for evaluation of systemic infections.

**Results:** The study revealed that 6.5% and 10% of investigated pregnant and non-pregnant women, respectively, were positive for UTI. In the pregnant group, 2.5% were symptomatic UTI, while 4% were asymptomatic UTI. In the non-pregnant group 4% and 6% were symptomatic and asymptomatic UTI, respectively. *Candida sp.* and *E. coli* were the most frequently isolated pathogens from all investigated UTI cases at a rate of 39.1% and 17.4%, respectively. The antimicrobial sensitivity test revealed Augmentin, Amikacin and piperacillin as the least resistant antibiotics (7.1%), while Nitrofurantoin and Ampicillin were the most resistance (42.9%) for the isolated UTI-causative bacterial agents.

**Conclusions:** Un-expectedly, the prevalence of UTI was higher among non-pregnant women than pregnant ones. *Candida spp.* was the most frequently (39.1%) isolated pathogen from all UTI cases, followed by *E. coli* at a rate of 17.4%. Augmentin, Amikacin and piperacillin were the most effective antibiotics for the treatment of bacterial cause of UTI.

***Keywords:*** Candida, Urinary tract infection, Prevalence

# INTRODUCTION

Urinary Tract Infection (UTI) is a medical condition that affects urinary tracts in both sexes. While UTI can affect both sexes, studies showed that the disease affect more women than men. The short female urethra (3-4 cm) as compared to the long male one (20 cm) has makes females more susceptible than men to UTI that result from rectal bacterial contamination (Winterling, 1997). In Kolawole's study, for example, equal random groups of male and female subjects were examined for UTI, 60% of the female subjects were infected whereas only 33% of the male subjects were infected (Kolawole *et al*., 2009). Similar studies that underscore the same findings led researchers to believe that UTI is a predominant disease of women (Forbes *et al*., 2007). However, even among women, UTI is susceptible to different factors, such as age, pregnancy, and other health conditions. The natural relocation of bladder as well as the hormonal changes that occur during pregnancy was described among the factors that increase the risk of UTI among pregnant women (Abdullah and Al-Moslih, 2005).

Urinary Tract Infections are usually associated with bacterial infection. However, some other infectious agents had been reported as possible cause of the infection. These include viral agents as *human papilloma virus* (HPV), *human immunodeficiency virus* (HIV) and *herpes simplex virus type 2* (HSV-2), which may infect the urethra (Shankel, 2007). Fungal agents may also be associated with UTI include *Candida*, which infects people who have an impaired immune system or those with a bladder catheter in place. Other types of fungi include *Blastomyces and Coccidioides.* Fungi and bacteria may infect the kidneys at the same time (Shankel, 2007). Parasitic agents associated with infection of urinary tract include *Trichomonas spp*., *Schistosoma spp*. and *Filaria* (Shankel, 2007). More than 85% of UTIs caused by bacteria comes from the normal flora of the intestine or the vagina in women (Hooton and Stamm, 2001).

Urinary Tract Infection can be classified according to the clinical picture into symptomatic UTI, showing accompanied symptoms, or asymptomatic one. In both cases, urinalysis and urine culture are the definitive tests for the diagnosis, which is based on the detected number of bacteria and white blood cells (pus cells) in urine sample (American Academy, 1999). UTI is special problem in the women, both for pregnant and non pregnant. In many studies of UTIs in pregnant women, the incidence of UTI can be as high as 30% (Al-Haddad, 2005); while in Saudi Arabia the prevalence was 14.2% (Al-Sibai *et al*., 1989). Rate of 10.58% have been reported from Iran (Zeighami *et al*., 2008), and 58.3% in Ireland (Barr. *et al*., 1984). The prevalence of UTI in pregnant with gestational diabetes mellitus (DM) was 7.9%. This was not significant different from that found in non- diabetes mellitus women (6.3%) (Rizk, 2002).

The prevalence of asymptomatic bacteriuria in pregnant women was 9.9% in Qatar and the dominant bacteria isolates were *E.coli* (31%) and *streptococcus agalaticae* (30%) (Mona *et al.,* 2009). In UAE the prevalence was 4.2% and the most common causative organism was also *E.coli* (66.67%) (Abdullah, 2005). Rate of 7.3% have been reported from Ghana (Turpin *et al.,* 2007), 16% in Ireland (Barr *et al.,* 1984) and 3-5% in Iran (Zeighami *et al*., 2008). Recurrent UTI are problem in 20-25% of pregnant women in Iran (Zeighami *et al*., 2008) and 31% of pregnant women in UAE (Rizk, 2002).

In studies of UTIs in non-pregnant women the incidence of UTI can be as high as 66.67% in Nigeria (Kolawole *et al.,* 2009), while10.8% have been reported in USA (Foxman

*et al.*, 2000). The prevalence of asymptomatic bacteriuria in non- pregnant women was 28.8% in Pakistan (Sheikh *et al*., 2000). The prevalence of asymptomatic bacteriuria in non-pregnant women was 5 % (Hooton and Stamm, 2001). The prevalence of asymptomatic bacteriuria is higher in women with DM than in women without DM. The prevalence of ASB in women with DM was 26% while the prevalence was 6% in women without DM (Geerlings *et al.,* 1999) and in similar study in turkey the prevalence of asymptomatic bacteriuria in women with type II DM was 18.6% (Turpin *et al.*, 2008).

The diagnosis of UTI may be made on the basis of clinical signs and symptoms in combination with urinalysis results. The most common screening tests for UTI are urine dipstick & microscopic urinalysis. Urinalysis reveals both bacteriuria and pyuria. The number of bacteria and white blood cells are the basis for diagnosing UTI. The use of centrifuged urine in the microscopic analysis has sensitivity of 94% and specificity of 84-92 % (Shaw *et al.*, 1998).

Urine culture remains an important test in the diagnosis of UTI, because it helps to documentation of the infection, determination the identity of infecting bacteria and for antimicrobial susceptibility testing. It is not necessary for outpatients with uncomplicated UTI.

The aim of the current study was to investigate the prevalence of UTIs among pregnant and non pregnant women attending OPD clinics at Hera'a Hospital and to determine the common microbial agents associated with it.

## MATERIAL AND METHODS

### Study population and specimens

A total of 300 women with age range of 18 – 60 years, who agreed to enter the study, were subjected to the investigation. The study sample included 200 pregnant women and 100 non pregnant ones. The pregnant women were selected consecutively from those attending the Gynecology and Obstetrics (GOB) clinic at Hera'a Hospital, Makkah Al-Mukaramah, Saudi Arabia for prenatal care from December 2008 to July 2009. On the other hand, non-pregnant women were selected from those attending GOB and other clinics of the same hospital for different reasons other than prenatal care over the same period. Sterile urine samples for urinalysis, and urine culture were collected from all studied cases. Urinalyses and urine cultures were used for the detection of UTI. A UTI was defined as the presence of significant bacteriuria ≥ 100, 000 colony-forming units (CFU) per mL of urine.

### Urine Collections and Examination

All women were instructed how to give a clean-catch midstream urine specimen. Briefly, they were asked to clean the area around urethral opening with clean water, dry it and then collect a midstream urine sample by discarding the first part of urine and collecting 10-20 ml of the midstream in sterilized containers.

All urine containers were properly labeled and sent to the laboratory with a request for complete urinalysis and urine culture. Each sample of urine was divided into 2 parts for urinalysis and urine culture.

**Urinalysis:**
Wet preparation from the first part of each urine sample was prepared and examined microscopically at X40 for detection of white blood cells as an indicator of pyuria. Samples with ≥ 10 WBC/$mm^3$ were regarded as pyuria. The rest of the first part of urine sample was examined by dipstick tests using Comber 10 reagent test strips (Analyticon, Germany) that have panels to detect protein, blood and nitrite and leukocyte esterase in urine (Smith et al., 2003).

**Urine Culture:**
The second part of urine sample was cultured on plates of blood agar and CLED (cystine-lactose-electrolyte-deficient) agar with standard calibrated loop delivering 0.01 mL of urine. After streaking, the plates were incubated aerobically at 35°C for 18-24 hours. The plates were then examined macroscopically and microscopically for bacterial growth. The bacterial colonies were counted and multiplied by 100 to give an estimate of the number of bacteria present per milliliter of urine. Urinary tract infection was positive diagnosed by growth of ≥100,000 colony forming unit (CFU) of urinary tract pathogen per ml in culture of midstream urine sample, regardless of the presence or absence of leukocytes (Stamm and Hooton 2003). Urine cultures with 103–104 CFU/mL were regarded as suspected infections, cultures with less than 103 CFU/mL were considered contaminated, while cultures with no growth of bacteria were said to be negative. Identification of bacterial pathogens was confirmed by observation of gram staining, colony characteristics, and a battery of biochemical tests (Cheesbrough, 2000). Any specimen containing more than one species of bacteria was considered contamination.

**Antibiogram of Isolated Bacterial Agents:**
Antibiotic sensitivity tests were carried out for all urine samples with significant bacteriuria using the Kirby-Bauer NCCLS modified disc diffusion technique with the following antibiotics: ampicillin, amoxicillin-clavulanic acid, nitrofurantoin, ciprofloxacin, nalidixic acid, trimethoprim, cephalexin, gentamicin. After incubation at 35$^{o}$C for 16-18 hour, sizes of inhibitory zones were measured and interpreted using NCCLS standards.

## RESULTS

**Prevalence of UTI among pregnant and non-pregnant women**
Out of 200 pregnant women, 13 (6.5%) were positive for UTI, while out of 100 non-pregnant women, 10 (10%) were found positive for UTI. In the pregnant group, 5 (2.5%) UTI-positive cases were associated with symptoms and classified as symptomatic UTI, while 8 (4%) cases were not associated with symptoms and considered as asymptomatic UTI. On the other hand, in the non-pregnant group 4 (4%) UTI-positive cases were associated with symptoms and represented the symptomatic UTI, and 6 (6%) cases were symptomless and were described asymptomatic UTI (Table 1).

**Table 1. Prevalence of UTI among pregnant and non-pregnant women.**

| Examined women | Positive UTI Cases | | Symptomatic UTI | | Asymptomatic UTI | |
|---|---|---|---|---|---|---|
| | n | % | n | % | n | % |
| Pregnant Women (200) | 13 | 6.5 | 5 | 2.5 | 8 | 4 |
| Non-pregnant Women (100) | 10 | 10 | 4 | 4 | 6 | 6 |

**Urinalysis Findings in UTI Cases**

With regard to the microscopic findings of examined urine samples from UTI cases, pus cells, RBCs and microbial cells were recorded at different frequencies. In pregnant women, the study revealed that out of the examined cases, 60% and 37.5% showed pus cells, 20% and 0% showed RBCs, and 40% and 87.5% showed microbial cells among symptomatic and asymptomatic groups, respectively. In non-pregnant women, the results revealed that 25% and 16.7% of UTI cases were showing pus cells, 25% and 0% were showing RBCs, and 75% and 50% were showing microbial cells among symptomatic and asymptomatic groups, respectively (Table 2).

**Table 2. Microscopic urinalysis findings of UTI cases among pregnant and non-pregnant women.**

| Microscopic Urinalysis | Pregnant Women | | | | Non-pregnant Women | | | | Total (23) | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Symptomatic UTI (5) | | Asymptomatic UTI (8) | | Symptomatic UTI (4) | | Asymptomatic UTI (6) | | | |
| | n | % | n | % | n | % | n | % | n | % |
| Pus Cells | 3 | 60 | 3 | 37.5 | 1 | 25 | 1 | 16.7 | 8 | 34.8 |
| RBC | 1 | 20 | - | - | 1 | 25 | - | - | 2 | 8.7 |
| Microbial Cells | 2 | 40 | 7 | 87.5 | 3 | 75 | 3 | 50 | 15 | 65.2 |

**Frequency of Microbial Agents Associated with UTI Cases**

In the pregnant group, out of the 5 symptomatic UTI cases. *Candida spp.* was the most frequently isolated pathogen followed by *Entercoccus coloacae* representing 80% and 20 %, respectively. In the asymptomatic group, out of the 8 recorded cases, *E. coli*, *Streptococcus agalactia*, *Klebsiella pneumonia* and *Candida spp.* were isolated at equal frequency (25% each) (Table 3).

**Table 3. Frequency of isolated UTI-associated microbial agents among both pregnant and non-pregnant women**

| Microbial Agents | UTI cases among Pregnant Women | | | | UTI cases among Non-pregnant Women | | | | Total (23) | |
|---|---|---|---|---|---|---|---|---|---|---|
| | *Symptomatic (5)* | | *Asymptomatic (8)* | | *Symptomatic (4)* | | *Asymptomatic (6)* | | | |
| | n | % | n | % | n | % | n | % | n | % |
| Candida spp. | 4 | 80 | 2 | 25 | 1 | 25 | 2 | 33.3 | 9 | 39.1 |
| Escherichia coli | - | - | 2 | 25 | - | - | 2 | 33.3 | 4 | 17.4 |
| Streptococcus agalactia | - | - | 2 | 25 | - | - | 1 | 16.7 | 3 | 13.0 |
| Streptococcus bovis | - | - | - | - | 1 | 25 | 1 | 16.7 | 2 | 8.7 |
| Klebseilla pneumonia | - | - | 2 | 25 | - | - | - | - | 2 | 8.7 |
| Enterobacter cloacae | 1 | 20 | - | - | - | - | - | - | 1 | 4.3 |
| Pseudomonas aeruginosa | - | - | - | - | 1 | 25 | - | - | 1 | 4.3 |
| Protius mirabilis | - | - | - | - | 1 | 25 | - | - | 1 | 4.3 |

Regarding the non-pregnant group, *streptococcus bovis*, *Pseudomonas aeruginosa*, *Proteus mirabilis and Candida spp.* were isolated at equal frequency (25% each) from the symptomatic UTI cases. On the other hand, *E.coli* and *Candida spp.* were the most frequently isolated pathogens (33.3% each) from the asymptomatic UTI cases followed by *Streptococcus*

*agalagtia* and *Streptococcus bovis* (16.7 % each) as shown in (Table 3). Overall, *Candida spp.* was the most frequently isolated microbial pathogen (39.1%) from all recorded UTI cases. However, *E.coli* was the most frequently isolated bacterial pathogen (17.4%) from all UTI cases followed by *Streptococcus agalactia* (13 %). On the other hand, *Enterobacter cloacae, Pseudomonas aeruginosa* and *Protius mirabilis* were the least frequently isolated bacterial pathogen (4.3% each) from all UTI cases (Table 3).

**Antibiogram of Isolated UTI-causative Bacterial Agents.**
In the current study, antibiotic sensitivity tests were carried out for the recovered bacterial isolated from UTI cases. The outcome of the sensitivity tests were shown in (Table 4). The results revealed that out of the recovered 14 bacterial isolates, 42.9% were resistant to Nitrofurantoin and Ampicillin, 35.7% were resistant to Gentamycin and Cotrimoxazol, 28.6% were resistant to Cephalothin, 14.3% were resistant to Norfloxacin and Cefatoxime and finally 7.1% were resistant to Augmentin, Amikacin and piperacillin.

## DISCUSSION

The aim of the present study was to investigate the prevalence of UTI and its causative agent among both pregnant and non-pregnant women attending Hera'a hospital at Makkah Al-Mokarramah including both symptomatic and asymptomatic cases. Interestingly, the overall prevalence of UTI was higher among non-pregnant women (10%) as compared to pregnant ones (6.5%) with asymptomatic UTI frequency of 4% and 6% among pregnant and non-pregnant women, respectively. This finding was on the contrary with the notion of the increasing frequency of UTI among pregnant women due to the physiological changes (both hormonal and mechanical) that occur during pregnancy as well as the difficulty with hygiene due to a distended pregnant belly (Mikhail and Anyaegbunam, 1995; Andrews *et al.*, 1990). Although these studies verify the relation between pregnancy and UTI, it can hardly be accurate to claim that pregnant women are more susceptible to UTI than non-pregnant ones. The current finding could be attributed to the increased awareness among pregnant women of the UTI and its possible complication during the routine doctor visit for pregnancy follow up with the subsequent implementation of more restrict hygienic measurements as compared to the routine hygiene practiced by non-pregnant women.

Although the current rate of UTI frequency is in accordance with recently reported prevalence in Middle East countries as UAE (4.8%) and Iran (6.1%) (Abdullah, 2005 and Hazhir, 2007). This rate was lower than what was reported earlier (14.2%) in Saudi Arabia (Al-Sibaie *et al*., 1989). The alteration of UTI frequencies in Saudi Arabia could be attributed to the currently improved health care and hygienic measurements taken by women and the increased awareness and level of education as compared to earlier periods. Moreover, the prevalence of asymptomatic bacteruria varies from one community to another. For example, in Asian studies, while the asymptomatic bacteriuria was 4.3% among Filipino pregnant women (Seccon *et al*., 2003), it reaches up to 12% in rural areas in Bangladesh (Ullah *et al.*, 2007). Similarly, in Africans studies the prevalence of asymptomatic bacteriuria in Ethiopia and Ghana was 9.3% and 7.3%, respectively (Uncu *et al*., 2002 and Turpin *et al.*, 2007). Also, in western studies the same differences were recorded, for example while the prevalence of asymptomatic bacteriuria in the US was 2-7% (Delzell and Lefevre, 2000), it reached up to 16% among Spanish pregnant women (Akinloye *et al*., 2006). This variation can be attributed to several factors such as the geographical variation, ethnicity of the subjects,

setting of the study (primary care, community based, or hospitals) and the variation in the screening tests (urine dipstick, microscopy and culture).

Regarding the frequency of UTI-associated pathogens, the present study revealed *E. coli* as being the most common bacterial pathogen isolated from all currently studied UTI cases, which are in consistent with the majority of the reported studies. However, *E. coli* formed only 17.4% of isolated organism which is lower than what have been reported in different countries like Ethiopia (79%) (Turpin *et al*., 2007), Turkey (77%) (Tugrul *et al.,* 2005), Philippines (50%) (Seccon *et al*., 2003) and Ghana (37%) (Ullah *et al.,* 2007). The predominance of *E. coli* is usually attributed to the urinary stasis, which is common in pregnancy (Delzell and Lefevre, 2000). Moreover, the anatomical and the functional changes that occur during pregnancy results in a high risk of acquiring UTI from *E. coli* (Abdullah and Al-Moslih, 2005).

Although nonbacterial infections are less common causative agents of UTI and tend to occur more often in immunosuppressed individuals or those with diabetes mellitus, the current study revealed that 39.1% of currently detected UTI cases were infected with *Candida* species. This could be attributed to the excessive use of antibiotic therapy, as certain types of bacteria that live naturally in the vagina usually keep *Candida spp.* from growing out of control. If the balance of these microorganisms becomes upset, *Candida spp*. may be allowed to grow uncontrollably and lead to lower UTI. The use of certain medications, changes in hormone levels, or certain diseases are examples of factors that can allow a vaginal yeast infection to develop. (Hsueh *et al*., 2002) have reported *Candida spp.* as the most frequent isolates (23.6%) from UTIs at a university hospital in Taiwan during the period 1993 - 1998 followed by *E.coli* (18.6%) and *P. aeruginosa* (11.0%).

The most useful antibiotics, as revealed in the current study, were augmentin, amikacin and piperacillin followed by norfloxacin and cefatoxime as they showed the least resistance frequency (7.1% and 14.3%, respectively) among isolated causative bacterial agents and were able to inhibit most commonly isolated UTI pathogens. Meanwhile, nitrofurantoin and ampicillin followed by gentamycin and cotrimoxazol, which are commonly used antibiotics, were poorly effective against majority of the organisms isolated in this study with a resistance rate of 42.9% and 35.7%, respectively. This differ from the studies and findings in Caucasian women where ampicillin and septrin remain the most useful antimicrobial agents (Ronald, 1987) and the findings by Ebie *et al*. (2001) among patients in Military Hospital, Jos, Nigeria where the isolates were highly susceptible to nitrofurantoin and that of Olaitan (2006) which has septrin (co-trimoxazole) as very effecttive.

The high efficacy of augmentin, piperacillin, norfloxacin and cefatoxime as reported in the current study could be attributed to the fact that these drugs are relatively expensive when compared to most antibiotics frequently used. This probably had restricted their procurement and indiscriminate use, therefore making the organisms susceptible to it. This is similar to other reports where quinolones are the most effective (susceptible) (Krumpermann, 1983; Burbige *et al*., 1984; Ebie *et al.,* 2001; Ehinmidu, 2003; Mbata, 2007). On the other hand, the high resistance to other drugs may be due to the practices of self medication and indiscriminate use of these antibiotics with the subsequent resistance acquirement.

## CONCLUSION

The results of our study show that Urinary tract infection in pregnancy is a very frequent medical problem, which if untreated on time or inefficiently treated it may lead to severe maternal and fetal complications. The study also revealed that symptoms are poor markers of UTI during pregnancy and therefore antenatal care should include direct questioning and urine examination. Therefore, all pregnant women should be screened at least once by urine culture for asymptomatic bacteriuria throughout their antenatal controls.

During early pregnancy if possible and when the result is positive, they should be treated by oral antibiotics for a period of 3-7 days. Those women should also be followed-up for recurrent infection after the treatment by means of periodic culture processing. Also, the results from this study revealed that the important infecting organisms were found to be the commensals of perianal and vaginal regions. This calls for an increase attention towards personal hygiene. The findings have no doubt highlighted the need for constant monitoring of susceptibility of specific pathogens in different populations to commonly used anti-microbial agents. These data may be used to determine trends in antimicrobial susceptibilities, to formulate local antibiotic policies, to compare local with national data and overall to assist clinicians in the rational choice of antibiotic therapy to prevent misuse or overuse of antibiotics.

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# Incidence of bacterial and fungal infections among infected diabetic patients

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## العدوى البكتيرية والفطرية في مرضى السكري

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**الملخص العربي**

**الخلفية العلمية:** المرضى المصابين بداء السكري أكثر عرضة للإصابة بمختلف الأمراض البكتيرية والفطرية من غير المرضى بداء السكري. و يعزى ذلك إلى العديد من عوامل الخطر الناجمة عن السكري مثل تشوهات الأوعية الدموية والأعصاب و اعتلال الكلية وتأخر التئام الجروح ونقص المناعة.
**الهدف من البحث:** يهدف هذا البحث إلى معرفة أكثر الأمراض البكتيرية والفطرية التي تصيب مرضى السكري بالعدوى.
الطرق: تم تجميع مائة وتسعة وثلاثون عينة في هذا البحث من مرضى السكري خلال عام كامل من مستشفيات مختلفة من مدينتي مكة وجدة بالمملكة العربية السعودية وتم فحص هذه العينات مخبريا باستخدام الطرق القياسية المستخدمة في الإحياء الدقيقة الطبية.
**النتائج:** من المائة وتسعة وثلاثون عينة التي تم جمعها من مرضى السكري المصابين بالعدوى في هذه الدراسة كانت الإصابات أكثر شيوعا في الإناث (53.2 ٪) من الذكور (46.8 ٪)، وفي الفترة العمرية 51-70 سنة (45.3 ٪) وكانت الإصابة بالعدوى البكتيرية أكثر شيوعا (92.8 ٪) من العدوى الفطرية (7.2 ٪) وشملت الإصابات: التهابات القدم السكري (40.3 ٪)، والتهابات المسالك البولية (20.1 ٪)، والتهابات الجهاز التنفسي (16.5 ٪)، والتهابات الجلد (10.8 ٪) ، وتسمم الدم (10.1 ٪)، والتهابات الجهاز التناسلي (1.4 ٪) والتهابات العين (0.7 ٪). وكانت أكثر الجراثيم المعزولة من مرضى السكري المصابين بالعدوى هي بكتريا اي كولاي (19.4 ٪) ، والمكورات العنقودية الذهبية (18.7 ٪). ا كما أظهرت الدراسة أن المبيضات كانت هي الأكثر شيوعا من بين الفطريات المعزولة في مرضى السكري المصابين.بالعدوى في هذه الدراسة.
**الاستنتاجات :** أظهرت هذه الدراسة أن العدوى بين مرضى السكري كانت أكثر شيوعا في الإناث من الذكور و في الفترة العمرية 51-70 سنة. بالإضافة إلى ذلك ، كان مرضى السكري أكثر عرضة للإصابة بالعدوى البكتيرية من العدوى الفطرية.

## ABSTRACT

**Background:** Patients with diabetes are more vulnerable to various bacterial and fungal infections than non-diabetic patients. This may be attributable to many risk factors resulting from diabetes such as; vascular abnormalities, neuropathy, nephropathy, delayed wound healing and immune depression.

**Aim:** the aim of the current study was to determine the most common bacterial and fungal infections among infected diabetic patients.

**Methods:** One hundred and thirty nine different specimens were collected over a period of one year from diabetic patients from different hospitals in Makkah and Jeddah cities of Saudi Arabia. The collected specimens were cultured and identified using standards microbiological methods.

**Results:** Out of the 139 specimens collected from infected diabetic patients in the present study the infections were more common in female (53.2%) than male (46.8%), and in the age period 51-70 years (45.3%). The detected infections among infected diabetic patients were (92.8%) bacterial infections and (7.2%) fungal infections and included diabetic foot infections (40.3%), urinary tract infections (20.1%), respiratory tract infections (16.5%), skin infections (10.8%), septicaemia (10.1%), genital tract infections (1.4%) and eye infection (0.7%). The isolated organisms from those infected diabetic patients were commonly *Escherichia coli* (19.4%) and *Staphylococcus aureus* (18.7%). This study also showed that *Candida species* were the most common fungi among infected diabetic patients.

**Conclusions:** This study showed that the infections among diabetic patients were more common in female than male and in the age period 51-70 years. In addition, infected diabetic patients were more susceptible to bacterial infections than fungal infections.

***Keywords*: *Diabetes, Infections, Bacteria, Fungi***

## INTRODUCTION

Diabetic patients are more susceptible to infections than normal individual[1]. This may be attributable to many factors which resulting from diabetes especially in conditions of poor glycaemic control and long duration of diabetes.

Infections contributed factors are such as; vascular abnormalities, neuropathy, nephropathy and delayed wound healing[2,3]. The vascular abnormalities especially microvascular may lead to organ dysfunction[4].

In addition, the immune depression has essential role in increasing the susceptibility of infections among diabetic patients. This depression in immunity can be showed by impaired leukocyte function, decrease T cell–mediated immune response, reduced chemotaxis releasing and failure of neutrophils and macrophages migration to the affected area.
All of these risk factors can be accelerated with increasing of metabolic abnormalities of diabetes[5].

Furthermore, there are other factors at the cellular level, which might increase the risk of infections, these include; increase in the number of acute inflammatory cells, absence of cellular growth and some cellular changes[3].

Treatment of any infection in diabetic patients is more difficult than non-diabetic ones especially when there is poor glycaemic control[4].

Although various infections can affect diabetic patients, the following infections are more commonly seen in diabetic patients and include; skin and wound infections[3] (like foot infection[6], cellulites[7], erysipelas[8], gas gangrene[9], and necrotizing fasciitis[10]), urinary tract infections[11], respiratory tract infections[12], genital tract infections[13] and septicaemia.[14]

In this study, we have evaluated the most common bacterial and fungal infections among infected diabetic patients.

## MATERIAL AND METHODS

**Specimens collection**
One hundred and thirty nine different specimens were collected over a period of one year from diabetic patients (74 males and 65 females) (106 Saudi and 33 non-Saudi) from different hospitals in Makkah city of Saudi Arabia (81 samples in total) including: King Abdulaziz Hospital (35 samples), King Faisal Hospital (30 samples), Ajyad General Hospital (6 samples), Hera General Hospital (6 samples), and Al-Noor Specialised Hospital (4 samples) and Jeddah city of Saudi Arabia (58 samples in total) cities including; King Fahad General Hospital (43 samples) and King Abdulaziz Medical City (15 samples).

**Specimens handling**
All specimens were delivered to the Microbiology laboratory of the Faculty of Medicine at Umm Al-Qura University and tested without delay.

**Culture of the Specimens**
Specimens except urine and stool were cultured in the following media: columbia blood agar, macConkey agar, chocolate agar and sabouraud dextrose agar.

Urine specimens were cultured in cystine electrolyte deficient media (CLED) and in a biplate; half containing MacConkey agar and the other half blood agar.

Stool specimens were cultured in deoxycholate citrate agar (DCA), xylose lysine desoxycholate agar (XLD), MacConkey media and *campylobacter* selective media (skirrows). The culture plates were incubated aerobically at 37ºC (under 5% CO2, chocolate blood agar) (42ºC for *Campylobacter* selective media) and examined at 24 and 48 hour. For anaerobic cultures, the specimens were inoculated onto blood agar containing kanamycin and vancomycin (75 µg/ml and 7.5µg/ml, respectively). This media was incubated in Gas Pak (BBL) jars at 37ºC and examined after 48 and 96 hour of incubation. While, for fungal culture, the sabouraud dextrose plate were incubated for 1-2 weeks at 25º C.

**Identification of culture**
Bacterial and fungal growth in culture media were identified according to growth characteristics, colonial morphology, gram stain and proper biochemical tests. Aerobic bacteria and fungi were identified according to standard methods[15]. Anaerobic bacteria were identified by techniques described previously[16]. In addition, all positive cultures identifications were confirmed using VITEK II machine according to manufacturer's instructions.

**Data analysis**
Results were statistically analysed by calculating the mean, median, standard deviation, range and p value, using a Fisher test (Graph Pad Instat programme statistical software). P-values of less than 0.5 were considered significant.

## RESULTS

**Study samples description**
One hundred thirty nine positive samples were identified in this study from infected diabetic patients, age range = 15-100 years, mean age = 61 years, median age = 61 years, mode age = 60 years and standard deviation of age = 15.6 years.
Most of the infected diabetic patients in our study were more than fifty years old (74.8%) and 25.2% of them were less than fifty years old and this difference was statistically extremely significant (p-value is <0.0001). (Table 1).

**Table 1 Distribution of positive samples from infected diabetic patients according to age differences**

| Age period (per years) | <30 | 30-40 | 41-50 | 51-60 | 61-70 | 71-80 | 81-90 | >90 |
|---|---|---|---|---|---|---|---|---|
| Number of positive samples | 4 (2.9%) | 10 (7.2%) | 21 (15.1%) | 33 (23.7%) | 30 (21.6%) | 26 (18.7%) | 13 (9.4%) | 2 (1.4%) |

**Distribution of infections among infected diabetic patients**

Out of 139 positive samples collected in this study from infected diabetic patients, 129 (92.8%) were positive for bacterial growth and only 10 (7.2%) were positive for fungal growth. This difference was statistically extremely significant (p-value is <0.0001).

The most common infections found in diabetic patients in this study were diabetic foot infection 56 (40.3%) followed by urinary tract infection 28 (20.1%), respiratory tract infection 23 (16.5%), skin infection 15 (10.8%), septicaemia 14 (10.1%), genital tract infection 2 (1.4%) and eye infection 1 (0.7%) (Table 2).

**Table 2 Distribution of infections among infected diabetic patients**

| Type of infections | Male | Female | Saudi | Non-Saudi | Total (%) |
|---|---|---|---|---|---|
| Diabetic foot infection | 33 (58.9%) | 23 (40.1%) | 44 (78.6%) | 12 (21.4%) | 56 (40.3%) |
| Urinary tract infection | 7 (25%) | 21 (75%) | 22 (78.6%) | 6 (21.4%) | 28 (20.1%) |
| Respiratory tract infection | 12 (52.2%) | 11 (47.8%) | 18 (78.3%) | 5 (21.7%) | 23 (16.5%) |
| Skin infection | 8 (53.3%) | 7 (46.7%) | 10 (66.7%) | 5 (33.3%) | 15 (10.8%) |
| Septicaemia | 4 (28.6%) | 10 (71.4%) | 10 (71.4%) | 4 (28.6%) | 14 (10.1%) |
| Genital tract infection | 0 | 2 (100%) | 1 (50%) | 1 (50%) | 2 (1.4%) |
| Eye infection | 1 (100%) | 0 | 1 (100%) | 0 | 1 (0.7%) |
| Total (%) | 65 (46.8%) | 74 (53.2%) | 106 (76.3%) | 33 (23.7%) | 139 (100%) |

**Distribution of bacterial infections among infected diabetic patients**

In this study, out of 129 (92.8%) bacterial positive samples identified from diabetic patients, 87 (67.4%) were positive for gram-negative bacteria and 42 (32.6%) were positive for gram-positive bacteria. This difference was statistically extremely significant (p-value is <0.0001). The most common isolated bacteria from diabetic patients in our study were *E. coli (*19.4 %) and *S. aureus* (18.7%). Other bacteria isolated from infected diabetic patients in this study are shown in (Table 3).

**Table 3 Distribution of isolated bacteria from infected diabetic patients according to infection type**

| Bacteria | Diabetic foot infection | Urinary tract infection | Respiratory tract infection | Skin infection | Septicaemia | Genital tract infection | Eye infection | Total %) |
|---|---|---|---|---|---|---|---|---|
| Escherichia coli | 14 (25.5%) | 9 (40.9%) | 0 | 1 (6.7%) | 3 (21.4%) | 0 | 0 | 27 (20.9%) |
| Staphylococcus aureus | 13 (23.6%) | 0 | 5 (23.8%) | 5 (33.3%) | 2 (14.3%) | 0 | 1 (100%) | 26 (20.2%) |
| Pseudomonas aeruginosa | 8 (14.5%) | 1 (4.5%) | 3 (14.3%) | 1 (6.7%) | 2 (14.3%) | 0 | 0 | 15 (11.6 %) |
| Klebsiella pneumoniae | 3 (5.5%) | 4 (18.2%) | 3 (14.3%) | 1 (6.7%) | 2 (14.3%) | 0 | 0 | 13 (10.1%) |
| Acinetobacter species | 3 (5.5%) | 1 (4.5%) | 5 (23.8%) | 2 (13.3%) | 1 (7.1%) | 1 (100%) | 0 | 13 (10.1%) |
| Proteus mirabilis | 3 (5.5%) | 2 (9.1%) | 2 (9.5%) | 2 (13.3%) | 0 | 0 | 0 | 9 (7%) |
| Enterococcus fecalis | 2 (3.6%) | 4 (18.2%) | 1 (4.8%) | 1 (6.7%) | 0 | 0 | 0 | 8 (6.2%) |
| Staphylococcus epidermidis | 0 | 0 | 1 (4.8%) | 0 | 3 (21.4%) | 0 | 0 | 4 (3.1%) |
| Morganella morganii | 3 (5.5%) | 0 | 0 | 0 | 0 | 0 | 0 | 3 (2.3 %) |
| Providencia stuartii | 0 | 0 | 1 (4.8%) | 1 (6.7%) | 0 | 0 | 0 | 2 (1.6 %) |
| Streptococcus pyogenes | 1 (1.8%) | 0 | 0 | 0 | 0 | 0 | 0 | 1 (0.8%) |
| Proteus vulgaris | 1 (1.8%) | 0 | 0 | 0 | 0 | 0 | 0 | 1 (0.8%) |
| Staphylococcus hemolyticus | 0 | 0 | 0 | 1 (6.7%) | 0 | 0 | 0 | 1 (0.8%) |
| Klebsiella oxytoce | 0 | 1 (4.5%) | 0 | 0 | 0 | 0 | 0 | 1 (0.8%) |
| Enterococcus faecium | 0 | 0 | 0 | 0 | 1 (7.1%) | 0 | 0 | 1 (0.8%) |
| Enterobacter cloacae | 1 (1.8%) | 0 | 0 | 0 | 0 | 0 | 0 | 1 (0.8%) |
| Enterobacter aerogenes | 1 (1.8%) | 0 | 0 | 0 | 0 | 0 | 0 | 1 (0.8%) |
| Citrobacter koseri | 1 (1.8%) | 0 | 0 | 0 | 0 | 0 | 0 | 1 (0.8%) |
| Chromobacterium violaceum | 1 (1.8%) | 0 | 0 | 0 | 0 | 0 | 0 | 1 (0.8%) |
| Total (%) | 55 (39.7%) | 22 (15.8%) | 21 (15.1%) | 15 (10.8%) | 14 (10.1%) | 1 (0.7%) | 1 (0.7%) | 129 (92.8%) |

**Distribution of fungal infections among infected diabetic patients**

Out of 10 (7.2%) fungal positive samples identified from diabetic patients in the current study, 5 (3.6%) were positive for *Candida species*, 4 (2.9%) were positive for *Candida albicans* and only 1 (0.7%) were positive for *Aspergillus species* (Table 4).

**Table 4 Distribution of isolated fungi from infected diabetic patients according to infection type**

| Organism name | Diabetic foot infection | Urinary tract infection | Respiratory tract infection | Genital tract infection | Total (%) |
|---|---|---|---|---|---|
| Candida albicans | 0 | 3 (50%) | 0 | 1 (100%) | 4 (40%) |
| Candida species | 0 | 3 (50%) | 2 (100%) | 0 | 5 (50%) |
| Aspergillus species | 1 (100%) | 0 | 0 | 0 | 1 (10%) |
| Total (%) | 1 (0.7%) | 6 (4.3%) | 2 (1.4%) | 1 (0.7%) | 10 (7.2%) |

## DISCUSSION

Diabetes is a worldwide disease that is not only considered as a chronic disease but also as a fatal disease. World health organisation estimated that diabetes affects more than 180 million people and leads to about 1.1 million deaths per year worldwide. In Saudi Arabia, the prevalence of diabetes is more than 24% of adult population[17]. Diabetes has long been suspected as a risk factor of infections so that diabetic patients are more susceptible to bacterial and fungal infections than normal individuals[1].

Bacterial infections are so far more prevalent than fungal infections to infect the normal people and diabetic patients worldwide. From those bacteria, *S. aureus*, *Enterococcus species*, and *Streptococci group B* are frequently the most isolated gram-positive bacteria while E. *coli*, *Pseudomonas aeruginosa* and *Proteus mirabilis* are frequently the most isolated gram-negative bacteria[18].

In agreement with Abdulrazak *et al*[18] findings, bacterial infections among infected diabetic patients were 13 times more prevalent than fungal infections in our study (92.8%) versus (7.2%). In addition, the most common isolated organisms from diabetic patients in this study were *E. coli* (19.4%) and *S. aureus* (18.7%).

In the current study, the most common infection found in diabetic patients was foot infection (40.3%). This was in accordance to Hirsch *et al*[3] findings whom reported that wound infection (in particular foot wound infection) considers the major infection in diabetic patients that

affecting 25% of them. In addition, Frykberg *et al*[19] reported that diabetic foot infection is the major source of morbidity and the leading cause of hospitalisation for diabetic patients.
Rathur and Boulton[20] stated that diabetic foot infection affects men more than women, which was in agreement with findings of this study, where 58.9% of diabetic foot infections were from male patients and 40.1% were from female patients.
In the current study, 98.2% of diabetic foot infections were of bacterial origin in which *E. coli* formed 25.5% of infection followed by *S. aureus* (23.6%) and *Pseudomonas aeruginosa* (14.5%). In contrast to the finding of this study, Hirsch *et al.*[3] found that the most common causative organism of diabetic foot infection is *S. aureus*. Abdulrazak *et al*[18] reported that *Pseudomonas aeruginosa* is one of the common bacterial causes of diabetic foot infection which is in agreement with our finding.
In the other hand, 1.8% of diabetic foot infections in this study were of fungal origin, and the only isolated fungi were *Aspergillus species*. This was in contrast to Abdulrazak *et al.*[18] whom reported that *Candida species* are the most common fungal causative agents of foot infection.

Skin infections other than diabetic foot infections are also common in diabetic patients such as; cellulitis, necrotizing fasciitis and others[8,9]. In the present study, skin infections other than foot infections constituted 10.8% of all infections among infected diabetic patients, and 33.3% were caused by *S. aureus*. This was in accordance to several studies[7-9] which reported that *S. aureus* is the main cause of skin infection among diabetic patients.

After diabetic foot infection, urinary tract infection (UTI) was the second most prevalent infection among infected diabetic patients in this study (20.1%). This was in accordance to Geerlings *et al.*[11] findings whom reported that UTIs are highly prevalent and more complicated among diabetic patients.

In addition, Geerlings *et al.*[11] found that UTIs are more common in female than male, which was in agreement with findings of this study, where 75% of diabetic patients with UTIs were female and 25% of diabetic patients with UTIs were males.

In the present study, 78.6% of UTIs among infected diabetic patients were of bacterial origin where *E. coli* constituted 40.9% of them followed by *Klebsiella pneumoniae* and *Enterococcus fecalis* (18.2%) for each. In accordance to findings of this study, several studies[11,21,22] found that the most common causative bacterial agents of UTIs among diabetic patients were *E. coli*, *Klebsiella pneumoniae* and *Enterococcus fecalis* .

For fungal UTI among diabetic patients, several studies[11,21,22] reported *Candida albicans* as a common causative fungus. This was in agreement with findings of this study where *Candida albicans* (50%) and *Candida species* (50%) were the causative fungal agents of UTIs among infected diabetic patients.

Respiratory tract infections (in particular lower respiratory tract infections) considered one of the common infections seen in diabetic patients[5].

In agreement to Muller *et al.*[5] findings, respiratory tract infections were found to be the third most common infection among infected diabetic patients in this study (16.5%). For these respiratory tract infections, 91.3% of them were of bacterial origins where *S. aureus* constituted the most common causative bacteria (23.8%) followed by *Pseudomonas aeruginosa* and *Klebsiella pneu*moniae (14.3%) for each. Worth noting that *Acinetobacter species* found to be more common among infected diabetic patients with respiratory tract

infections acquired from hospital through intensive care units (23.8% of respiratory tract infections in this study were due to *Acinetobacter species*) which was in agreement with Kuo *et al.*[23]

For fungal respiratory tract infections, 8.7% of respiratory tract infections among diabetic patients in this study were due to fungal infections and *Candida species* were the only fungi isolated in these cases.

Septicaemia is one of most common leading cause of death among diabetic patients. It is mostly caused by *S. aureus*, *E. coli*, *Pseudomonas aeruginosa* and *Klebsiella pneumoniae*[4,14]. In accordance to the above-mentioned studies, septicaemia or specifically bacteraemia was the fourth most common infection among infected diabetic patients in this study (10.1%). Bacteraemia was mostly caused by *E. coli* (21.4%) and *S. epidermidis* (21.4%) followed by *S. aureus*, *Pseudomonas aeruginosa* and *Klebsiella pneumoniae* (14.3%) for each.

In the current study, only two (1.4%) infections among infected diabetic patients were genital infections, caused by *Candida albicans* and *Acinetobacter* baumannii and both of them were in female patients. This was in agreement with several studies which reported that genital infections among diabetic patients are more commonly seen in female than in male and they mainly caused by *Candida*, *Chlamydia trachomatis*, *Neisseria gonorrhoea* and *Streptococci viridans*[13,24,25].

Other infection found in diabetic patients in the current study was eye infection, in which one Saudi diabetic male patient suffered from eye infection that caused by *S. aureus*.

## CONCLUSIONS

In conclusion**,** this study showed that the infections among diabetic patients were more common in female than male and that diabetic patients were at high risk to infections in the age period 51-70 years. In addition, infected diabetic patients were more susceptible to bacterial infections than fungal infections and that the most common bacteria isolated from infected diabetic patients were *E. coli* and *S. aureus* while the most common fungi isolated from them was *Candida*. Furthermore, the most common types of infections found among infected diabetic patients were diabetic foot infections followed by UTI and respiratory tract infection .

It is hoped that the results obtained from this study will be of great benefits to physicians who frequently deal with diabetic patients in their proper identification and diagnosis of bacterial and fungal infections.

As a recommendation from this study, we recommend extending this project to cover different regions and cities of Saudi Arabia to give a broader picture about the situation of bacterial and fungal infections among diabetic patients. In addition, we may recommend adding viral and parasitic causes of such infections

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UQU Medical Journal

*Case Report*

# Adult onset still's disease in a 60 year old male patient with fever of unknown origin and chronic diarrhea

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## مريض بداء ستيل عمره ستون عاما , يعاني من حمى مجهولة المنشأ و إسهال مزمن

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### الملخص العربي

قمنا بكتابة وصفية لحالة لمريض سعودي يبلغ من العمر 60 عاماً مصاباً بداء ستيل. كان المريض يشكو من حمى مجهولة المنشأ, طفح جلدي, التهاب في الحلق, نقص في الوزن, التهاب في المفاصل و إسهال مزمن. الإسهال المزمن لم يذكر في البحوث الوصفية السابقة كأحد الأعراض السريرية لمرض ستيل.

كانت نتائج تحاليل الأمصال سالبة, اما مختبر التشريح فقد اتضح وجود التهاب جلدي وعائي و التهاب بسيط في القولون. ولقد تمت السيطرة على المرض بإعطاء المريض علاج الكوتيزون و الميثوتريكسات.

## ABSTRACT

**Abstract**

We report a case of Adult onset Still's disease (AOSD) in a 60 year old Saudi male patient. He presented with fever of unknown origin, skin rash, sore throat, weight loss, arthritis and chronic diarrhea. Chronic diarrhea was not listed as one of the manifestations in several large case series of AOSD. Serological tests were negative. Pathological findings revealed cutaneous inflammatory vascular reaction and mild colitis. The disease has been successfully controlled with prednisone and methotrexate.

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***Keywords*: *Stills disease, Fever of unknown origin, Chronic diarrhea.***

## INTRODUCTION

Adult onset Still's disease (AOSD) is a rare, systemic inflammatory disease of unknown etiology, characterized by daily high spiking fevers, evanescent rash and arthritis [1,2]. There are several gastrointestinal manifestations reported with AOSD. Chronic diarrhea was not listed as one of these manifestations in several large case series [3,7]. We report a case of AOSD in a 60 year old Saudi male patient with synchronous onset of gastrointestinal symptoms including chronic diarrhea.

## CASE REPORT

A 60 year old Saudi male patient known to have diabetes mellitus and hypertension was referred to our hospital as a case of fever of unknown origin. He presented initially to his local health authorities with history of sore throat and recurrent upper respiratory tract symptoms. He sought medical advice and received a course of antibiotic therapy but without benefit. Detailed history at time of his presentation to our hospital revealed one month history of fever, sore throat, diarrhea, left knee joint pain and swelling and generalized fatigability. His body temperature was reported to reach 38 - 40 degrees Celsius on several occasions during the day. Diarrhea was watery and large in amount, three to four times daily and contained no mucus or blood. He had no prior history of diarrheal illnesses before. There was mild epigastric discomfort but no history of jaundice or hepatitis exposure. He had significant weight loss of around 20 kg during this period. He complained of migratory joints pains but persistent left knee pain and swelling that affected his activity level. He also described an intermittent, macular skin rash that occasionally may accompany his fevers. It was salmon-colored that may involve arms, trunk, face and knees. It only lasted a day or two maximum. The patient was exposed to raw camel milk ingestion and was treated in a peripheral hospital as a case of brucellosis with no improvement. He is a bus driver with no history of contact with sick patients including tuberculosis and no history of mosquito bites. His medications include gliclazide, lizinopril, simvastatin and aspirin.

Physical examination revealed the presence of tachycardia with heart rate at 112 beats per minute and temperature 36.8. The salmon-colored macular rash was present on several parts of his body during hospitalization; face trunk and extremities particularly during febrile attacks. His pharynx was mildly congested and erythematous. There was no abdominal tenderness and no organomegaly or lymphadenopathy. There was joint line tenderness in several metacarpophalangeal (MCP) and wrist joints bilaterally. His shoulder joints were both tender on active and passive range of motion. There was joint line tenderness in his left knee with significant amount of effusion. He had no signs of infective endocarditis. The rest of the examination was unremarkable.

Routine laboratory investigation showed the following: ESR 98 mm/hour, CRP 66.3 mg/litre, WBC 6.17/ UL (28000/UL in the report requested from the previous hospital with a 83% neutrophilic predominance), hemoglobin 12.6 g/dL, platelets 328000/UL, an extremely high ferritin level of 17234 ng/mL, serum albumin 2.7 g/dL, ALT 15 U/L, ALP 61 U/L, Brucella titer was negative, Cultures were negative for microorganisms, antinuclear antigen and rheumatic factor were all negative as well. Synovial fluid examination obtained from left knee showed turbid appearance with WBC count of 6600/mm3. It was predominantly neutrophils and negative for malignant cells and crystals. A pelvi-abdominal ultrasound and an abdominal CT scan shows hepatomegaly with fatty changes and no lymphadenopathy. A radiograph of the hands and knees were normal with mild osteoarthretic changes and joint effusion of both knees. Skin biopsy was taken and histopathology showed inflammatory vascular reaction. There was no major abnormalities detected with upper and lower gastrointestinal endoscopy. Histopathological examination revealed chronic gastritis and mild colitis.

After establishment of the diagnosis a course of prednisone 1mg/kg was initiated in addition to methotrexate 10 mg weekly. During clinic visits an obvious improvement of his symptoms was noticed, his CRP declined to 6.40 – 0.91 mg/L and ferritin level dropped steadily from 2055 to 1146 ug/L. His last clinical visit 9 months after initial presentation showed maintained clinical improvement with no symptoms on prednisone 15 mg daily and methotrexate 17.5 mg weekly. CRP and ferritin level were normalized.

## DISCUSSION

AOSD usually presents with a variety of clinical symptoms, including quotidian fever, rash, arthritis, lymphadenopathy, and splenomegaly.[8] There are other symptoms mostly related to pharyngitis, hematologic, cardiopulmonary and hepatic involvement. Fever is the dominant symptom and infectious etiologies must always be ruled out. AOSD represents the most frequent etiology among connective tissue diseases causing fever of unknown origin.[5]

There are variable gastrointestinal manifestations of AOSD. Liver abnormalities, predominantly hepatomegaly and elevated liver enzymes are present in approximately 50-75% of patients.[6,9] Several observations of severe hepatitis have been reported [9-11] justifying strict monitoring of liver enzymes in these patients.[9, 12, 13] It is not believed that AOST can coexist with autoimmune hepatitis.[14,15] Use of non-steroidal anti-inflammatory drugs may be a significant cofactor [6, 9]. Splenomegaly has been reported in 52% of cases, while weight loss (>10%) in 76% of cases [6, 16]. Abdominal pain as a feature of AOSD was underreported, it

has been described in only 12% of cases worldwide,[17] but in one report it has been present in approximately 50% of patients and it can simulate a surgical abdomen in severe cases.[6, 17]

In the case described here there was hepatomegaly but normal liver enzymes and no splenomegaly. There was significant weight loss and chronic diarrhea. Chronic diarrhea has never been reported as one of the gastrointestinal features of AOSD. In addition, AOSD was not listed as a possible cause to consider in the diagnostic workup for patients with chronic diarrhea.[18] The associated mild colitis reported with this case may be related to AOSD or just a non-specific mild form of idiopathic colitis. All symptoms reported with this case including chronic diarrhea responded well to high dose steroid and methotrexate therapy.

AOSD affects young people and has a bimodal age distribution with two peaks-at 15-25 and 36-46 years of age.[19] It is generally considered a disorder of youth, but there are several reports of AOSD in the elderly.[20,22] Low-grade and atypical pattern of fever is sometimes seen in older patients,[23] otherwise no major differences in clinical manifestations have been observed. Good response to steroid therapy and use of low dose methotrexate has been observed in these reports consistent with our findings in the case presented.

Other features presented in this case are similar to common features reported with AOSD in the literature. Sore throat is known as a cardinal sign of AOSD and may be associated with odynophagia.[24] The most common joints involved in AOSD are the knees, wrists, ankles and elbows. [25] Our patient had arthritis affecting his left knee, wrists, several MCPs, shoulders and hip joints. The classical destructive form of arthritis that affects the carpal joints was not observed in the patient presented. It is reported that destructive arthritis of the hips occurs in 5% to 33% of patients.[6] Joint fluid aspirate often discloses marked leukocytosis with a neutrophilic predominance[26] consistent with the observation in the case presented. The reported rash for the case presented with maculopapular, salmon-pink eruption which appeared during febrile attacks was classical. Skin biopsy findings in the literature, as in the case presented, usually shows nonspecific and mild perivascular inflammation.[27] Hyperferritinemia in AOSD is not related to iron metabolism and is likely to be a consequence of cytokine secretion induced by the reticuloendothelial system or hepatic damage.[28,29] A fivefold increase in serum ferritin has 41% specificity and 80% sensitivity for the diagnosis of AOSD.[30] The levels correlate with disease activity as was demonstrated in our case. The constellation of clinical manifestations in the case presented has met the Yamaguchi's classification criteria for AOSD.[31] Several drugs have been used in the treatment of AOSD from multiple case reports and small scale retrospective studies. In general most patients will require corticosteroids treatment at some point in their disease course, with responses ranging from 76 to 95%.[1] Methotrexate was particularly found effective in patients with arthritis and joint destruction.[21,32] Drugs like azathioprine, cyclosporine, cyclophosphamide and biological therapies like infliximab, etanercept, anakinra have all been used in management of AOSD with favorable outcomes.[33]

We reported an elderly patient with classical manifestations of AOSD in addition to chronic diarrhea. We would like to remind clinicians to consider autoimmune diseases like AOSD in the diagnostic workup of patients with chronic diarrhea. In addition, AOSD should be considered in the differential diagnosis of elderly patients presenting with fever of unknown origin. AOSD in the elderly responded well initially to prednisone and methotrexate.

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Submitted manuscripts are reviewed for originality, significance, adequacy of documentation, reader interest and composition. Manuscript not submitted according to instructions will be returned to the author for correction prior to beginning the peer review process. Revised manuscripts are judged on the adequacy of responses to suggestions and criticisms made during the initial review after which they are sent to selected Reviewers for assessment and evaluation. All accepted manuscripts are subject to editing for scientific accuracy and clarity by the office of the Editor.

## *FORMAT REQUIREMENTS*

Manuscript should be written in English. Both the American and British style of writing and spelling will be acceptable. The acceptable file format is Word. Please do not submit your manuscripts in PDF format. Manuscripts should be typed using ***New Times Roman font and point 12 without any formatting.*** Number pages consecutively, beginning with the title page. Type the page number in the upper right-hand corner of each page.

**Title Page**
The title page of the manuscript should include:

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Authors' affiliation (department, institution)
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Email (for the corresponding author)

**Abstracts**
Provide on a separate page a structured abstract of not more than 300 words for original article and an unstructured abstract of no more than 200 words for other submission types. The structured abstract should consist of four paragraphs labeled Objective, Methods, Results and Conclusion. They should briefly describe, respectively, the problem being addressed in the study, how the study was performed, the salient result and what the authors conclude from the results. The unstructured abstract is in the form of one paragraph covering these headings.

**Introduction**
State the purpose of the article and summarize the rationale for the study or observation. Give only strictly pertinent references and do not include data or conclusions from the work being reported. Clearly mention the objective(s) of the study in this section without any sub-heading.

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Describe your selection of the observational or experimental subjects (patients or laboratory animals, including controls) clearly identify the age, sex and other important characteristics of the subjects. Identify the methods, apparatus study design, sampling method, sample size, inclusion/exclusion criteria wherever applicable without adding any sub-headings. Give references to established methods if necessary.

**Results**
Present your results in logical sequence in the text, tables and illustrations. Do not repeat in the text all data in the tables or illustrations emphasize or summarize important observations.

**Discussion**
Emphasize the new and important aspects of the study and conclusions that follow from them. Do not

repeat in detail data or other material given in the introduction or the results section. Include in discussion section the implications of the findings and their limitations including implications for future research. Relate the observations to other relevant studies.

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Link the conclusions with the goals of the study but avoid unqualified statements and conclusions not completely supported by data. State new hypothesis when warranted but clearly label them. Such

**Acknowledgements**
Persons who have contributed intellectually to the paper but whose contributions do not justify authorship may be named and the function or contribution described.

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References should be cited in the Vancouver style in consecutive numerical order at first mentioned in the text and designated by the reference number in superscript. References appearing in a table or figure should be numbered sequentially with those in text.

> **Vancouver style of references:**
> Snowdon J. Severe depression in old age. Medicine Today. 2002 Dec;3(12):40-47.
>
> Skalsky K, Yahav D, Bishara J, Pitlik S, Leibovici L, Paul M. Treatment of human brucellosis: systematic review and meta-analysis of randomised controlled trials. BMJ. 2008 Mar 29;336(7646):701-4.

**Illustrations**
Illustrations should clarify and augment the text. The selection of sharp, high-quality illustrations is of paramount importance. Photographs including all types of images should be prepared as .jpg uncompressed files at a resolution of 300 dpi. Figures of inferior quality will not be acceptable.

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**Original article:** maximum 3000 words excluding title page and a structured abstract of 250 words and references with no more than three tables or figures and 40 references Short Reports / Short Communications / Special Communications / Case reports: maximum 1250 words excluding title page and an unstructured abstract of 150 words and references with no more than two tables or figures and 10 references. It should not have more than six authors

**Case Report:** Abstract; Introduction; Case Report; Discussion and Conclusion.

**Short Report:** Abstract; Introduction; Patients Methods and Results; and Conclusion.

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