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S1 Management of diabetic foot wounds
Use of ethnic specific BMI and waist cut-offs for prevention of diabetes and cardiovascular disease

P Katulanda¹, R Jayawardena²


Introduction

Burden of obesity and its implications

The terms overweight and obesity are used to identify states in which abnormal or excessive fat accumulation has occurred in the body leading to adverse effects on health of an individual (1). According to the World Health Organization (WHO) estimates, nearly 2 billion adults are suffering from overweight and 600 million from obesity in the world (1). Each year nearly 3 million adults die due to being overweight and obese and it is estimated that 35.8 million (2.3%) of global DALYs can be accounted to be due to overweight or obesity (1). Obesity is strongly associated with diabetes, dyslipidaemia, hypertension, cardiovascular disease, non-alcoholic fatty liver disease and mechanical problems like obstructive sleep apnoea, osteoarthritis and even psychological issues such as depression and anxiety (2).

Sri Lanka is not an exception; obesity associated metabolic diseases have reached epidemic proportions. One-fifth Sri Lankan adults are suffering from dysglycemia and 10% from diabetes (3). Moreover, 25% of adults have hypertension (4) and a similar percentage of adults are having metabolic syndrome (5). Deaths due to cardiovascular diseases in Sri Lanka are more prevalent than many developed countries (6). However, according to the international BMI cut-offs, derived based on data from White Caucasians obesity prevalence is very low. Sri Lanka Diabetes and Cardiovascular Study reported only 4% of obesity in 2005-2006 (7). This level has not changed significantly in our second data collection carried out in 2011 (8). Hence there seems to be a paradox between obesity data according to the international cut-offs and obesity related co-morbidities based on prevalence data.

Use of anthropometric measurements to classify adiposity

Body Mass Index (BMI) is a simple index of weight-for-height that is commonly used to classify underweight, overweight and obesity in adults. It is defined as the weight in kilograms divided by the square of the height in metres (kg/m²). BMI values used internationally are age-independent and same for both sexes.

However, BMI may not correspond to the same degree of fatness in different populations – in part due to different body proportions and fat distribution patterns [9]. Although the health risks associated with BMI shows a continuous association, the absolute risk may differ in different populations (10).

Over the last two decades, there was an ongoing debate on using same BMI cut-offs in different ethnic groups (11). This was based on growing evidence that the association between BMI, percentage of body fat, and body fat distribution were different across populations. It was shown that the South Asians had higher fat percentage for a given BMI compared to White Caucasians and therefore the obesity related diseases appeared at a lower BMI (11).

Waist circumference (WC) is another clinically relevant and increasingly used method of assessing adiposity. Whereas BMI provides a marker of overall adiposity, WC is a better marker of abdominal adiposity, and is the best correlate of visceral fat mass (12). Higher levels of WC are strongly associated with cardiovascular disease. To identify those with an European origin with an increased and a substantially increased risk of developing chronic diseases, the WHO currently recommends WC cut-off points of 80 cm and 88 cm respectively for women and 94 cm and 102 cm respectively for men. However, as with BMI, population specific cut-off points have been shown to be more appropriate for WC as well. The International Diabetes Federation recommends a WC cut-off point of 80cm for women and 90cm for men to diagnose metabolic syndrome in South Asians (13).

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Differential effects of BMI on diabetes and other outcomes in different populations

Several clinicians and researchers from India, Sri Lanka and other populations have shown that the WHO cut-off points derived according to White Caucasian data may not be applicable to Asians (14, 15).

The group led by Misra et al. in India has showed that BMI cut-off of 21kg/m² was optimum in identifying individuals with at least one obesity related comorbidity (14). In another study Snehalatha et al showed that a BMI cut-off of 23kg/m² was optimal in identifying at least two obesity related risk factors (16). Similar data have also shown by other groups in India. Based on Indian studies, a consensus group of experts in India has arrived at BMI cut-offs of 23kg/m² to diagnose overweight and 25 kg/m² to diagnose obesity (14). In addition they recommended a waist circumference of 80cm in men and 90cm in women to diagnose abdominal adiposity.

The Sri Lanka Diabetes and Cardiovascular Study (SLDCS) conducted in 2005 also showed nearly identical data to those of India (15). According to SLDCS data the cut-off values for BMI and WC for males were 20.7kg/m² and 76.5cm. The respective values for females were 22.0 kg/m² and 76.3cm. The common cut-off value for BMI for males and females was 21.5 kg/m².

Nurses’ health study and SLDCS

The nurses’ health study conducted in USA clearly showed the association of BMI with diabetes risk (Figure 1) (10). The diabetes risk started to double when the BMI was more than 25kg/m². When Sri Lankan data were considered (Table 1) the prevalence of diabetes, metabolic syndrome, hypertriglyceridaemia doubled when the BMI was 18kg/m² and blood pressure and low HDL cholesterol proportions increased by more than 25% when the BMI was over 23kg/m².

<table>
<thead>
<tr>
<th>BMI category (Kg/m²)</th>
<th>&lt; 16.0</th>
<th>16.0-18.4</th>
<th>18.5-22.9</th>
<th>23.0-27.4</th>
<th>≥ 27.5</th>
<th>p value p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes</td>
<td>4.2%</td>
<td>4.4%</td>
<td>9.8%</td>
<td>19.3%</td>
<td>19.0%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Elevated blood pressure</td>
<td>26.7%</td>
<td>28.5%</td>
<td>38.2%</td>
<td>55.6%</td>
<td>63.7%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Low HDLC</td>
<td>33.2%</td>
<td>38.3%</td>
<td>45.9%</td>
<td>61.0%</td>
<td>61.9%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>High triglycerides</td>
<td>7.6%</td>
<td>10.2%</td>
<td>20.9%</td>
<td>34.5%</td>
<td>33.4%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Metabolic syndrome</td>
<td>3.6%</td>
<td>4.6%</td>
<td>15.9%</td>
<td>49.4%</td>
<td>65.7%</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

[¹ systolic blood pressure ≥ 130 mmHg, diastolic blood pressure ≥ 85 mmHg or on antihypertensive treatment, *NCEP criteria, ‡p value for trend]
Use of ethnic specific BMI and waist cut-offs for prevention of diabetes and cardiovascular disease

WHO perspective

A WHO expert consultative committee was appointed to look into the controversy of anthropometric cut-offs and to review scientific evidence on this important issue. After extensive literature review the committee suggested that Asian populations have different associations between BMI, percentage of body fat, and health risks than their White Caucasian counterparts (11). They concluded that the Asians are at high risk of type 2 diabetes and cardiovascular disease at substantially lower BMI compared to the existing WHO cut-off level for overweight (>25 kg/m²). However, since they considered data from different Asian groups including South Asians and Chinese they were unable to arrive at a uniform cut-off. Instead of considering different cut-offs for South Asians and Chinese no attempt was made, to redefine cut-off points for each population separately.

American Diabetes Association perspective

In the United States, the prevalence of overweight and obesity is lower in South Asians than the White Caucasians (17). However the clinicians have noticed a very high prevalence of diabetes and CVD in Asians at a lower BMI. Based on the studies among the Asian Americans and studies done in South Asian countries, the American Diabetes Association (ADA) have taken a more bold approach compared to the WHO. The ADA has lowered the cut-off for screening for type 2 diabetes from 25kg/m² to 23kg/m².

Way forward

There is overwhelmingly good quality data from India, Sri Lanka and from South Asians living in USA and the other developed countries to redefine anthropometric cut-offs for South Asians (14-17). Therefore clinicians, epidemiologists and other professionals working on health of South Asians need to accept and follow the South Asian specific cut-offs for defining overweight, obesity and central obesity. BMI cut-offs of 23kg/m² and 25kg/m² should be considered to classify overweight and obesity respectively. A waist circumference cut-off of 80cm for females and 90cm for males should be considered to classify abdominal obesity. Compared to the BMI and WC robust data comparable between different studies are lacking for waist to hip ratio (WHR). Therefore further research is needed before arriving at consensus values for WHR.

References

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Value of testing glycated hemoglobin in non-diabetic patients presenting with acute coronary syndrome

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Abstract

Objectives: To estimate the proportion of patients with no previous diagnosis of diabetes admitted with acute coronary syndrome having normal, impaired fasting glucose and diabetes on fasting blood glucose testing and normal, pre-diabetes and diabetes on glycated hemoglobin. To compare the clinical profiles of patients with acute coronary syndrome with no diabetes according to both tests, with those having no diabetes on fasting blood glucose but having diabetes according to glycated hemoglobin.

Methods: In a cross sectional study, fasting blood sugar and glycated hemoglobin were estimated in 125 patients without a previous history of diabetes admitted with acute coronary syndrome. Glycemic category was ascertained according to fasting blood glucose and glycated hemoglobin levels recommended by the American Diabetes Association.

Results: According to glycated hemoglobin testing, 47% and 53% of patients with acute coronary syndrome had diabetes and pre-diabetes respectively. The corresponding percentages in each category according to fasting blood glucose testing were six (4%) and twenty (16%). There were no significant differences in the mean age, body mass index or waist circumference of patients in the categories with no diabetes on both testing methods and diabetes only on glycated hemoglobin testing.

Conclusions: According to glycated hemoglobin testing, every patient with acute coronary syndrome has either diabetes or pre-diabetes. Compared to fasting blood glucose testing alone, additional testing for glycated hemoglobin in patients with acute coronary syndrome increase the number of patients with newly diagnosed diabetes by eight fold and pre-diabetes by two and a half fold.

Key-words: Glycated hemoglobin, acute coronary syndrome, Pre-diabetes, Diabetes.

Introduction

Coronary artery disease (CAD) affects individuals with type 2 diabetes more frequently than those without diabetes (1). Acute coronary syndrome (ACS) represents a major clinical presentation of CAD. Studies reveal a positive correlation between the admission plasma glucose level and morbidity and mortality from CAD (2,3). Individuals with diabetes benefit from more intensive and aggressive management protocols such as early referral for coronary angiography and preferential use of coronary artery bypass surgery over coronary angioplasty compared to those without diabetes (4).

Fasting blood glucose (FBS) is used to verify the glycaemic status of both diabetic and non-diabetic patients admitted to hospital with ACS. Occurrence of stress hyperglycemia and test result values in the range of impaired fasting glucose (100-125 mg/dL) limits its specificity in detecting the correct glycaemic status among individuals with no history of diabetes presenting with ACS. Thus, in patients with ACS and previously undiagnosed diabetes, testing only for FBS could yield false positive or false negative results, depriving them of being managed according to their correct glycaemic category with the most optimal management protocol.

Recent guidelines recommend testing of glycated hemoglobin (HbA1c) level to diagnose pre-diabetes and diabetes (5). Individuals with HbA1c > 6.5% are classified as having diabetes and those with HbA1c between 5.6-6.4% are categorized having pre-diabetes. Testing for HbA1c does not require fasting, and it reflects glycaemic load over a longer period (three to four months). It is a more specific test than fasting plasma glucose in the diagnosis of the underlying glycaemic status.

Testing of HbA1c level in previously undiagnosed diabetic patients with ACS could help in detecting the correct glycaemic category than testing FBS alone. More specific information on the correct glycaemic category in

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Testing HbA1c in non-diabetic patients presenting with acute coronary syndrome

The patients with ACS could supplement therapeutic decision making and potentially improve clinical outcomes. We planned to study the clinical utility of testing for HbA1c in detecting pre-diabetes and diabetes among patients without the previous diagnosis of diabetes mellitus admitted to hospital with acute coronary syndromes.

The main objectives of this study were
1. To assess the proportion of patients with no previous diagnosis of diabetes mellitus admitted with acute coronary syndrome having normal, impaired fasting blood glucose and diabetes on FBS and normal, pre-diabetes and diabetes on HbA1c.
2. To compare the clinical profiles of patients with ACS with no diabetes on both FBS and HbA1c with those having no diabetes on FBS but HbA1c above the diabetic cut-off value.

Methodology

This is a cross sectional study conducted in a medical ward of a tertiary care hospital in Sri Lanka. We used convenient sampling method to include all male and female patients with no previous history of diabetes, admitted over a period of three months with any of the three types of acute coronary syndromes; ST elevation myocardial infarction, non-ST elevation myocardial infarction and unstable angina. Patients with previously diagnosed diabetes and those with a history of steroid use during the past three months were excluded.

We obtained data on age, gender, body mass index (BMI), waist circumference, drug treatment for previously diagnosed dyslipidemia, hypertension or coronary artery disease from the bed head tickets. Testing for HbA1c was done from the same sample of blood obtained for fasting blood glucose on the second day after admission. High performance liquid chromatography (HPLC) method was used to estimate HbA1c level. Diagnostic cut-off values laid down by the American Diabetes Association for using HbA1c to detect pre-diabetes and diabetes were used for categorization of glycaemic status.

Statistical analysis

All numerical data were represented as mean (SD) and categorical data as proportions. Student’s t test was used to compare the differences between numerical data and chi-squared test was used for the categorical data and level of 0.05 was considered as statistically significant.

Results

There were 64 males (51%) in the study sample. Majority (83/125, 66%) had unstable angina and 20% and 14% were diagnosed as non-ST elevation and ST elevation myocardial infarction, respectively. Descriptive data on the study sample are shown in table 1.

Table 1. Descriptive statistics of study participants

<table>
<thead>
<tr>
<th></th>
<th>Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>63.3 (13.4)</td>
</tr>
<tr>
<td>Body mass index (Kg/m²)</td>
<td>21.9 (4.3)</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>81.4 (12.2)</td>
</tr>
<tr>
<td>FBS (mg/dL)</td>
<td>91.1 (26.9)</td>
</tr>
<tr>
<td>HbA1c %</td>
<td>6.5 (0.62)</td>
</tr>
</tbody>
</table>

Forty two (33%) patients gave a previous history of CAD, and the percentage of patients under antihypertensive and lipid lowering therapy were 47% and 34% respectively. Family history of diabetes was elicited in 23%, and 35% were current smokers.

Of the 125 patients studied, 99 (80%) had normal blood glucose (< 125 mg/dL), 20 (16%) had impaired fasting glucose (IFG) and 6 (4%) were newly diagnosed to have diabetes, based on FBS. HbA1c levels of all 6 newly diagnosed patients with diabetes according to FBS were above 7% and ranged from 7 - 8.9% (Figure 1 and 2).
Based on HbA1c, 59 (47%) had diabetes and 66 (53%) were in the category of pre-diabetes. None of the study subjects had HbA1c level below 5.5% to be categorized as having normal blood glucose. Out of the 66 in the pre-diabetes category, only 7 subjects had FBS in the range of IFG, leaving 59 (89%) patients with pre-diabetes on HbA1c having normal FBS (< 100 mg / dL).

Number of patients in the three different glycemic categories (normal, impaired fasting glucose/ pre-diabetic and diabetes) with FBS and HbA1c is shown in the table 2.

Table 2. Number of patients in different glycemic categories

<table>
<thead>
<tr>
<th></th>
<th>FBS</th>
<th>HbA1c</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>99</td>
<td>None</td>
</tr>
<tr>
<td>IFG / Pre-diabetes</td>
<td>20</td>
<td>69</td>
</tr>
<tr>
<td>Diabetes</td>
<td>6</td>
<td>56</td>
</tr>
</tbody>
</table>

Out of the 119 patients with FBS in the non-diabetic range (< 125 mg / dL), 50 were categorized having diabetes according to HbA1c (> 6.5%) and 69 were in the pre diabetic range (5.5- 6.5%).

Comparison of the clinical profiles of patients with no-diabetes on both tests and those with no diabetes on FBS but diabetes on HbA1c is shown in the table 3.

Table 3. Comparison of patients with no diabetes by both tests vs diabetes on HbA1c with no diabetes by FBS

<table>
<thead>
<tr>
<th>No diabetes on both FBS &amp; HbA1c</th>
<th>No diabetes on FBS but diabetes on HbA1c</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>69</td>
<td>50</td>
</tr>
<tr>
<td>Age in years (mean ± SD)</td>
<td>62.41 (14.32)</td>
<td>64.02 (12.51)</td>
</tr>
<tr>
<td>BMI Kg/ m² (mean ± SD)</td>
<td>22.42 (4.46)</td>
<td>20.95 (4.07)</td>
</tr>
<tr>
<td>Waist circumference CM (mean ± SD)</td>
<td>80.77 (13.00)</td>
<td>82.15 (11.61)</td>
</tr>
<tr>
<td>% with complications during hospital stay</td>
<td>18%</td>
<td>20%</td>
</tr>
</tbody>
</table>

Discussion

We found that every patient without previous history of diabetes presenting with ACS has either diabetes (47%) or pre diabetes (53%) according to HbA1c. Altogether 59 patients were found to have diabetes on HbA1c as opposed to 6 patients on FBS. All the 6 patients who had diabetic FBS had HbA1c above the diabetic range. HbA1c detected an additional 50 patients as having diabetes among the 119 with FBS in the non-diabetic range. There was an eight-fold increase (6 vs 50) in the number of diabetics when HbA1c was used as the diagnostic criteria as opposed to FBS. Proportion with pre-diabetes was also two and a half times more when HbA1c was used as the method of diagnosis than when FBS was used.

We used HbA1c cut-off points recommended by the American Diabetes Association for the diagnosis of diabetes and pre diabetes. Studies have reported variations in the HbA1c levels in different ethnicities and some have recommended higher HbA1c cut-off values for the categorization of pre-diabetes and diabetes (6). Our findings could have been different had we known the ethnic specific HbA1c for our population.

As a diagnostic tool, HbA1c is less sensitive and more specific than FBS in detecting diabetes and pre diabetes, hence its use may be associated with an over diagnosis of individuals with both conditions (6). But considering the rising incidence of diabetes in the Sri Lankan community and the relatively high mean age (62 years) of patients included in our study, the 43% prevalence of diabetes and 57% of pre diabetes is not surprising and it only strengthens the notion that that type 2 diabetes is cardiovascular disease (7).

Prevalence of glucose abnormalities among patients with no previous history of diabetes presenting with ACS in previous studies vary between 21% - 84% (8,9). A study conducted in urban India revealed that 84% of patients with ACS with no previous history of diabetes have abnormalities in glucose metabolism based on the findings of OGTT (10). Using HbA1c cut-off level of 6.5%, the prevalence of diabetes in that study was 25%. The mean age of their study sample is lower than in our study (55 vs 62 years) and it is well established that the prevalence of diabetes increases with age. Another group that aimed to define the acceptable HbA1c cut-off value to recognize individuals with pre-diabetes and diabetes in the setting of ACS have reported that HbA1c level of 6.7% detects diabetes with 85.45% sensitivity and 91.89% specificity (11).

Based on the findings in several studies showing high rates of prevalence of glucose abnormalities among patients with ACS, Gholap and coworkers have drawn-up a simple algorithm to identify the correct glycemic category and implement appropriate management protocols for...
these patients (12). According to their algorithm, HbA1c should be done in everyone with ACS. Patients with ACS and no previous history but symptoms of diabetes, and with HbA1c of over 6.5% should be managed as having diabetes. For the same category without symptoms repeating the test in 8 weeks is recommended and they too should be managed as diabetes if the repeat HbA1c exceeds 6.5%. For those with repeat value between 6.4% - 6.2%, they recommend OGTT. And those with post discharge HbA1c < 6.2%, annual screening for diabetes is recommended. Cost effectiveness and the short and long term clinical outcome of this approach has not been elucidated. But this approach ensure giving due recognition for high prevalence of glucose abnormalities among patients presenting with ACS and obviate the need for OGTT for each and every patient found to have borderline HbA1c in the setting of an ACS.

We found that the additional 50 patients with diabetes according to HbA1c but with non-diabetic FBS were older and had higher waist circumferences and lower BMI when compared to 69 patients who had no diabetes on both FBS and HbA1c. It implies that older patients and those with central but not global obesity without a previous diagnosis of diabetes are more likely to be detected by testing for their HbA1c than FBS. But lack of statistical significance between the studied variables precludes us from arriving at such conclusions.

Finding of eight-fold (6 vs 50) increase of number of patients with diabetes and two and a half fold increase in the category with pre-diabetes by testing for HbA1c compared to FBS among patients in this study challenges the diagnostic utility of FBS in correctly recognizing the glycaemic status of individuals presenting with acute vascular catastrophes such as acute coronary syndrome. It exposes the need for a test with more sensitivity and specificity. Findings of our study may not be compelling at present for clinicians to test HbA1c in each and every patient with ACS with no previous history of diabetes, but they serve as an eye opener of higher prevalence of glucose abnormalities among patients presenting with ACS in the Sri Lankan setting.

There are few limitations in our study. We used convenient sampling method to recruit patients and there is a substantial majority with unstable angina than the other two categories of ACS in the study sample. Had we included only the patients with ST elevation infarctions the results may have been different due to more robustness in the diagnosis of ST elevation MI compared to unstable angina. The other limitation in this study is that we did not verify the glycemic status of patients included with a subsequent OGTT. Nevertheless the long held notion that “type 2 diabetes is a cardiovascular disease” is aptly endorsed by the findings of our study. As the study was conducted in a medical ward rather than in a coronary or intensive care unit, the recruited patients were stable. Failure to find any patient with stress hyperglycemia (FBS > 126 mg/dLwith HbA1c < 6.5%) may be due to the inclusion of clinically stable patients with acute coronary syndrome in this study and the relatively small sample size.

In conclusion, we report nearly a 50% prevalence of diabetes and pre-diabetes according to HbA1c among patients with no previous history of diabetes presenting with ACS. We emphasize the need for detecting correct glycemic category of these patients using a better diagnostic tool than FBS. Whether or not testing of HbA1c in this category of patients could fill this gap need to be investigated by further studies including a gold standard test such as OGTT for the diagnosis of different glycemic categories.

References
Use of EZSCAN for detection of pre-diabetes and diabetes and comparison with standard screening methods

S Bajaj1, R K Pandey1, A K Chaurasia1, R P Shukla1

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Abstract

Objectives: Pre-diabetes is almost always a precursor to the development of type 2 diabetes. Comparison of EZSCAN with existing screening methods for detection of pre-diabetes and diabetes was done.

Settings and Design: Cross sectional epidemiological study.

Material and Methods: All cases underwent the EZSCAN test and had fasting plasma glucose (FBG), post-prandial plasma glucose (PPBG) and HbA1c level estimation. The results of EZSCAN were compared with fasting blood glucose, post-prandial blood glucose and HbA1c levels.

Statistical analysis used: Mean, Standard deviation, sensitivity, specificity, positive and negative predictive value.

Results: The sensitivity and specificity of EZSCAN when compared with FBG in diabetes was 87.2% and 87.2% respectively, for pre-diabetes 80.4% and 74.3% respectively and for non-diabetes 51.1% and 97.8% respectively. The sensitivity and specificity of EZSCAN when compared with PPBG in diabetes was 86.5% and 85.2% respectively, for pre-diabetes 76.9% and 72.6% respectively and for non-diabetes 52.8% and 98.9% respectively. The sensitivity and specificity of EZSCAN when compared with HbA1c in diabetes was 86% and 90.2% respectively, for pre-diabetes 87.8% and 71.4% respectively and for non-diabetes 46.3% and 98.8% respectively.

Conclusions: EZSCAN proved to be a sensitive, specific, easy to perform screening test for diabetes and pre-diabetes which can be performed in non fasting state. EZSCAN is a simple device that can be operated by non medical personnel in non-healthcare settings with minimal subject preparation.

Key-words: EZSCAN, diabetes, pre-diabetes.

Key messages: Type 2 diabetes often progress silently, without symptoms. Timely screening and early detection of diabetes and pre-diabetes will enable clinicians to intervene early in the course of the disease, preventing complications and adverse outcomes.

Introduction

Diabetes mellitus (DM) is a major healthcare problem affecting the whole world. Type 2 DM often progress silently, without developing clinical symptoms. It frequently remains undiagnosed until complications appear. As much as one third of cases may not be detected at all (1). At the same time, epidemiologic evidence suggest that complications are triggered at a much earlier stage of the disease than previously thought (2). For example, patients with impaired glucose tolerance (IGT) and impaired fasting glucose (IFG), now commonly referred to as pre-diabetes, are exposed to an increased risk of cardiovascular disease and death (3). For a substantial number of patients, irreversible tissue damage (peripheral vascular disease, nephropathy, retinopathy, and peripheral neuropathy) have already set in at the time of diagnosis (4). The prevalence of type 2 DM is increasing and this appears to be greater in developing countries. The aetiology of this increase involve changes in diet, a higher fat intake, sedentary lifestyle, and decreased physical activity (5, 6). According to the ICMR-INDIAB national diabetes study, currently, there are an estimated 62.4 million individuals with diabetes in India (7).

Pre-diabetes indicates the state of a person born with genetic liability to diabetes from conception up to the stage when his glucose tolerance test (GTT) becomes abnormal. Therefore, pre-diabetes refers to a state and not a diagnosis.

There is a general agreement on the potential value

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Use of EZSCAN for detection of pre-diabetes

Screening for DM is recommended because, a large number of individuals who meet the current criteria for DM are asymptomatic and unaware that they have the disorder. Some individuals with type 2 DM have one or more diabetes-specific complications at the time of their diagnosis, and treatment of type 2 DM may favourably alter the natural history of DM.

The American Diabetes Association recommends screening all individuals more than 45 years every 3 years and screening individuals at an earlier age if they are overweight [body mass index (BMI) >25 kg/m²] and have one additional risk factor for DM. In those without risk factors for T2DM, testing should begin at 30-45 years of age. If test results are normal, repeat testing should be carried out at 3 to 5 year intervals.

EZ-SCAN is a new method for screening and assessment of early DM. The EZ-SCAN (Impeto Medical, Paris, France) is a patented device based on electrophysiological and electrochemistry principles which uses low level DC-induced reverse iontophoresis, together with chronoamperometry, to evaluate the behaviour of tissues in the body.

EZ-SCAN is basically SUDOSCAN and EZ-SCAN is the trade name given by the developers (Impeto Medical, Paris, France) because of ease of use. EZ-SCAN is non-invasive and provides immediate results, without any need for patient preparation, fasting or a blood draw. EZ-SCAN has demonstrated superior sensitivity and specificity ratings of 92% and 86%, respectively (9), with a variation coefficient of less than 5% (10).

**EZ-SCAN working principle**

Sympathetic innervation of eccrine sweat glands is progressively reduced at an early stage in the evolution of diabetes. This alteration of autonomous control of sweat glands causes a durable shift in the ionic balance of sweat conducts, which is independent from temperature and physical exercise.

Reverse iontophoresis, the process carried out by EZ-SCAN, extracts ions from the sweat which is secreted by sympathetically controlled sweat glands. The extracted sweat creates a current when it encounters specific sensors such as nickel electrodes. The current produced is proportional to the chloride concentration that reacts specifically with the nickel electrodes at a low DC stimuli. A time/ampere curve is recorded for each derivation. The conductance, expressed as micro-Siemens (mSi) is the ratio between the current generated and the constant DC stimulus. The measurement of the conductance is done by chronoamperometry (EZ-SCAN) and graphically displayed on a standard PC computer. Higher readings in mSi indicate a lower risk of any abnormality. According to the conductance measured on forehead, hands and feet, an EZSCAN score is calculated and results are displayed using a risk score with a colour index.

- Green (0-25%): no risk
- Yellow (26-50%): moderate risk / pre-diabetes
- Orange-red (51-100%): high risk / diabetes with or without complications

**Material and methods**

The present study was conducted at M.L.N. Medical College, Allahabad and its associated hospital SRN hospital/ Nazareth hospital, Allahabad during a period from July 2013 to July 2014.

Subjects aged more than 18 years were selected from the patients who attended medicine out patient department or were admitted in department of medicine in SRN hospital/ Nazareth hospital. Patients with a first degree relative with DM and with risk factors for developing DM were included in the study. Risk factors included hypertension (140/90 mmHg), high-density lipoprotein cholesterol level <35 mg/dL and/or a triglyceride level >250 mg/dL, physical inactivity, polycystic ovary syndrome, delivery of a baby weighing >4 kg, having been diagnosed with gestational DM, IGT, IFG on previous testing or having other clinical conditions associated with insulin resistance (eg, acanthosis nigricans).

**Exclusion criteria**

Known cases of DM and persons taking drugs that affect blood glucose levels.

All cases underwent the EZSCAN test and had their FPG, PPPG and HbA1c level estimated. The results of EZSCAN were compared with FBG, PPPG and HbA1c levels. The data were analysed and assessed with appropriate statistical methods within different groups.

**Criteria for diagnosis of pre-diabetes:**

- IFG = fasting plasma glucose 100 mg/dL to 125 mg/dL
- IGT = 2-h plasma glucose 140 mg/dL to 199 mg/dL
- HbA1c-5.7 to 6.4%

**Criteria for diagnosis of DM:**

- Fasting plasma glucose ≥ 126 mg/dL
- 2 hour plasma glucose ≥ 200 mg/dL
- HbA1c ≥ 6.5%

**Results**

Out of the total 125 patients included in the study there were 66 males and 59 females. The mean age was 50±14 years. Each patient was categorized as a pre-diabetes, DM, and non-diabetes on the basis of FBG, PPPG and HbA1c. Finally each category was compared with EZSCAN.
The sensitivities, specificities, positive predictive values (PPV) and negative predictive values (NPV) of EZSCAN in relation to FBG, PPBG and HbA1c in DM are depicted in tables 1-3.

Table 1. Association of EZSCAN with fasting blood glucose

<table>
<thead>
<tr>
<th>EZ-Scan Results</th>
<th>Diabetes status based on FBG</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>D (Diabetes)</td>
</tr>
<tr>
<td>D</td>
<td></td>
</tr>
<tr>
<td>34</td>
<td>87.2%</td>
</tr>
<tr>
<td>8</td>
<td>15.7%</td>
</tr>
<tr>
<td>PD</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>12.8%</td>
</tr>
<tr>
<td>14</td>
<td>40.0%</td>
</tr>
<tr>
<td>ND</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>0%</td>
</tr>
<tr>
<td>14</td>
<td>40.0%</td>
</tr>
</tbody>
</table>

Sensitivity | 87.2 | 80.4 | 51.4 |
Specificity | 87.2 | 74.3 | 97.8 |
PPV | 75.6 | 68.3 | 90.0 |
NPV | 93.8 | 84.6 | 83.8 |

D (Diabetes), PD (Pre-diabetes), ND (Non-diabetes)

Table 2. Association between EZSCAN and PPBG

<table>
<thead>
<tr>
<th>EZ-Scan Results</th>
<th>Diabetes status based on PPBG</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>D (Diabetes)</td>
</tr>
<tr>
<td>D</td>
<td></td>
</tr>
<tr>
<td>32</td>
<td>86.5%</td>
</tr>
<tr>
<td>2</td>
<td>5.6%</td>
</tr>
<tr>
<td>PD</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>13.5%</td>
</tr>
<tr>
<td>15</td>
<td>41.7%</td>
</tr>
<tr>
<td>ND</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>0%</td>
</tr>
<tr>
<td>19</td>
<td>52.8%</td>
</tr>
</tbody>
</table>

Sensitivity | 86.5 | 76.9 | 52.8 |
Specificity | 85.2 | 72.6 | 98.9 |
PPV | 71.1 | 66.7 | 95.0 |
NPV | 93.0 | 81.5 | 83.8 |

PD (Pre-diabetes), D (Diabetes), ND (Non-diabetes)

Table 3. Association between EZSCAN and HbA1c

<table>
<thead>
<tr>
<th>EZ-Scan Results</th>
<th>Diabetes status based on HbA1c</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>D (Diabetes)</td>
</tr>
<tr>
<td>D</td>
<td></td>
</tr>
<tr>
<td>37</td>
<td>86.0%</td>
</tr>
<tr>
<td>3</td>
<td>7.3%</td>
</tr>
<tr>
<td>PD</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>11.6%</td>
</tr>
<tr>
<td>19</td>
<td>46.3%</td>
</tr>
<tr>
<td>ND</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>2.3%</td>
</tr>
<tr>
<td>19</td>
<td>46.3%</td>
</tr>
</tbody>
</table>

Sensitivity | 86.0 | 87.8 | 46.3 |
Specificity | 90.2 | 71.4 | 98.8 |
PPV | 82.2 | 60.0 | 95.0 |
NPV | 92.5 | 92.3 | 79.0 |

PD (Pre-diabetes), D (Diabetes), ND (Non-diabetes)
In this study EZSCAN best co-related with HbA1c. The sensitivity and specificity for diabetes were 86 and 90.2 percent respectively and sensitivity and specificity for pre-diabetes were 87.8 and 71.4 percent respectively.

Discussion

This study demonstrates that EZSCAN, as a screening tool, had an acceptable accuracy for the diagnosis of pre-diabetes and DM.

To the best of our knowledge, only 5 published studies have investigated the accuracy of EZSCAN for the diagnosis of impaired glucose metabolism. In 212 subjects recruited in India by Ramachandran et al (11), the sensitivity of EZSCAN was 75% to detect DM, 70% for IGT and 84% for normal glucose tolerance with Metabolic syndrome (NGT with MetS) at a threshold of 50%. In our study when EZSCAN was compared with FBG, the sensitivity for detection of DM was 87.2% and specificity 87.2%. The sensitivity for detection of pre-diabetes was 80.4 percent and specificity 70.4%.

In the Chinese study done by Sheng et al (12) where the EZSCAN diabetes index of 40 was used as the threshold for the diagnosis of DM in all subjects, the sensitivity and specificity were 85 and 64 percent respectively. In our study when EZSCAN was compared with FBG, PPBG and HbA1c for detection of diabetes it showed sensitivities and specificities of 87.2 and 87.2%, 86.5 and 85.2% and 86.0 and 90.2% respectively.

Chen et al evaluated the performance of EZSCAN as a screening tool for impaired glucose metabolism (IGM), including impaired glucose tolerance, impaired fasting glucose and undiagnosed diabetes in a Chinese population (13). Their cut-off point of EZSCAN for IGM detection was 40% with a sensitivity of 80% and a specificity of 72%. In our study we used cut-off points as 25-49% for pre-diabetes. For detection for pre-diabetes, EZSCAN showed sensitivity and specificity of 80.4 and 74.3 percent when compared with FBS, 76.9 and 72.6 percent when compared with PPBG and 87.8 and 71.4 percent when compared with HbA1c.

Yang et al (14) using an EZSCAN value higher than 30% as cut-off point, provided reasonable sensitivities (70.3-83.7%) to detect dysglycaemia not only in the total population regardless of sex but also in individuals with high risk of developing diabetes. In our study subjects with an EZSCAN score more than 25% who were considered as pre-diabetes, should be further advised for lifestyle modification for prevention of DM and related complications.

Peter eh schwaz (15) used a cut-off value of 50% on its scale had 75% sensitivity to detect diabetes, 70% for IGT and 84% for NGT with metabolic syndrome. In our study EZSCAN score more than 25-49% considered as pre-diabetes and ≥50 considered as DM.

Taking the results of the previous studies and this research together, EZSCAN seemed to have consistent and constant sensitivity but divergent and variable specificity across populations.

The heterogeneous specificity might be attributable to the differences in characteristics of participants between these studies. In our study sensitivity for non-diabetes were low because of early detection of pre-diabetes in comparison to standard screening methods. In early stages of disease blood glucose level does not correctly reflect disease burden because of initial hyperinsulinemic phase to overcome excess glucose in blood and maintain the normal blood glucose level.

Nonetheless, our study had a small sample size and a cross-sectional design. A larger prospective study may be required.

Limitations of the study

EZSCAN may give false positive results for elderly age groups – age may be considered as a confounding factor.

Implications

The EZSCAN technique proved to be a sensitive, specific, easy to perform screening test for diabetes and pre-diabetes which can be performed in non fasting state.

EZSCAN seems to be a simple device that can be operated by non medical personnel in non-healthcare settings with minimal subject preparation.

Keeping the rising trend of diabetes and pre-diabetes in mind, EZSCAN can be used for mass screening of the population on a large scale.

Future research

To develop a study which will facilitate further longitudinal follow up of patients diagnosed as pre-diabetics by EZSCAN with standard screening method and OGTT.

Regional/ ethnic cut off value for detection of pre diabetes and diabetes by EZSCAN.

References


3. DECODE Study Group EDEG. Is the current definition for diabetes relevant to mortality risk from all causes and cardiovascular and noncardiovascular diseases *Diabetes Care* 2003; 26(3): 688-96.


Premature ejaculation and its management

L S Malavige1,2, S Jayawickrema3


Introduction

Premature Ejaculation (PE) is a condition in which a man ejaculates earlier than he or his partner would like him to, causing distress to either or both partners. It is also known as rapid ejaculation, or premature climax.

PE is the most common type of male sexual dysfunction, affecting 14-30% of males aged 18 years and over (1,2). According to recently published Oxford Sexual Dysfunction Study, men of South Asian origin living in the UK have shown to have a higher prevalence of PE compared to Caucasians (3). PE has shown to be associated with negative personal consequences such as distress, bother, frustration and the avoidance of sexual intimacy. Both affected men and their partners report interpersonal difficulties and an overall reduction in their quality of life. Despite significant distress, many suffer in silence; only a minority seeks professional help, owing to the sensitiveness of the issue, and lack of attention paid by the clinicians towards sexual issues.

Definition and classification of PE

There is no universally accepted definition for PE. According to the most accepted definition given by International Society for Sexual Medicine (ISSM) three criteria have to be met to diagnose PE. Those are (i) a short ejaculatory latency – the time from penetration to ejaculation; Intra vaginal Ejaculatory Latency Time (IELT) should be less than one minute, however, IELT between one to two minutes can be considered short if it causes significant distress either to the man or his partner. (ii) a lack of perceived self-efficacy or control about the timing of ejaculation; and (iii) distress and interpersonal difficulty related to the ejaculatory dysfunction.

Over the years, diverse PE classifications have been introduced. It could be broadly classified as lifelong PE (primary) or acquired (secondary) PE (4). Men with lifelong PE experience rapid ejaculation in all sexual encounters including masturbation, and with all partners, which begins when a man first becomes sexually active. Men with acquired PE develop the problem later in life after having a normal ejaculatory latency time previously. Anteportal ejaculation (ejaculation happening before vaginal penetration) is considered the most severe form of PE. Between 5% to 20% of lifelong PE men suffer from anteportal PE (5), such men/couples typically present when they are having difficulty conceiving.

In addition, ‘Natural Variable PE’ is a condition in which ejaculation happens too rapidly only in certain sexual situations or acts. This may represent a variation of natural ejaculatory function with some subjective sense of diminished control of ejaculation. ‘Premature like Ejaculatory Dysfunction’ is a condition where a man is distressed about the ejaculatory latency time, despite normal IELT exceeding two minutes (6). In multinational studies, average time from penetration to ejaculation is 5 to 6 minutes with a median IELT of 5.4 minutes (range, 0.55–44.1 minutes) (7).

In clinical practice, self estimation of the ejaculatory time by the patient and the partner is recommended for the assessment of IELT, which is also used to monitor the success of PE treatment. Use of stopwatch to determine the IELT is used in clinical trials. In addition, several questionnaires are available for aiding the diagnosis of PE and monitoring treatment change or outcome measures. Despite the presence of the diagnostic tools a diagnosis of PE should only be made following a full sexual history taken by a clinician.

Etiology of PE

It was previously thought that this condition is primarily due to psychological factors. Over the last two decades many biological factors for PE have been described. In certain cases, PE is more complicated and involves a complex interaction of both psychological and biological factors. Genetic predisposition plays a role in most men with lifelong PE (8).

Psychological causes

There are diverse psychological factors that either predispose or augment PE. Certain personality traits are more vulnerable to PE. Anxiety regarding sexual function is a common precipitating factor. In some, early sexual experiences which may have established a particular pattern that becomes difficult to change later in life could predispose to PE. Examples of such situations are hurry-
A number of biological factors may contribute to PE, including, abnormal testosterone or prolactin levels (10), disturbances in central serotonergic neurotransmission (11), abnormal reflex activity of the ejaculatory system, penile hypersensitivity (12), hyper- arousability, a higher cortical representation of the pudendal nerve, erectile difficulties (13), prostatitis/ chronic pelvic pain syndrome (14), detoxification from prescribed drugs e.g. raboxetine, trifluoperazine or recreational drugs (narcotics) (15), chronic pelvic pain syndrome (16), thyroid disorders (17) and genetic factors.

A high prevalence of lifelong PE among first degree relatives has been shown in a study among Dutch men with lifelong PE (18). Genetic study to demonstrate the genetic predisposition was performed by Janssen et al which demonstrated an association of the 5-HTLPR gene polymorphism and the IELT (19).

PE is common in mild to moderate erectile dysfunction (3). This could be due to men who are anxious about obtaining or maintaining their erection during sexual intercourse forming a pattern of rushing to ejaculate before losing erection. Therefore men who have PE secondary to erectile problems, need careful evaluation in order to identify the cause for their erectile dysfunction. In such men, treating erectile problem will often improve ejaculatory time.

Clinical assessment
As PE is a clinical diagnosis, a full clinical history and a focused physical examination play an important role in its diagnosis. Nevertheless, as the patients may be embarrassed and shy when relating details of their sexual experiences, clinical assessment can be challenging. As it is more an issue of a couple, it is useful to involve the partner in the consultation. In diagnosis, the three main components of PE should be addressed; ie. timing, control and distress associated with the condition.

The stopwatch assessment of ejaculatory time is not recommended in routine clinical management due to potential disruption of sexual pleasure. It is usually used in clinical trials and observational studies. ISSM recommends to use self-estimation by the man or his partner as the accepted method of determining IELT in clinical practice (20).

There are 3 recommended questionnaires used to diagnose and evaluate PE. Premature Ejaculation Diagnostic Tool (PEDT) is developed specifically to be used as a screening questionnaire based on DSMIV-TR criteria, whereas the Premature Ejaculation Profile (PEP) and Index of Premature Ejaculation (IPE) are used to measure the treatment outcome (21).

Establishing PE diagnosis, diagnostic subtype and its impact on the relationship with the partner and the quality of life is important in perceiving the scope of the problem and to determine management plan. In clinical practice this is established with detailed sexual history. Symonds T et al has developed questions as a guide to establish the diagnosis and impact of PE (22) (Table 1).

For lifelong PE, a physical examination is advisable but not compulsory. In cases of acquired PE, a targeted physical examination is mandatory to find out associated problems, such as risk factors for ED, thyroid dysfunction, and prostatitis. Apart from the general examination a focused examination of the genitalia, digital rectal examination for the prostate is recommended to exclude prostatitis. Laboratory and other physiological tests are rarely indicated. History and examination are often sufficient to reach a diagnosis.

Treatment
All men need careful evaluation before treatment in order to achieve better outcome. Treatment options for premature ejaculation include psychosexual counselling, behavior therapy and medications; guided by the type of PE (lifelong/acquired), bio-psycho-social assessment and patient preference. For many men, a combination of these treatments work best. Nonetheless, according to ISSM Standard Operating Procedures all men seeking treatment for PE should receive basic psychosexual counselling. Inclusion of the partner in the treatment process is important for treatment success though it is not mandatory. The management algorithm of PE is given in figure 1.
Psychotherapy and behavioral therapy

Psychotherapy includes both psychosexual counselling and relationship or marital counseling. This usually involves both the male patient and the partner. Psychosexual counselling includes improving awareness on the prevalence of PE and the average IELT of the general population, and expanding the diversity of sexual activities of the couple thus preventing the avoidance of sexual activities. Psychosexual counselling also include increasing man’s confidence in sexual performance, and his overall self-confidence, lowering performance anxiety; increasing communication with his partner, and unravelling issues between the couple which may have precipitated PE. Men with Premature-Like Ejaculatory Dysfunction require psychotherapy whereas men with Natural Variable PE should be provided necessary information and reassured.

Behavioural therapy

The ‘stop-start’ technique and the ‘squeeze’ technique has been used since 1950s but with no conclusive long-term results (23). These two techniques are designed to make the man aware when he approaches ejaculatory inevitability which involves stopping of the stimulation and resumption once the arousal subsides. In addition learning to relax the body and certain sexual positions such as women on top position or lateral position can be helpful in controlling ejaculation. Pre-coitus masturbation is used by younger men suffering from PE, as a method of partial desensitization of the penis but this is not an acceptable method for many (24).

However, if partners are not involved in treatment, they may be resistant to changing the sexual interaction. A cooperative partner can enhance the man’s self-confidence, sexual techniques, self-esteem, and sense of masculinity and assist the man to develop ejaculatory control. These measures will improve PE, as well as sexual relationship and the broader aspects of their relationship.

Pharmacological therapy

In the current context, pharmacological management of PE is through drug groups including antidepressants, local anaesthetic agents and phosphodiesterase type 5 inhibitors. Yet at present only Dapoxetine is licensed for the treatment of PE. While some drugs are administered

<table>
<thead>
<tr>
<th>Table 1. Useful questions in clinical assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Recommended questions for diagnosis</strong></td>
</tr>
<tr>
<td>• What is the time between penetration and ejaculation (coming)?</td>
</tr>
<tr>
<td>• Can you delay ejaculation?</td>
</tr>
<tr>
<td>• Do you feel bothered, annoyed and/or frustrated by your premature ejaculation?</td>
</tr>
<tr>
<td><strong>Optional questions – Differentiate lifelong and acquired PE</strong></td>
</tr>
<tr>
<td>• When did you first experience premature ejaculation?</td>
</tr>
<tr>
<td>• Have you experienced premature ejaculation since your first sexual experience on every/almost every attempt and with every partner?</td>
</tr>
<tr>
<td><strong>Optional questions – Assess erectile function</strong></td>
</tr>
<tr>
<td>• Is your erection hard enough to penetrate?</td>
</tr>
<tr>
<td>• Do you have difficulty in maintaining your erection until you ejaculate during intercourse?</td>
</tr>
<tr>
<td>• Do you ever rush intercourse to prevent loss of your erection?</td>
</tr>
<tr>
<td><strong>Optional questions – Assess relationship impact</strong></td>
</tr>
<tr>
<td>• How upset is your partner with your premature ejaculation?</td>
</tr>
<tr>
<td>• Does your partner avoid sexual intercourse?</td>
</tr>
<tr>
<td>• Is your premature ejaculation affecting your overall relationship?</td>
</tr>
<tr>
<td><strong>Previous treatment</strong></td>
</tr>
<tr>
<td>• Have you received any treatment for you premature ejaculation previously?</td>
</tr>
<tr>
<td><strong>Impact on quality of life</strong></td>
</tr>
<tr>
<td>• Do you avoid sexual intercourse because of embarrassment?</td>
</tr>
<tr>
<td>• Do you feel anxious, depressed or embarrassed because of your premature ejaculation?</td>
</tr>
</tbody>
</table>
on demand others are administered daily. An on demand drug offers the advantage of less side effects of the drug whereas the daily dosage allows spontaneous sex but more pronounced side effects of the drug.

Desensitizing agents
The most conventional type of pharmacological therapy is desensitizing or local anaesthetic agents.
Desensitizing or local anaesthetic agents used to delay ejaculation include lidocaine, prilocaine and benzocaine which come in different forms such as creams and sprays (25). However as the application of a cream is cumbersome due to the requirement of a condom to minimize its anaesthetizing effects on the vagina, aerosol sprays have become more popular. The sprays are odourless, adherent solutions that act within 5 minutes by penetrating the glans, without penetrating intact keratinized skin, making them more user friendly. Hypoanesthesia of the penile shaft is a common side effect which in some men can affect erection. Local irritation is rare.

**Oral drug therapy**

Monoamine oxidase (MAO) inhibitors and alpha-blockers were the first oral medication used for the treatment of PE, which are not used for PE treatment anymore. However, selective alpha-blockers like Terazosin have shown to be effective in treating PE in patients with concurrent lower urinary tract symptoms (26). More recently, drugs acting on central serotonergic neurons by blocking the axonal reuptake of serotonin from synaptic clefts and thereby enhancing the neurotransmission (including Selective Serotonin Reuptake Inhibitors and Tricyclic Antidepressants) have transformed pharmacological therapy.

**Antidepressants**

Clomipramine is a Tricyclic Antidepressant (TCA) that increases the IELT in patients with PE both through continuous and on-demand dosing (27). Main side effects of clomipramine include fatigue, dizziness, dry mouth and hypotension.

Selective Serotonin Reuptake Inhibitors (SSRIs) such as escitalopram, fluoxetine, fluvoxamine, sertraline and paroxetine are serotonergic agents that work by activation of the 5-HT2C receptor (28). With the use of SSRIs the IELT is increased between twofold and eightfold (29). Paroxetine produced the best ejaculatory delay, increasing IELT by 8.8 fold from the baseline (29).

In daily dosage, paroxetine 10-40 mg, clomipramine 12.5-50 mg, sertraline 50-200 mg, fluoxetine 20-40 mg or citalopram 20-40 mg is effective in expanding the IELT(30-33). Although the full therapeutic effect takes 2-3 weeks to ensue, usually the ejaculatory delay occurs within few days of commencing treatment. On demand administration of clomipramine, paroxetine, sertraline, and fluoxetine 4-6 hours before intercourse is moderately efficacious and better tolerated, but results in considerably less ejaculatory delay than daily dosing (34). On-demand dosing can be combined with either an initial trial of daily treatment or concomitant low dose daily treatment.

Adverse effects with SSRIs are nausea, fatigue, yawning, perspiration and loose stools which usually resolve in 2-3 weeks. SSRIs should be avoided in patients with a history of bipolar depression (35). It is essential to perform follow-up assessments to evaluate the efficacy of the drug as well as for the potential side effects, especially regarding associated sexual dysfunction and suicide risks. Furthermore, due to the risk of SSRI withdrawal syndrome, patients should be advised to avoid abrupt cessation or dose reduction without medical advice (36). Treatment with SSRIs had shown a lower incidence of side effects than clomipramine (37).

Out of all the available medication, Dapoxetine, a rapid acting and short half-life, potent SSRI is the only licensed drug for the treatment of PE and is used as an on-demand drug. Dapoxetine is structurally similar to fluoxetine and has a $T_{max}$ of 1.4-2.0 hours and a terminal half life of 19 hours. It is taken only when needed, 1–3 hours before sexual intercourse is anticipated (38). It is extensively metabolized in the liver and eliminated in urine. Therefore it is contraindicated to be administered with potent CYP3A4 inhibitors such as ketoconazole and have to be cautious in co administration with moderate CYP3A4 inhibitors and potent CYP2D6 inhibitors such as fluoxetine. Dapoxetine has a relatively mild side effect profile including nausea, diarrhea, headache and dizziness whilst proven to be effective for the treatment of PE. It has shown to increase the IELT by 3 folds and effective on both men with lifelong and acquired PE (39). At the time of writing Dapoxetine is not registered in Sri Lanka.

**PDE5 inhibitors**

Sildenafil, vardenafil, tadalafil are PDE5 inhibitors used in the management of PE when it is associated with erectile dysfunction. Since a third of men with ED also suffer from PE, the association between PE and ED may be explained by the fact that when a man suffers from ED, he makes an effort to achieve ejaculation before he loses the erection, leading to PE (40). PDE5 inhibitors are ineffective in men with normal erectile function.

**Tramadol**

Tramadol, a centrally acting opiate is used to treat PE though the exact mechanism of action is not known. It’s efficacy has been proved in studies with a 2.9 fold increase in IELT specifically as an on-demand medication (41). However due to the limited data availability on its safety, and the potential for addiction, the use of tramadol in PE treatment is limited to specialists.

The newest addition to the management of PE is the delay device of which the efficacy was shown in a small clinical trial involving 52 patients. There is no evidence to support use, intra-cavernosral injections, selective dorsal nerve neurotomy or hyaluronic acid gel glans penis augmentation in management of PE.
Conclusion

Knowledge on physiology and management of PE has changed drastically over last two decades. Despite the lack of controlled clinical trials, a wide range of psychological and behavioural interventions have been developed for the treatment of PE. In men with acquired PE, identifying and correcting underlying causes such as erectile dysfunction, hyperthyroidism, prostatitis, psychological and relationship issues are important. Premature-Like Ejaculatory Dysfunction and Natural variable PE often needs only behavioural therapy and psychosexual counselling. For life long and acquired PE pharmacotherapy is often indicated. In addition to increasing IELT, psychosexual and behavioural therapies help improve the relationship, self confidence and sexual confidence.

The pharmacotherapy can be classified as daily dosing and on demand dosing. The use of SSRIs have revolutionised the management of PE. There is level 1a evidence to support the efficacy and safety of on-demand dosing of dapoxetine for the treatment of lifelong and acquired PE. Off-label daily dosing of the SSRIs paroxetine, sertraline, citalopram, fluoxetine, and the serotonergic tricyclic, clomipramine has also shown level 1a evidence. There is level 1a evidence for off-label on-demand dosing of clomipramine, paroxetine, and sertraline in the management of PE. The use of topical local anaesthetics such as lidocaine and/or prilocaine as a cream, gel, or spray is well established and is moderately effective in delaying ejaculation (level 1b). PDE5 inhibitors are indicated in the treatment of premature ejaculation only when there is co-existing erectile dysfunction.

References


Pitfalls in interpreting thyroid function tests: antibodies causing assay interferences

S Pathmanathan¹, N P Somasundaram¹, S Siriwardena²


Abstract

Many factors can compromise results of thyroid function tests, leading to possible misinterpretation and misdiagnosis. Presence of antibodies in the human serum can react with the immunoglobulins included in the assay components and cause anomalous results. We describe below three cases where spurious hormone results were obtained due to interfering antibodies.

Introduction

Thyroid dysfunction has diverse clinical presentations, where the majority of thyroid disease symptoms are often subtle and nonspecific. Therefore requests for investigation of assessing thyroid function are often made even in the absence of supporting clinical evidence. Unlike in the West, where thyroid function tests (TFT) are performed as routine tests in an asymptomatic patient, these tests are not widely performed in our setup unless there are certain indications. When the clinical suspicion is strong, TFT are helpful in confirming the diagnosis. However in situations where the managing physicians receive ‘abnormal’ test results discordant with the clinical findings, these results may be misinterpreted resulting in an erroneous diagnosis leading to inappropriate management being instituted. Thus clinicians should be vigilant while interpreting abnormal and unusual TFT. We present three brief case histories to emphasize the importance of clinicians having a vigilant mind in interpreting these unusual TFT (1-4).

Case 1 – a lady with primary hypothyroidism (heterophile antibodies causing assay interferences)

A 52-year-old woman was referred from Ear Nose Throat (ENT) unit for abnormal thyroid functions. She had symptoms and signs suggestive of hypothyroidism. She had a low FT₄ along with a low TSH which was reconfirmed by repeated testing; 3rd generation TSH was 0.08 (normal 0.5 - 4.0 mIU/L), and the FT₄ 0.3 ng/dL (normal 0.8 - 1.8 ng/dL). As she had had early menopause at 40 years, secondary hypothyroidism was suspected and she underwent detailed anterior pituitary function tests which were all within normal limits. (FSH and LH were in the menopausal range, 9 AM cortisol was 325 nmol/L and cortisol value 30 minutes after 250 mcg of synacthen (synthetic ACTH) was normal with a 30-minute value of 1011 nmol/L). When such a clinically discrepant result was observed in this patient, we suspected the possibility of heterophile antibodies causing assay interferences and decided to retest with a different immunoassay method (she was initially tested by chemiluminescence method). Re-analysis by manual immunoradiometric assay (IRMA) gave an elevated TSH of >50 μIU/mL and further polyethylene glycol (PEG) precipitation by 1:1 dilution studies were carried out which yielded a TSH result of 91.8 μIU/mL. She was diagnosed as having primary hypothyroidism with heterophile antibodies causing TSH assay interference. She was started on L-thyroxine replacement, which promptly resolved her symptoms. It was decided to follow her with free T4 to look for adequacy of thyroxine replacement and if TSH has to be repeated, to do her blood tests using assays that shows no interference to avoid confusion.

Case 2 – euthyroid hyperthyroxinaemia due to assay interference

A 33-year-old lady on antipsychotic medications (Olanzapine 5mg nocte and Benzhexol 2 mg mane) was noticed to have a weight loss of 2 kg which prompted the managing clinician to request for a TFT. She was shown to have elevated FT₄ and normal TSH which was reconfirmed on two occasions (FT₄ -2.09 ng/dL (0.89-1.76), 3rd generation TSH - 1.07 μIU/mL). These tests were done by chemiluminescence method. She was otherwise well and did not have any other symptoms of hyperthyroidism or family history of thyroid disorders. At the time of

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presentation her psychiatric condition was stable and clinically the patient was euthyroid with no goiter and normal in all respects.

A possibility of assay interference was considered to be the most likely explanation for the elevated free thyroxine level. Thyroid hormone resistance and TSH-producing tumour seemed less likely in our patient. Blood samples were retested by IRMA which reconfirmed persistently high FT₃ with normal TSH. Therefore we decided to measure total T₃ which was well within the normal adult range (5.17 μg/dL (normal 4.5-12)). An antibody interfering with the free hormone assay was thought to be the most likely cause as she did not have any other conditions that could explain a raised free thyroxine level. The patient was reassured and it was recommended to her that in the future she should have her thyroid function tests done using the total hormones to avoid confusion and unnecessary investigations and treatment.

Case 3 – elevated free T₃ due to assay interference

A 33-year-old overweight lady was referred from a medical unit for abnormal thyroid function tests. She has been screened for secondary causes for her overweight state. During examination she was noticed to have a thyroid lump which prompted the managing clinician to request for TFT, which revealed elevated FT₃, normal FT₄ and TSH (FT₃ 4.23 pg/ml (1.5 - 4.1), FT₄ 1.1 ng/dL (0.89 - 1.76), 3rd gen TSH - 1.74 μIU/ml). (These tests were done by chemiluminescence enzyme immunoassay method). She denied any other symptoms of hyperthyroidism or family history of thyroid disorders. At the time of presentation her psychiatric condition was stable and clinically the patient was euthyroid with no goiter (which was confirmed on USS) and normal in all respects.

In view of the clinical findings, a possibility of assay interference was considered to be the most likely explanation for the lack of clinical correlation with the blood results. Therefore we decided to measure total T₃ which was well within the normal adult range (1.18 ng/ml (0.58-1.59). (These tests were done by chemiluminescence micro particle immunoassay method) The patient was reassured but continued follow-up for management of her overweight state.

Discussion

The presence of circulating, endogenous antibodies directed against a number of antigens may cause either falsely depressed or falsely increased values in TFT. The outcome mainly depends on the nature of the interfering antibody or the assay design. The major importance of appreciating antibody interference as a confounding factor in the interpretation of TFT is that it can prevent inappropriate investigations and treatment, and unnecessary stress to the patient (3, 5).

The three major possible sources of antibody interference in thyroid hormone immunoassays are autoantibodies, heterophile antibodies, and rheumatoid factors (RF). Autoantibodies cause analyte-specific interference while heterophile antibodies and rheumatoid factors are responsible for method-specific disturbances. Autoantibodies include antibodies to thyroglobulin, microsomal thyroid peroxidase and TSH receptor, as well as antibodies reacting with T₄ and T₃. Many different approaches may be utilized to overcome the interference, e.g. PEG precipitation (3, 5).

Heterophile antibodies are antibodies against specific animal immunoglobulins which could cross react with the antibodies used in the assay. The effect of heterophile antibodies on laboratory results depend on the nature and concentration of the interfering antibody and on the immunoassay method used. These antibodies when present can promote binding between the capture antibody and the signal antibody, even in the absence of the analyte. This type of nonspecific binding results in abnormally high values. However heterophile antibody can also bind only to the capture antibody and can affect the conformation of the variable region, even without binding directly to the recognition site of the analyte, thereby causing abnormally low values (3,5,6,7).

When interpreting TFT, it is important to consider antibody interference in a patient with discrepant results. Routine communication between the chemical pathologist and the clinician is essential to arrive at the correct diagnosis. The laboratory should then be requested to repeat the suspect sample to confirm whether the presence of the interfering antibodies were responsible for the spurious result. Samples are typically re-evaluated using an alternative method and the removal of the interfering antibody (e.g. by PEG), or by using antibody-blocking reagents. Results on reanalysis that are different after the removal of interfering antibodies are indicative of antibody interference and usually will correlate well with the clinical picture (8-11).

Conclusion

TFT should not be interpreted in isolation. A good rule of thumb is that the tests should be concordant with the clinical picture and between themselves – demonstrating feedback loops. If the clinical picture and biochemistry are discordant, various possibilities including assay interferences should be considered. If the TSH and thyroxine hormone tests are discordant i.e. feedback loop appear to have been broken, then common as well as rare
illnesses (patient non compliance, TSHoma, Thyroid Hormone Resistance Syndrome) as well as antibody interference should be considered. Communication between the requesting clinician and the chemical pathologist is therefore key for correct interpretation and management of these patients.

References

Introduction
Gynecomastia refers to benign enlargement of the male breast caused by proliferation of glandular breast tissue due to an imbalance between the inhibitory effect of androgen and stimulatory effect of estrogen. Gynecomastia can be physiological during neonatal period, puberty or old age. Various drugs, systemic disorders, benign or malignant tumours and hypogonadism can also lead to gynecomastia, while about 25% of cases are idiopathic. Gynecomastia should be differentiated from pseudogynecomastia (adipomastia), which is characterized by excessive accumulation of adipose tissue without glandular proliferation. A detailed history and examination helps to exclude differential diagnosis, identify the underlying etiology and to assess the severity of the disease and the concerns of the patient. The management of gynecomastia depends on the underlying etiology and the concerns of the patient. This may include interventions for relief of pain or discomfort, restoration of normal appearance and reassurance regarding cancer. Treatment options include watchful waiting, pharmacotherapy and surgery.

Pathophysiology of gynecomastia
In both males and females, estrogen causes enlargement of the breast by inducing proliferation and differentiation of ductal and periductal tissues. However in males acinar development usually does not occur due to lack of progesterone (3).

Gynecomastia is caused by an imbalance between the stimulatory effect of free estrogen on growth and differentiation of breast tissue and inhibitory effect of free androgen. An increased estrogen-to-androgen ratio due to absolute increase in estrogen production, relative decrease in androgen production or a combination of both can give rise to gynecomastia (1).

The extent of glandular proliferation depends on the intensity and the duration of stimulation. The early stages (first six months after onset) of gynecomastia are characterized by hyperplasia of ductal and peri ductal tissues with increased stromal fibroelastic proliferation and periductal inflammation leading to pain or tenderness in the breast. The later stages (after a year) are characterized by marked stromal fibrosis without an inflammatory response, thereby causing painless gynaecomastia (4).

Etiology and differential diagnosis of gynecomastia
Gynecomastia can be physiological or pathological. Physiological gynecomastia shows a trimodal age distribution with first, second and third peaks occurring during infancy, puberty and old age respectively (5). Neonatal gynecomastia occurs in about 60-90% of boys due to exposure to high concentration of maternal estrogens in utero. It is transient and resolves within a few weeks after birth (1).

Pubertal gynecomastia usually begins at ages of 10-12 years and peaks at ages of 13-14 years. Breast enlargement of more than 0.5 cm in diameter occurs in about 60-70% of boys by the age of 14 years. It is attributed to a transient more rapid rise of serum estrogen relative to testosterone during early puberty. It usually regresses within 1-2 years with pubertal progression and rise in testosterone levels. Senile gynecomastia occurs in 24-65% of men at 50 to 80 years of age and is thought to be due to increased adiposity with aging (1). Androgens are converted into
estrogens in adipose tissue by aromatase and age-related increase in aromatase activity result in higher estrogen production rates in older men.

Pathological gynecomastia may result from the excessive estrogen, deficient androgens or androgen resistance (Table 1). Various drugs (Table 2), systemic disorders, benign or malignant tumors and hypogonadism leads to gynecomastia. About 25% of cases are idiopathic. Environmental contamination with xenoestrogens or estrogen-like substances and abuse of anabolic steroids are increasingly recognized causes.

Gynecomastia should be differentiated from pseudogynecomastia (adipomastia) which is characterized by excessive accumulation of adipose tissue without glandular proliferation. Presence of any atypical features like unilateral enlargement, skin changes, hard consistency and nipple discharge should trigger evaluation for breast cancer.

**Clinical evaluation**

A detailed history and examination helps to exclude differential diagnosis, identify the underlying etiology and to assess the severity of the disease and the concerns of the patient.

History should include the onset and duration of breast enlargement, nipple discharge, retraction, symptoms of pain or tenderness, weight loss or gain, medication history, the presence of systemic illness, fertility, sexual function. Family history of gynecomastia may suggest androgen insensitivity syndrome or familial aromatase excess (8).

### Table 1. Causes of gynecomastia (6)

<table>
<thead>
<tr>
<th>Physiologic causes</th>
<th>Neonatal, pubertal, involutional (senile)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systemic disorders</td>
<td>Organ failure: Hepatic cirrhosis, chronic kidney disease</td>
</tr>
<tr>
<td>Endocrine disorders</td>
<td>Hyperthyroidism, Cushing syndrome, acromegaly</td>
</tr>
<tr>
<td>Estrogen excess</td>
<td>Estrogens or estrogen receptor agonists: Marijuana, smoke, digoxine, testosterone</td>
</tr>
<tr>
<td></td>
<td>Increased peripheral aromatase activity: Obesity, aging, familial</td>
</tr>
<tr>
<td></td>
<td>Estrogen secreting tumors: Leydig/Sertoli cell tumor, adrenal carcinoma</td>
</tr>
<tr>
<td></td>
<td>hCG secreting tumors: Germ cell, lung, hepatic carcinoma</td>
</tr>
<tr>
<td>Androgen deficiency or resistance</td>
<td>Androgen deficiency: Primary or secondary hypogonadism, hyperprolactinaemia</td>
</tr>
<tr>
<td></td>
<td>Androgen resistance: Congenital or acquired androgen resistance, drugs eg. spironolactone</td>
</tr>
<tr>
<td>Idiopathic causes</td>
<td></td>
</tr>
</tbody>
</table>

### Table 2. Drugs associated with gynecomastia (7)

<table>
<thead>
<tr>
<th>Hormones&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Androgens, anabolic steroids, estrogens, estrogen agonists and hCG&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antiandrogens/inhibitors of androgen synthesis</td>
<td>Flutamide, nilutamide, cyproterone, GnRH&lt;sup&gt;a&lt;/sup&gt; agonists</td>
</tr>
<tr>
<td>Antibiotics</td>
<td>Ketoconazole&lt;sup&gt;b&lt;/sup&gt;, metronidazole, isoniazid</td>
</tr>
<tr>
<td>Antiulcer medications</td>
<td>Omeprazole, ranitidine, cimetidine&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Chemotherapeutic agents</td>
<td>Methotrexate, alkylating agents</td>
</tr>
<tr>
<td>Cardiovascular drugs</td>
<td>Digoxin&lt;sup&gt;a&lt;/sup&gt;, ACEI&lt;sup&gt;a&lt;/sup&gt;, CCB&lt;sup&gt;b&lt;/sup&gt;, amiodaronespironolactone, methyldopa</td>
</tr>
<tr>
<td>Psychoactive drugs</td>
<td>Tricyclic antidepressants, haloperidol and atypical anti psychotic agents, diazepam</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>Metoclopramide, phenytoin, theophylline, anti retroviral therapy</td>
</tr>
</tbody>
</table>

<sup>a</sup> ACEI - angiotensin converting enzyme inhibitor; CCB - calcium channel blocker; GnRH - gonadotropin releasing hormone; hCG - human chorionic gonadotropin

<sup>b</sup> Denotes stronger association
Figure 1. Differentiation of gynecomastia from pseudogynecomastia (7)

Figure 2. Diagnostic algorithm for gynecomastia (11)
Gynecomastia is identified clinically as a generalized enlargement of male breast with palpable glandular tissue. The later is firm or rubbery and contains fibrous-like cords. The breast should be examined when the patient lies on his back with his hands behind his head. The examiner should place her/his thumb and forefinger on each side of the breast and slowly bring them together (Figure 1). In true cases of gynecomastia, the examiner will feel a rubbery to firm disc of tissue that is concentric with the nipple-areolar complex and freely mobile. In contrast, in pseudogynecomastia the fingers will not meet any resistance until they reach the nipple (9).

Biochemical evaluation

Biochemical evaluation should be considered in the cases of true gynecomastia without clear explanation. Patients with physiologic gynecomastia do not require further evaluation. Patients with breast enlargement that is large (glandular tissue > 5 cm in obese men, > 2 cm in lean men), recent and rapid in onset, progressive, symptomatic or suspicious for malignancy need further investigations (6). Common medical conditions like renal, liver and thyroid disease should be excluded by appropriate investigations. Hormonal evaluation including measurement of levels of total testosterone, Luteinizing Hormone (LH), estradiol, prolactin and hCG may reveal an underlying pituitary, gonadal, and extragonadal pathologies including neoplasms. Measurement of bioavailable testosterone may be considered in patients with marginally low testosterone or those who have conditions causing altered SHBG level. A stepwise approach for bio chemical evaluation is shown in algorithm depicted in the (Figure 2). Idiopathic gynecomastia is diagnosed when all the biochemical testing is negative.

Mammography can be used to differentiate benign and malignant male breast diseases fairly accurately (10).

Management of gynecomastia

The management of gynecomastia depends on the underlying etiology and the concerns of the patient. This may include interventions for relief of pain or discomfort, restoration of normal appearance and reassurance regarding cancer.

Watchful waiting

Gynecomastia of recent onset (less than six months) often regresses spontaneously in vast majority of patients and symptoms like pain, tenderness tend to resolve with time as the inflammation settles and fibrosis occurs (12). Therefore observation alone with periodical follow up (once in 6 months) would be sufficient for most adolescents, and also for most men without considerable underlying pathology according to appropriate workup after stopping offending medications and/or treating any underlying disorders. Pubertal gynecomastia regresses in 85 to 90 percent within six months to two years. However if gynecomastia is associated with severe breast enlargement, pain, tenderness, and embarrassment that interferes with the patient’s normal daily activities treatment should be initiated. Treatments may also be needed to the patients with persistent gynecomastia which is lasting more than a year. The degree of breast enlargement and symptoms that trigger treatment are dependent upon the perception of the patient.

Pharmacotherapy

Pharmacotherapy is likely to be effective usually at early stage of the disease (within a year) where there is predominant inflammation and less fibrosis. Several medications can be used to modify hormonal changes involved in gynecomastia. Anti-estrogens, aromatase inhibitors and androgens are the available options. However the data on efficacy and safety of these drugs comes from small studies.

Although clinical trial data are limited, the selective estrogen receptor modulators (SERMs) appear to be effective and generally well-tolerated. It may rapidly reduce the pain and should be considered as first-line therapy for symptomatic cases of acute gynecomastia, or those who have persistent symptoms. However, complete breast regression is usually not achieved with this approach. Raloxifene, tamoxifen and clomiphine citrate are the available options. The latter has limited and variable effect. Lawrence, et al has shown that raloxifene is more effective than tamoxifen in reducing persistent pubertal gynecomastia (13). SERM therapy is usually used for pubertal boys with severe gynecomastia, which is often associated with tenderness. However, the degree of breast enlargement and symptoms that trigger the treatments are dependent upon the perception of boys and their parents. The commonly used doses of SERM are raloxifene 60 mg/ day and tamoxifen 10-20 mg/ day.

Tamoxifen has been shown to be effective in reducing breast size and tenderness in adult men. A brief trial (three to six months) of tamoxifen (10 mg twice daily) is recommended for relief of tenderness. The regression of gynecomastia is always partial (14). There is inadequate experience with raloxifene in adult men. In males with hypogonadism, testosterone replacement often improves gynecomastia (15).

Androgens like dihydrotestosterone, danazol, clomiphene, and aromatase inhibitors such as testolactone and anastrozole may also be effective but has limited data and less commonly used (16).

Surgery

Surgery should be considered for patients whose
gynecomastia does not regress spontaneously or with medical therapy and causes considerable discomfort and or psychological distress.

Surgery should be considered in men with persistent gynecomastia (more than 1-2 years) since the breast tissue has probably become fibrotic and unresponsive to medical therapy. The Surgery should be delayed in adolescents until the puberty is complete and testis has reached adult size because otherwise the breast tissue may re-grow.

Reduction mammoplasty can be performed using peri areolar or transareolar approach. Skin resection may be necessary for more advanced cases. The surgery can be combined with liposuction in cases with significant amount of fat tissue (14). The potential surgical complications include breast asymmetry, nipple necrosis or flattening, hypertrophic scars, contour irregularity, hematomas, numbness of the nipple and areolar areas. The less invasive techniques (endoscopic subcutaneous mastectomy) offer minimal surgical incision and lesser complication rates. Histological analysis of the glandular breast tissue is recommended since an unexpected finding such as spindle-cell hemangioendothelioma and papilloma may occur in about 3% of cases (17).

References

Clinical update

Evidence-based management of non-alcoholic fatty liver disease

S K Kodisinghe¹, M A Niriella¹²


Abstract

Non-alcoholic fatty liver disease (NAFLD) is the commonest cause of chronic liver disease in developed countries and is rapidly increasing in the Asia-Pacific region. NAFLD has important long term health implications. There is increased overall mortality most commonly from cardiovascular disease, and also increased liver-related mortality.

Treatment options available for NAFLD include general measures at managing obesity and correcting the metabolic syndrome and liver-directed therapies aimed at reducing the liver inflammation and hepatocellular injury. This article reviews the current evidence based management of NAFLD and associated metabolic comorbidities.

Key words: Fatty liver, Non-alcoholic fatty liver, NAFLD, evidence-based, treatment, management

Introduction

Non-alcoholic fatty liver disease (NAFLD) is defined as hepatic steatosis detected either on imaging or histology, in the absence of secondary causes. It is an umbrella term covering a spectrum of diseases ranging from simple non-alcoholic fatty liver (NAFL) (i.e. fat deposition without inflammation or hepatocellular injury), to non-alcoholic steatohepatitis (NASH) (i.e. fat deposition with inflammation and hepatocellular injury) to cirrhosis (1).

Global prevalence of NAFLD in adults ranges from 6-33% depending on the population studied and the assessment methods used (1). In the paediatric age group this ranges from 0.7 - 17.3% (2). As NAFLD affects up to a third of the population in developed countries, it is the commonest cause of chronic liver disease in these parts (3). In Sri Lanka, the community prevalence of ultrasonically detected NAFLD was 32.6% in an adult urban population (4) and 18% in a rural physically active population (5).

NAFLD has important long term health implications in that there is an increased overall mortality most commonly from cardiovascular disease, as a result of the shared metabolic risk factors common to both NAFLD and cardiovascular disease (6). With NASH there is also increased liver-related mortality, due to the risk of progression to cirrhosis and hepatocellular carcinoma (HCC)(1).

Treatment

Treatment options available for NAFLD can be broadly categorized into two groups: first, general measures at managing obesity and correcting the metabolic syndrome; second, liver-directed therapies aimed at reducing the liver inflammation and hepatocellular injury. As patients with NAFL have excellent prognosis from a liver point of view, they require only correction of the associated metabolic co-morbidities. Patients with NASH on the other hand, require liver-directed therapies in addition to the general measures, since they have increased liver-related morbidity and mortality. Liver-directed therapies are also indicated in NAFLD patients without biopsy evidence of NASH, where an adequate trial of general life style measures has failed.

In all patients with NAFLD, management of the associated metabolic risk factors such as type 2 diabetes mellitus (T2DM), hypertension (HT) and dyslipidaemia, is vital to reduce the patients’ cardiovascular risk profile.

General measures

General measures aimed at correcting the associated metabolic syndrome which are backed by good levels of evidence are, weight loss, healthy eating with dietary restrictions, increasing physical activity and avoiding unsafe levels of alcohol.

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Weight loss

Weight loss improves patients’ cardiovascular risk profile and improves stastosis (7). Reduction in hepatic steatosis has been found to occur when a 3-5% weight loss occurs, but improvement in hepatic necroinflammation requires a weight loss up to 10% (8). Therefore, patients are encouraged to lose >10% of their baseline body weight and maintain the loss, and to reduce the BMI and waist circumference to the ethnicity-specific normal ranges. A target BMI of <23 kg/m² and waist circumference of <90 cm for men and <80 cm for women, is recommended for Asians (9, 10). Improvement with weight loss is seen even in normal weight patients (11) and in patients with advanced NASH with hepatic fibrosis (12). Weight loss can be achieved by consuming a hypocaloric diet, increased physical activity, or both, while histological improvement occurs irrespective of the method used to achieve the weight loss (8, 13).

Dietary restrictions

There is only sparse evidence regarding the composition of an optimal liver-friendly diet, other than the recommendation of a hypocaloric diet. Patients should be advised to follow a calorie-restricted diet (600 kcal less than a person needs to remain at the same weight), aiming to lose 0.5-1 kg per week until they achieve their target weight (14). General recommendations are for a diet avoiding saturated fats, simple carbohydrates and sweetened drinks, and an emphasis on increasing the intake of fruits and vegetables. Some studies including a small RCT have found benefit with a Mediterranean diet (15). Evidence regarding low fructose intake is controversial (16). Dietician input is also valuable in NAFLD patients, since dietician-led lifestyle interventions have been found to be more effective than standard care (17).

Increasing physical activity

Exercise, in addition to being an important component of any weight-loss program, has been found to improve hepatic steatosis even in the absence of weight loss [18]. There is limited evidence regarding an exercise programme specifically designed for patients with NAFLD. One study has found moderate to vigorous physical activity of ≥ 250 minutes per week, was associated with a significant reduction in hepatic steatosis compared to <150 minutes per week (19). Other studies also support a dose-dependent association between physical activity and NAFLD (20). Therefore, all patients with NAFLD should be advised to increase physical activity and undertake regular exercise. One approach is to recommend approximately 200 minutes of moderate physical activity per week (40-50 minutes 5 times per week) (14). Many patients with NAFLD find it difficult to comply with these recommendations and using pedometers (aiming for >10,000 steps per day) can be useful. Individuals with NAFLD are less active than healthy controls (21), and there is evidence to suggest that they lack the confidence to exercise and have reduced readiness to make lifestyle changes (22). This suggests that behavioural counselling may also have a place in the management of these patients.

Safe alcohol intake

Patients with NAFLD should not consume alcohol beyond the safe limit. Safe limits of alcohol intake for males and females are <14 units and <7 units per week respectively (23). Although no firm recommendation can be made with regards to alcohol consumption within the safe limit, some data indicate that light alcohol consumption may even be beneficial (24).

Other general measures

Some other general measures which do not have robust evidence to support their use are, other weight reducing measures such as orlistat and bariatric surgery, and adequate sleep.

Orlistat may reduce transaminases and steatosis on imaging but has not been shown to improve liver histology (25). Bariatric surgery has been recommended in eligible obese patients as a means to control the weight, but not as a specific treatment modality for NAFLD (26). However some new evidence is coming through, suggesting a direct beneficial effect for bariatric surgery on NAFLD (27). Improvement seems to be significantly more following roux-en-Y gastric bypass than after adjustable gastric banding (27).

Recently there has been interest in the association between duration of sleep and NAFLD. Studies have shown conflicting results, with some suggesting that insufficient sleep undermines the effectiveness of dietary measures on reduction of adiposity (28), while others suggest that lack of sleep reduces the risk of NAFLD onset in males (29). It is generally recommended that NAFLD patient to have 7-9 hours of sleep each night.

Liver-directed therapies

Liver-directed therapies with good levels of evidence include vitamin E, thiazolidinediones and coffee consumption. Two other drugs which have shown promise are obeticholic acid and pentoxifylline. Although metformin and ursodeoxycholic acid have historically been used, they are not backed by evidence.

Vitamin E

Out of the pharmacological measures the best evidence is available for vitamin E, which is considered the first-line pharmacotherapy for non-diabetic adult
patients with biopsy-proven NASH without cirrhosis (1). When administered at daily dose of 800 IU, vitamin E improves hepatic steatosis and inflammation (30). Due to lack of evidence, vitamin E is not recommended in patients without liver biopsy, in diabetic patients or in patients with NASH cirrhosis (1). In paediatric patients, evidence of clear histological improvement is still lacking (31). Whether long term vitamin E therapy increases the all-cause mortality is still a contentious issue (32). What is 'long term' is also contentious, but a major trial has used vitamin E for a duration of 2 years (30). Other concerns are the potential increase in haemorrhagic strokes and prostate cancers with long term use of vitamin E (33).

Pioglitazone

Pioglitazone improves hepatic steatosis and inflammation in NASH (30,41), and therefore is recommended in patients with biopsy-proven NASH (1). However, dropout rates during clinical trials were high due to side effects such as weight gain. Majority of the participants in these clinical trials were non-diabetic. With evidence on increased risk of bladder carcinoma (34), bone loss (35) and cardiac failure (36) emerging, the long term safety of pioglitazone is in question.

Coffee consumption

There is good evidence that coffee consumption can reduce the inflammation, and importantly the fibrosis, in patients with NASH (37). The effective dose has been shown to be more than 2.25 cups of regular coffee, while espresso coffee, caffeine from sources other than coffee and decaffeinated coffee have been found to be ineffective (38, 39). Therefore 2-3 cups of unsweetened coffee daily, is a reasonable adjunct to therapy for NAFLD patients. Furthermore, there is emerging evidence that coffee consumption is protective for the development of HCC (40).

Other potential liver directed therapies

A new drug earmarked with a bright future is obeticholic acid, which as a synthetic analogue of the natural bile acid chenodeoxycholic acid, and an activator of the farnesoid X receptor. It has been shown to improve the histological features of NASH in a phase 2b trial (41), but more evidence is needed before it is accepted into routine practice. Concerns have been raised regarding the worsening of the lipid profile and high incidence of pruritus found in the trial participants (41). Ursodeoxycholic acid although a bile acid, is not recommended in NAFLD following trial evidence showing absence of benefit (1).

Liraglutide is a human glucagon-like peptide-1 (GLP-1) analogue, approved to treat type 2 diabetes. In a phase 2b trial, Liraglutide Efficacy and Action in NASH (LEAN), overweight patients with biopsy proven NASH, were treated with once-daily Liraglutide 1.8 mg or Liraglutide-placebo subcutaneously for 48 weeks. Liraglutide group reached the primary end point of resolution of definite NASH and no worsening of fibrosis from baseline to end of treatment on histology, compared to placebo (39% vs. 9%). Results of this trial point towards a new treatment option for NASH and a phase 3 trial is needed to confirm the potential of this class of medication (42).

Another promising agent is pentoxifylline, which has been found to significantly improve liver histology and reduce BMI and fasting glucose (43). But again, more evidence is awaited.

Unproven therapies

Metformin although in vogue once as a major therapy in NAFLD, is no more recommended following robust trial evidence indicting lack of benefit (44).

Various lipid lowering drugs including omega-3 fatty acids (45), statins (46), fibrates (47), ezetimibe (48) and colesevelam (49) have been tested in NAFLD, but none have been found to unequivocally improve liver histology. Therefore, these are not recommended for the purpose of treating NAFLD, although they can be used to treat dyslipidaemias in patients with NAFLD.

Other drugs that have been studied in NAFLD, but which still have either very limited or conflicting evidence, are probiotics, vitamin D and traditional Chinese medicines.

Management of associated metabolic complications

Management of Type 2 Diabetes Mellitus

Screening for impaired glucose tolerance is required in NAFLD patients given the almost universal prevalence of insulin resistance in this population (50). Furthermore, more progressive liver fibrosis is seen in NASH patients with T2DM.

Metformin is recommended as the first-line pharmacological therapy for T2DM in NASH, since it aids weight loss, has cardiovascular benefits (51) and also seems to have a negative impact on the development of HCC (52). Pioglitazone is the preferred second-line agent in subjects with NASH, given the proven benefit in improving liver histology. Sulphonylureas on the other hand, may have a negative impact due to increasing insulin secretion and weight gain. For obese patients, GLP-1 analogues may be considered as a third-line agent. There is evidence of improvement in ALT and steatosis with liraglutide (53), although this may be due to the associated weight loss and improved glycemic control rather than due to a direct effect.
Management of dyslipidaemia

Since dyslipidaemia is very common in patients with NAFLD, screening is important.

Statins are considered the first-line agent for treating hypercholesterolemia in NAFLD. Contrary to the popular belief, statins are safe to use in patients with NAFLD with elevated transaminases, and routine liver enzyme monitoring is not warranted in this population (54). Statins may also reduce the risk of HCC (55).

Management of hypertension

All patients with NAFLD should have their blood pressure checked regularly, since hypertension is very common in this population. Antihypertensive therapy should be instituted if the blood pressure is >140/90 mmHg.

There is some evidence that angiotensin receptor blockers (ARBs) improve transaminase levels, liver histology and insulin sensitivity in hypertensive patients with NASH (56, 57). Although larger studies are needed, angiotensin-converting enzyme inhibitors or ARBs seem a logical choice in the management of hypertension in subjects with NAFLD.

Conclusion

Life style modifications should be prescribed to all patients, while liver-directed therapies are needed only in patients with NASH. Calorie restricted diet, regular exercise and weight loss are the most important life style modifications, while regular consumption of non-sweetened coffee may also be helpful. Vitamin E and pioglitazone are the main liver-directed pharmacotherapies, and should be considered in the right patient population. Angiotsenin receptor blockers are the antihypertensive agents of choice for hypertensive patients with NASH. Given the associated cardiovascular-related mortality and potential reduction in HCC risk, clinicians should have a low threshold for statin use.

Key points

- The treatment of NAFLD depends on the stage of disease
- Life style modifications should be prescribed to all patients with NAFLD
- Liver-directed therapies are needed only in patients with NASH
- Calorie restricted diet, regular exercise and weight loss are the most important life style modifications
- Vitamin E and pioglitazone are the main liver-directed pharmacotherapies, and should be considered in the right patient population
- Management of the associated metabolic risk factors are essential to reduce overall increased cardio vascular mortality in all patients with NAFLD

References


Clinical update


Evidence-based management of non-alcoholic fatty liver disease


Polyuria in a patient on chronic lithium therapy: a case report and literature review

C J Subasinghe¹, L D Ranasinghe¹, D U S Bulugahapitiya¹


Abstract

Lithium (Li) has been associated with several forms of renal injury, the most prevalent being impaired urinary concentrating ability, which is reported in individuals on chronic lithium therapy. Lithium is the most common drug implicated in acquired nephrogenic diabetes insipidus (NDI). Prevalence of NDI correlates with the Li dose and the duration of therapy. Here we report an elderly male, presented with hypotonic polyuria while being on prolonged Li therapy for more than 20 years for bipolar affective disorder. Further evaluation confirmed the diagnosis of Li induced NDI as the aetiology for polyuria which responded to Li dose reduction and Thiazide therapy. Proper evaluation of a patient presenting with hypotonic polyuria with water deprivation followed by a desmopressin challenge is necessary before diagnosis, as therapy differs according to the type of the disease. Usually the concentration defect is at least partially reversible with drug discontinuation. Amiloride minimizes lithium accumulation in collecting tubule cells and is recommended for those patients, in whom Lithium therapy cannot be discontinued.

Introduction

Lithium is recommended as the first-line therapy for treatment of bipolar disorder for more than 50 years due to excellent therapeutic efficacy despite various adverse effects. Polyuria has generally been defined as urine output exceeding 3 L/day in adults and 2 L/m² in children. It must be differentiated from the more common complaints of frequency or nocturia, which are not associated with an increase in the total urine output. Diabetes insipidus (DI) belongs to the spectrum of polyuric and polydipsic diseases, a group of hereditary or acquired disorders mainly associated with an inadequate Arginine Vasopressin (AVP) secretion or renal response to AVP, which clinically results in hypotonic polyuria and a compensatory or underlying polydipsia. Lithium is the commonest acquired cause of nephrogenic diabetes insipidus, which is caused by impaired renal concentrating ability due to various mechanisms. Polyuria in a patient who is on Lithium could be due to various causes including NDI, cranial DI, primary polydipsia and tubulointerstitial nephritis. Furthermore, long term Li therapy leads to hyperparathyroidism causing hypercalcaemia and polyuria. Therefore, polyuria in a patient who is on Li requires a proper diagnostic evaluation. Elderly psychiatric patients are more prone to develop complications of polyuria, such as dehydration, electrolyte imbalance, neurological problems irrespective of the underlying aetiology. Most importantly all these factors predisposes these patients to Li toxicity, and therefore proper evaluation and prompt correction should be done.

Case report

A 66 years old man with bipolar affective disorder who had been on LiCO₃ (current dose -1g nocte ) for 20 years presented with nocturia, polyuria and excessive thirst for 4 months duration. There was no past history of diabetes mellitus and he did not have other symptoms of hypercalcaemia. He also complained of a bilateral hand tremor, but not other symptoms suggestive of Li toxicity.

On examination, he was dehydrated and had coarse tremors of hands. Rest of the examination was unremarkable. Investigations revealed slightly elevated serum Li levels (1.22 mEq/L {therapeutic range; 0.6-1.2 , toxic > 1.5}). Fasting blood glucose and serum calcium were normal. Renal function test showed mild elevation of serum creatinine (1.41 μmol/l). Serum electrolytes revealed hypernatraemia (Na- 148 mmol/l) with normokalemia. Based on the history, Li induced NDI was suspected and further evaluation was done. His serum osmolality was high (304 mOsm/kg H₂O) with low urinary osmolality (192 mOsm/kg H₂O). A water deprivation test (Table 1) was done to confirm the diagnosis of Li induced nephrogenic DI.

With water deprivation, polyuria persisted and serum osmolality increased without appropriate concentration of urine, suggesting DI. Urine osmolality did not improve with Vasopressin, confirming complete nephrogenic DI in our patient. Li dose was reduced after psychiatrist opinion. Since Amiloride was not available, Hydrochlorothiazide 25 mg was started with close monitoring of serum

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Polyuria in a patient on chronic lithium therapy

Discussion and literature review

Polyuria is defined as a urine output of more than 3L/day in adults. With the exclusion of glucose induced osmotic diuresis, which occurs in uncontrolled diabetes mellitus, other three major causes of hypotonic polyuria (urine osmolality usually <250 mosmol/kg) are primary polydipsia, central DI and nephrogenic DI. Nephrogenic diabetes insipidus (NDI) results from renal resistance to antidiuretic action of Arginine Vasopressin (AVP), which clinically results in hypotonic polyuria and a compensatory polydipsia. Acquired form of NDI is much more common than congenital NDI, while chronic Lithium use and hypercalcemia being the most common causes of a defect severe enough to produce polyuria (1,2,3).

Normally water permeability of principal cells in collecting ducts (CD) is regulated by anti diuretic hormone (ADH). Aquaporin 2 (AQP2) water channels, which normally reside in endosomes of principal cells, move to and fuse with luminal membrane under influence of ADH, allowing water to be reabsorbed down the favourable concentration gradient. On average, Li reduces urinary concentrating ability by 15% of normal maximum by different mechanisms (2). Even at therapeutic concentration, lithium may interfere with intracellular Vasopressin signaling systems mainly including CAMP system, leading to decreased renal AQP2 receptor expression (1,4,5,6). In addition, Li also reduces protein abundances of urea transporters (UTA1, UTB), thereby reducing medullary interstitial osmolality, which causes impaired countercurrent exchange and renal concentrating ability (6). Lithium accumulates in the distal tubular cells of the kidneys at concentrations 10-20 times higher than in serum. Epithelial sodium channels (ENaC) play a crucial role as the entry route for intracellular Li accumulation (7). In most cases, there is a correlation between impaired concentration ability and duration of Li and total Li dose (8). In one study, patients who had been on the drug for more than 18 years invariably had an irreversible defect (3). Between 20-70% of patients taking Li have a moderate increase in urine volume (>2.5 L/d) while up to 12% have frank DI characterized by polyuria (>3 L/d), hypernatremia, and neurological symptoms (6,9). Our patient had been on variable doses of Li for about 20 years when he presented with symptoms.

It should not be assumed that polyuria in a patient taking Li is always due to NDI. Both cranial DI and primary polydipsia have also been described in patients treated with Li. Therefore once hypotonic polyuria is confirmed, these patients should undergo proper diagnostic evaluation of differential diagnosis. Current diagnostic test concepts of DI date back to animal studies from Gilman and Goodman in the 1930s, which first demonstrated that osmotic stimulation by dehydration induces an antidiuretic urinary response that is not observed in hypophysectomized dogs (10). A first standardized test protocol with detailed diagnostic test criteria was proposed by Miller et al. in 1970 after the evaluation of 36 patients with different disorders of polyuria and polydipsia syndrome (11). For the time being, we consider water deprivation followed by a desmopressin challenge as the most plausible test standard to assess the adequacy of AVP function (Figure 1). However, no agreement exists regarding the best test for diagnosis and most commonly followed protocols lack diagnostic accuracy (12).

The water restriction test in adults is continued until the maximal urinary concentration achieved, indicated by the urine osmolality reaching a clearly normal value, the urine osmolality being stable on two or three successive hourly measurements despite a rising plasma osmolality, the plasma osmolality exceeding 295 to 300 mosmol/kg or the plasma sodium being 145 meq/L or higher. Our patient failed to increase urine osmolality in response to water deprivation and to stimulation with Vasopressin, concluding the diagnosis of complete NDI.

Table 1. Water deprivation test

<table>
<thead>
<tr>
<th>Time</th>
<th>Weight(kg)</th>
<th>Urine vol.(mL)</th>
<th>S. Na+(mmol/L)</th>
<th>S. Osmolality (mOsm/kgH2O)</th>
<th>Urine osmolality (mOsm/kgH2O)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0800h</td>
<td>65.55</td>
<td>350 ml</td>
<td>143</td>
<td>303</td>
<td>77</td>
</tr>
<tr>
<td>0900h</td>
<td>65.4</td>
<td>360</td>
<td>144</td>
<td>81</td>
<td></td>
</tr>
<tr>
<td>1000h</td>
<td>65.55</td>
<td>360</td>
<td>143</td>
<td>307</td>
<td>89</td>
</tr>
<tr>
<td>1300h</td>
<td>65.5</td>
<td>300</td>
<td>147</td>
<td>384</td>
<td>168</td>
</tr>
<tr>
<td>1400h</td>
<td>65.1</td>
<td>250</td>
<td>147</td>
<td>314</td>
<td>121</td>
</tr>
</tbody>
</table>

IM Vasopressin 5U at 1200h
Other therapeutic options to manage polyuria are similar to those in other causes of NDI. Thiazide diuretics diminish distal water delivery and upregulate AQP2 receptors causing paradoxical effect of reducing polyuria while being a diuretic (15). Our patient’s polyuria responded well to thiazide therapy. NSAIDs inhibit prostaglandin synthesis and thereby minimize the ADH inhibition by prostaglandins, creating a therapeutic place in NDI. Since most patients are partially resistant to ADH, it is also possible that attaining supraphysiological levels of ADH will attenuate polyuria.

**Conclusion**

A psychiatric patient presenting with polyuric polydipsic syndrome, should be evaluated for possible Li induced diabetes insipidus, while excluding other possible causes such as primary polydipsia and cranial DI. Lithium is a very potent medication, which has proven renal toxicity on long term therapy with possible permanent damage.
Polyuria in a patient on chronic lithium therapy

with time. More validated test protocols will improve the diagnostic accuracy of diabetes insipidus and thereby treatment success in the future. Understanding the aetiology and pathophysiological basis of the underlying disease in depth to the molecular level would be of importance in selecting therapeutic options.

References


A patient with primary amenorrhoea and hypertension: 17 α hydroxylase deficiency – a rare cause of congenital adrenal hyperplasia

W C K Jayawardena¹, C N Antonypillai¹


Abstract

A 26 year old girl, who is a product of a consanguineous marriage, presented with hypertension and hypokalaemia. She had a history of primary amenorrhoea with absent secondary sexual characteristics. Laboratory investigations revealed low levels of serum cortisol and low 17hydroxyprogesterone levels with high ACTH levels. Furthermore her adrenal androgens and oestradiol were low with elevated gonadotrophins. Chromosomal analysis revealed a male karyotype of 46, XY. All these clinical and laboratory data were consistent with the diagnosis of congenital adrenal hyperplasia (CAH) due to 17 alpha hydroxylase deficiency in a genotypic male. She was started on steroid replacement therapy while monitoring blood pressure, serum potassium levels and ACTH levels.

Key words: Congenital Adrenal Hyperplasia (CAH), 17 α hydroxylase /17,20-lyase deficiency (17OHD)

Introduction

Congenital adrenal hyperplasia (CAH) comprises of a group of autosomal recessive disorders, caused by deficient adrenal corticosteroid biosynthesis. 17 α hydroxylase/17,20-lyase deficiency (17OHD) is a rare form of CAH accounting for roughly 1% of all cases of CAH, and most reports involve isolated cases from consanguineous families(1).

17 α hydroxylase (17 α OH) and 17,20-lyase activities are catalyzed by microsomal cytochrome P450c 17 which is encoded by a single gene, CYP 17 (2) located on chromosome 10q24-q25 (3).

Deficiencies in 17 α OH and 17,20-lyase activities result in impaired synthesis of 17-hydroxyprogesterone and 17-hydroxypregnenolone resulting in low cortisol, androgens and oestrogens (Figure1). Decreased cortisol synthesis causes excessive secretion of ACTH due to loss of negative feedback, which results in excessive secretion of 17-deoxysteroids by the adrenal cortex, including the mineralocorticoids, deoxycorticosterone (DOC) and corticosterone. Accumulation of corticosterone and DOC results in severe hypokalaemic hypertension.

Sex steroid deficiency caused by loss of 17,20-lyase deficiency manifests as under-virilization in male newborns and primary amenorrhoea in 46, XX individuals. There is lack of pubertal development due to hypergonadotrophic hypogonadism in both sexes (4).

Case report

A 26 year old girl was referred for further evaluation of hypertension and hypokalaemia, detected while being treated for a febrile illness. Her blood pressure ranged between 140/90 and 170/100 mmHg without any paroxysms and her potassium levels ranged between 2.5 mmol/L and 3.5 mmol/L. She however, remained asymptomatic. She was a product of a consanguineous marriage and had two healthy siblings.

She had primary amenorrhoea with absent secondary sexual characteristics which had been investigated at the age of 17 years, with a hormonal profile and a diagnostic laparoscopy. She had elevated gonadotrophins with low oestradiol and testosterone levels and diagnostic laparoscopy had not shown a uterus, ovaries or testicles. At that time she had been normotensive and thus her potassium levels not evaluated. She had been treated with ethinyl oestradiol for a short duration but further diagnostic procedures had not been carried out.

On examination, she had generalized and buccal hyperpigmentation. Her height was 175 cm, weight 48 kg and BMI 15.7 kg/m². Her blood pressure was 160/90 mmHg without postural hypotension and there was no significant discrepancy in the pressures between the right and left limbs. Her pulses were palpable in all extremities. There were no palpable masses or renal bruit in the abdomen. She had female external genitalia, but there were no secondary sexual characteristics. Breast and pubic hair were both tanner stage 1.

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A patient with primary amenorrhoea and hypertension

Table 1. Results of biochemical investigations

<table>
<thead>
<tr>
<th>Laboratory test</th>
<th>Results</th>
<th>Reference range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cortisol (9 a.m.)</td>
<td>78 nmol/L</td>
<td>180-620 nmol/L</td>
</tr>
<tr>
<td>17-hydroxyprogesterone</td>
<td>0.30 ng/mL</td>
<td>0.5-2.1 ng/mL</td>
</tr>
<tr>
<td>ACTH</td>
<td>1389 pg/mL</td>
<td>0-60 pg/mL</td>
</tr>
<tr>
<td>Progesterone</td>
<td>9.68 ng/mL</td>
<td>Follicular 9.6 ng/mL</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Luteal 45-285 ng/mL</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Males 2.9-13 ng/mL</td>
</tr>
<tr>
<td>DHEAS (Dehydroepiandrosterone sulphate)</td>
<td>&lt;15.0 μg/dL</td>
<td>Females 44-322 μg/dL</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Males 89-457 μg/dL</td>
</tr>
<tr>
<td>Testosterone</td>
<td>&lt;0.20 ng/mL</td>
<td>Females 1.7-9 ng/mL</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Males 29-100 ng/mL</td>
</tr>
<tr>
<td>Oestradiol</td>
<td>11.0 pg/mL</td>
<td>Follicular 60-936 pg/mL</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Luteal 648-3960 pg/mL</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Males 0-688 pg/mL</td>
</tr>
<tr>
<td>FSH (Follicular Stimulating Hormone)</td>
<td>86.1 mIU/mL</td>
<td>Follicular 0.5-5 mIU/mL</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Luteal 2-8 mIU/mL</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Males 1.4-18 mIU/mL</td>
</tr>
<tr>
<td>LH (Luteinizing Hormone)</td>
<td>102.0 mIU/mL</td>
<td>Follicular 3-12 mIU/mL</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Luteal 3-16 mIU/mL</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Males 3-8 mIU/mL</td>
</tr>
<tr>
<td>Renin (Upright)</td>
<td>3.45 pg/mL</td>
<td>5.41-34.53 pg/mL</td>
</tr>
<tr>
<td>Aldosterone (Upright)</td>
<td>255 pg/mL</td>
<td>34.7-275 pg/mL</td>
</tr>
</tbody>
</table>

Figure 1. Adrenal steroid synthesis. Deficiency in 17α hydroxylase/17,20-lyase results in accumulation of deoxycorticosterone (DOC) and consequent hypertension; reduced cortisol and androgen production.
Laboratory investigations revealed persistently low potassium levels (ranging between 2.5 to 3.5 mmol/l) with normal renal and liver profiles. She had a low serum cortisol, low 17-hydroxyprogesterone with very high ACTH levels. Furthermore, her adrenal androgens (DHEA and testosterone) and oestriadiol levels were low with elevated gonadotrophins. Plasma renin activity was low but her aldosterone remained in upper normal level (Table 1). DOC and 11-deoxycortisol levels could not be performed due to unavailability of tests.

Chromosomal analysis revealed a male karyotype of 46, XY. Contrast CT of the abdomen did not show a uterus, ovaries or testis. There was hyperplasia of the left adrenal gland.

A clinical diagnosis was made through these clinical, imaging and laboratory data, which were consistent with CAH due to 17α-hydroxylase/17,20-lyase deficiency in a genotypic male. Testing for specific gene mutations was unavailable.

**Discussion**

Congenital adrenal hyperplasia due to 17α OH/17,20-lyase deficiency leads to deficiency in glucocorticoid, adrenal androgens and sex steroid synthesis with a subsequent increase in ACTH and gonadotropin levels. Concomitant mineralocorticoid excess results in hypokalaemic hypertension. Although these patients have low cortisol levels, weaker glucocorticoid corticosterone in excess prevents adrenal crisis (4). This patient had the classic clinical features and laboratory data consistent with the diagnosis of CAH due to 17α hydroxylase/17,20-lyase deficiency. Her ACTH levels were very high causing generalized hyperpigmentation.

It is interesting to note that levels of aldosterone are suppressed in most cases in spite of the increased levels of corticosterone and DOC. The favoured explanation is that significantly increased DOC and corticosterone leads to expansion of blood volume which in turn suppress plasma renin and aldosterone secretion (5). On the other hand, a considerable number of cases of 17α OH deficiency have normal or elevated aldosterone levels despite low plasma renin activity (6) as in this patient. However, it is likely that aldosterone production in these patients was primarily ACTH-mediated rather than via the renin-angiotensin system. It is also likely that the seemingly high aldosterone concentrations may be due to cross-reactions between aldosterone and other mineralocorticoid precursors (7).

Affected 46, XX females have normal female internal and external genital tracts, but the ovaries cannot secrete oestrogens at puberty, resulting in absent breast development and hypogonadism with elevated gonadotrophins. Affected 46, XY individuals with complete combined 17α OH/17,20-lyase deficiency usually have female external genitalia. This patient probably has complete combined 17α OH/17,20-lyase deficiency as she also had female external genitalia and 46, XY karyotype. Testes may usually be intra-abdominal, in the inguinal canal or in the labio-scrotal folds although they were not found in this patient either radiologically or laparoscopically.

Complete 17α OH/17,20 lyase deficiency is associated with a variety of mutations in the CYP17 gene with resultant loss of function of enzyme. Due to lack of availability genetic mutation analysis, it was not performed in this patient.

Partial forms of combined 17α OH/17,20-lyase deficiency have been described (8). These conditions most frequently manifest as a 46, XY infants with ambiguous genitalia or severe hypospadiasis, in whom the steroid profile is consistent with the diagnosis. 46, XX individuals may present with menstrual problems or with infertility (9). Hypertension may or may not be present. Isolated 17,20-lyase deficiency has been reported in small number of patients. These 46, XY individuals usually have genital ambiguity, normal secretion of glucocorticoids and mineralocorticoids with marked reduction in sex steroids (10,11).

Management of CAH due to 17α OH deficiency comprises glucocorticoid replacement and normalization of ACTH, which in turn will remove the drive for oversecretion of deoxycorticosterone and corticosterone. This in most cases will bring about remission of hypertension and hypokalaemia. This patient was started on steroid replacement therapy; hydrocortisone 5 mg, 2.5 mg, 2.5 mg at 6 a.m, 12 noon and 6 p.m while monitoring the potassium, blood pressure and ACTH levels. ‘She’ chose to remain a phenotypic female after discussing with the parents.

**Conclusion**

The diagnosis of 17α OH/17,20-lyase deficiency is generally delayed, due to the low incidence of adrenal crisis and other severe symptoms in untreated patients. A high index of clinical suspicion is necessary when evaluating patients with 46, XY DSD (Disorders of sex determination) and adolescents with sexual infantilism. The diagnosis is strongly supported by the discovery of hypertension along with hypokalaemia.

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A patient with primary amenorrhoea and hypertension


Anti-obesity effects of green tea extracts on humans

K A Naser¹, D Niyangoda², R Wijesinghe³


Abstract

Introduction: Green tea is heavily promoted and sold over the counter for many illnesses, including obesity.

Methodology: Literature was reviewed focusing on the key words; tea, green tea, catechin, overweight, obesity, side effects, adverse effects, transient ischemic attack, stroke and liver function, up to December 2014.

Results and discussion: Majority of the studies on this topic were short term and involved only a small number of participants. Though these studies demonstrated very small reduction of weight, evidence was inadequate for the use of green tea as an anti-obesity agent. In this review, the effect of green tea on obesity and some possible harmful effects of green tea are discussed. Current evidence on green tea does not support the use of it as an anti-obesity agent. There are several reports of side effects. The liver side effects are a cause for concern.

Conclusions: Long term use of green tea as an over the counter supplement should not be encouraged. Rather it should be considered a drink, very much like any other tea or coffee, till further evidence of efficacy and safety are proven.

Key words: green tea, catechin, caffeine, overweight and obesity

Introduction

Obesity, the most prevalent metabolic disease worldwide, affects adults, adolescents and children by reaching epidemic proportions. Obesity is an excess of adipose tissue in relation to lean body mass. Body mass index (BMI) and waist circumference (WC) are used as surrogates for adiposity, on routine examinations (1). Obesity, especially central obesity is a risk factor for number of chronic diseases, including type 2 diabetes mellitus, ischaemic heart disease and hypertension (1, 2). Modest weight loss at 5-10% of the initial body weight, leads to reduction of risk of mortality and morbidity that have been linked with obesity and is a realistic goal (1, 3).

Judicial use of dietary agents combined with physical activity and reduction of energy consumption are safer than the surgical and pharmacological methods in controlling obesity (2, 4). Green tea, a non-fermented tea prepared by tea (Camellia sinensis, Theaceae) leaves, is a functional food ingredient and has been reported to have anti-obesity properties. Worldwide people consume this tea on a daily basis as a beverage, especially in Asian countries. Green tea, a dietary agent has been reported to be effective in prevention of obesity by epidemiological and laboratory studies (2, 5-8). However, it has been found that it imparts some harmful effects such as hepatotoxicity if consumed in large quantities for a long period of time. Anti-obesity effects of green tea on humans are discussed in this review.

Methodology

Literature was reviewed focusing on the key words; tea, green tea, catechin, overweight, obesity, side effects, adverse effects, transient ischemic attack, stroke and liver function up to December 2014. Discussion is targeted on obesity, composition of green tea, mechanism of action, epidemiological and interventional studies, body weight maintenance, pharmacokinetics, harmful effects and transient ischemic attack.

Results and discussion

Composition of green tea

Tea (Camellia sinensis, Theaceae) is the most popular beverage next to water, consumed by over two-
third of the world’s population (4, 5, 9, 10). The main types of tea; black, oolong and green tea differ in terms of processing and chemical composition. Green tea is prepared by initial heating to inactivate the endogenous enzymes, while oolong and black tea are fermented. Tea leaves contain main energy sources; protein, carbohydrate, lipids and other health beneficial and flavoring components such as polyphenols, tannins, vitamins, minerals, volatile compounds, pigments and caffeine. Polyphenols and caffeine, the main components in a cup of tea are responsible for astringency and refreshment, respectively (11-13). Catechin, a colorless polyphenol is highly present in leaves at harvest and varied with the processing conditions and the variety of tea. Green tea preserves a large amount of catechins from oxidation than of others due to absence of fermentation step in processing (9). Furthermore, the amount of catechins in a cup of tea is highly variable, depending on preparation method adopted including the ratio of dry tea to water, temperature of water and the immersion time of leaves in hot water (9, 14-16).

Tea contains four major catechins; (-)-epicatechin (EC), (-)-epigallocatechin (EGC), (-)-epicatechin-3-gallate (ECG), and (-)-epigallocatechin-3-gallate (EGCG). EGCG is the most abundant and possesses the most potent antioxidative activity (2, 6, 14, 17-20). A cup of green tea contains 50-150 mg of catechins and 7.8-30 mg of caffeine (9, 21-23). Canned tea contains 0.3-35 mg of catechins/100 mL (24). Iced tea was found not to contain any flavanols (25). Average green tea catechin content in United Kingdom (200 mL cup) is 405.5 mg/day and in Japan (120 mL cup) is 200-400 mg/day (23, 26).

According to label claims, commercially available green tea formulations supply 150-800 mg catechins/day, 22.5-700 mg EGCG/d and 5.5-8.0 mg caffeine/day when taken as recommended. However, measured catechins contents were found to be 9-48% though the label claimed 100%, according to a study conducted in USA (27-32).

Mechanism of action

Physiological functions of catechins are mainly ascribed to the gallate esters of ‘epi’ catechins (7, 10). Potential mechanisms by which catechins prevent development of overweight and obesity involve inhibition of adipocyte differentiation and proliferation, reduced fat absorption, inhibition of gastric and pancreatic lipases, increased energy expenditure and fat oxidation via stimulating thermogenesis by inhibition of catechol-o-methyl-transferase (COMT) which is a catecholamine-degrading enzyme, synergism with caffeine and suppression of fatty acid synthesis (17, 14, 33-37).

COMT inhibitory activity is possessed by all gallate-catechins and is highest for EGCG, a non-competitive inhibitor with half maximal inhibitory concentration (IC50) of 70nM (38). However, inter-individual variability of COMT activity could vary as much as threefold and the effects of catechins on energy expenditure may vary depending on genetic variability in COMT activity (14, 39, 40). Besides, there is a large subject-to-subject variability in the pharmacokinetics of catechins (41).

Epidemiological and interventional studies

Green tea is widely consumed in China, Japan, Korea and Morocco. Green tea has been considered by the traditional Chinese medicine as a healthful beverage. An epidemiological study revealed that 43% of Chinese were habitual tea drinkers and 96% of them were green or oolong tea consumers (42). The authors of this study found that longer the duration of tea consumption, lower the percent body fat, waist circumference (WC), hip circumference, and waist-to-hip ratio. Short term (375 mg catechins/d and 150 mg caffeine/d) as well as long term (570.4 mg catechins/d with regular exercise for 2 months) consumption of green tea increases fat utilization and energy expenditure in sedentary conditions (43, 44). The effect of EGCG (300 mg/d for 2 days) on fat oxidation is higher under post-prandial than fasting conditions in men (45). Long term ingestion of tea catechins stimulates dietary induced thermogenesis and dietary fat oxidation (34).

Two hundred and seventy (270) mg/d EGCG with 600 mg of caffeine a day has been reported to be the optimal concentration to produce an effect on macronutrient oxidation and to increase energy expenditure in sedentary conditions (46, 47). Beyond this threshold, the EGCG content of a compound containing a fixed dose of caffeine (600 mg/d) only produces a small non-significant additional increase in 24 h energy expenditure (46). However, the caffeine dose used here is twice as the habitual caffeine intake and may hinder the effects of EGCG. Table 1.0 shows the effect of different quantities of catechins and caffeine in tea on percentage body weight reduction of humans. Above studies show that 491 mg catechins/day resulted in lesser reduction in percentage of weight than 468, 458 and 444 mg catechins/day (9, 48, 49). The considerable higher percentage of weight loss with 666 mg catechins/day than with 680 mg EGCG/day may due to lower body mass index (BMI) of subjects and the synergistic effect of all the catechins rather than from EGCG only (50, 51). BMI ranges of subjects used by Maki et al. were wider and they lost more weight (2.2 kg) than the subjects in the other study (1.7 kg), although both 625 and 583 mg catechins/day have shown similar weight reduction (20, 52).

Hsu et al. studied Tai women having 27.6>BMI<34.8 and the subjects had ingested capsules containing green tea extract three times daily 30 min after a meal (48). In other two studies Japanese adults had ingested beverages twice daily with meal (9, 49). BMIs of the subjects ranged from 22.5-30 with Kajimoto et al. and 24-35 with Wang et al.
## Table 1. Effect of green tea on body weight reduction

<table>
<thead>
<tr>
<th>Composition</th>
<th>Intake period/ Body weight</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Catechin/ (mg/d)</td>
<td>Caffeine/ (mg/d)</td>
<td>Body weight reduction %</td>
</tr>
<tr>
<td>172 (EGCG)</td>
<td>138</td>
<td>06</td>
</tr>
<tr>
<td>236</td>
<td>97</td>
<td>24</td>
</tr>
<tr>
<td>300 (EGCG)</td>
<td>low habitual</td>
<td>12</td>
</tr>
<tr>
<td>444</td>
<td>50</td>
<td>12</td>
</tr>
<tr>
<td>458</td>
<td>104</td>
<td>12</td>
</tr>
<tr>
<td>468</td>
<td>126</td>
<td>12</td>
</tr>
<tr>
<td>491</td>
<td>27.3</td>
<td>12</td>
</tr>
<tr>
<td>583</td>
<td>130</td>
<td>12</td>
</tr>
<tr>
<td>625</td>
<td>115</td>
<td>12</td>
</tr>
<tr>
<td>665.9</td>
<td>50</td>
<td>12</td>
</tr>
<tr>
<td>680 (EGCG)</td>
<td>49</td>
<td>06</td>
</tr>
<tr>
<td>690</td>
<td>75</td>
<td>12</td>
</tr>
<tr>
<td>886</td>
<td>198</td>
<td>12</td>
</tr>
</tbody>
</table>

$^S$- Significant and $^{NS}$- Non-significant at p<0.05

(9,49). High catechin:caffeine ratio given by Hsu et al. and low bioavailability of catechins when given as capsules compared to the beverage form may have caused lesser reduction in percentage body weight (48). Furthermore, Tai women may be less sensitive to catechins.

Two hundred and thirty six (236) mg catechins/day caused 1.5% weight reduction while 458 mg catechins/day accounted for 1% reduction (9, 53). This can be justified by longer duration of treatment with frequent dosing which had led to stable catechin and caffeine plasma concentrations, by Stendell-Hollis et al., compared to Wang et al. (9, 53).

All these studies have been of short duration, most lasting 12 weeks. Most of the research have failed to show a clinically significant, i.e. 5-10%, weight loss. However, 5.5% and 14.3% weight losses have been reported by Diepvens et al. and Pierre et al., respectively (38, 54). In the former study, reduction was due to 1207 mg catechins/day and 300 mg caffeine/day with hypocaloric diet in healthy females while the latter was due to 300 mg/day of Monoselect Camellia® (a preparation containing a standardized green tea extract complexed with phospholipids amount of catechins was not cited) with hypocaloric diet (38, 54). However, when compared with placebo, green tea has no effect on body weight or body composition (54).

Table 2 shows the WC reduction in several studies with catechins. Significant decrease in total fat area was observed with the doses of 690, 666 and 444 mg catechins/day; reduction in visceral fat area with 666, 583 and 444 mg catechins/day were observed; reduction in subcutaneous fat area was observed with 690 and 583 mg catechins/day; and reduction in abdominal fat area was observed with 625 mg of catechins/day during exercise (20, 27, 49, 52).

Catechins render better results on body weight and WC when combined with dietary control, physical activity and caffeine intake than ingesting catechins alone. Furthermore, maintaining the ratio of catechins:caffeine around 1:1 is important in weight reduction strategies (50).

### Body weight maintenance

Habitual high caffeine (270 mg EGCG + 150 mg caffeine/day) consumption was found to reduce the body weight, fat mass and WC more than in low caffeine consumption, through thermogenesis and fat oxidation. Weight maintenance after weight loss was not affected by green tea, supplying caffeine (104 mg/d) and catechins (573 mg/d) for 13 weeks, in overweight and moderately obese humans (55). However, habitual high caffeine consumption was associated with a higher weight regain compared with habitual low caffeine consumption (55).

Administration of EGCG and caffeine with diet supplying $\approx$10% total energy from protein is effective for weight maintenance following weight loss in overweight and moderately obese humans (3). However, considerably
Table 2. Effect of green tea on WC reduction

<table>
<thead>
<tr>
<th>Composition</th>
<th>WC reduction/cm</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Catechin/ (mg/d)</td>
<td>caffeine/ (mg/d)</td>
<td>WC</td>
</tr>
<tr>
<td>236 -6 months</td>
<td>-</td>
<td>0.9 NS</td>
</tr>
<tr>
<td>300(EGCG)</td>
<td>-</td>
<td>1.0 S</td>
</tr>
<tr>
<td>375 in an uncontrolled study</td>
<td>-</td>
<td>4.1 NS</td>
</tr>
<tr>
<td>444</td>
<td>-</td>
<td>0.9 S</td>
</tr>
<tr>
<td>458</td>
<td>104</td>
<td>1.1 NS</td>
</tr>
<tr>
<td>468</td>
<td>126</td>
<td>1.3 NS</td>
</tr>
<tr>
<td>491</td>
<td>-</td>
<td>1.7 S</td>
</tr>
<tr>
<td>583</td>
<td>-</td>
<td>0.7 S</td>
</tr>
<tr>
<td>625</td>
<td>-</td>
<td>0.9 NS</td>
</tr>
<tr>
<td>666</td>
<td>-</td>
<td>0.8 S</td>
</tr>
<tr>
<td>690</td>
<td>75</td>
<td>3.4 S</td>
</tr>
<tr>
<td>886</td>
<td>198</td>
<td>1.9 S</td>
</tr>
<tr>
<td>1207</td>
<td>-</td>
<td>4.5 S</td>
</tr>
</tbody>
</table>

S- Significant and NS- Non-significant at p<0.05

Pharmacokinetics

After ingestion peak plasma concentrations (C_max) of catechins were reached rapidly and gradually reduced to undetectable levels in 24 h (19, 56, 57). C_max, time to reach C_max and elimination half-life of EGCG rise in a dose dependent manner (19, 41). Caffeine or other catechins have been reported to affect the pharmacokinetics of EGCG (19, 74). Bioavailability of EGCG is higher than that of EGC and EC (19).

Oral bioavailability of catechins from supplements exceeds that of brewed tea (14). A significant fraction of the orally administered catechins is eliminated presystemically or is decomposed during intestinal absorption and in blood (11, 19, 41). This can result from ingestion of catechins with meals, transportation of absorbed EGCG back into intestine by P-gp, multi drug resistance gene product, and/or ionization of catechins when stomach pH is increased (3, 11, 39, 41). In contrast, Van het Hof et al. found that addition of skimmed milk has no effect on bioavailability of catechins (56). However, the percentage of milk added to tea used in this study is lower than that used in previous studies (56). Catechins were found in human saliva, blood and urine after mouth rinsing and oral administration of catechins as solutions (11).

The catechins are metabolized by the liver and kidneys, and excreted in bile and urine (11). They are subjected to extensive biotransformation including methylation, glucuronidation, sulfation and ring-fission metabolism (11). In plasma, EGCG and ECG have been reported to be mostly present in the free form (41, 57). EGCD and EC have been detected in plasma and urine, predominantly as glucuronic acid and sulfate conjugates (19). Free EC levels were very low or undetectable in plasma (19, 41). In physiological conditions, it is very likely that EGCG is oxidatively decomposed, but not (+)-catechin (11). The decomposition of EGCG and EGC was found in a short time, even at pH 7.4 (11).

Harmful effects

Green tea has been widely consumed in China and Japan for many centuries and is generally regarded safe (39). Table 3.0 summarizes the health effects of green tea intake in different quantities of catechins, caffeine and flavanols.

However, several cases were reported on hepatotoxicity of green tea intake in different products consumed for ≥ 1 month as shown in Table 4. In all cases, patients had taken the relevant product of green tea extract for weight maintenance and had not any history of liver disease, alcohol use and risk factors for viral hepatitis. According to case reports of consumption of
Table 3. Effect of green tea on health

<table>
<thead>
<tr>
<th>Composition/ (mg/d)</th>
<th>Time duration of the intake</th>
<th>Health effects</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>886 catechins and 198 caffeine</td>
<td>90 days</td>
<td>No differences of liver function tests</td>
<td>Wang et al., 2010 [9]</td>
</tr>
<tr>
<td>844 catechins</td>
<td>14 days</td>
<td>Alter the activity of the enzymes cytochrome P-450 2D6 and 3A4</td>
<td>Donovan et al., 2004 [58]</td>
</tr>
<tr>
<td>800EGCG</td>
<td>4 weeks</td>
<td>No alteration of phenotypic indices of CYP1A2, CYP12D6, and CYP12C9, but resulted in a small reduction in CYP3A4 activity</td>
<td>Chow et al., 2006 [59]</td>
</tr>
<tr>
<td>670 flavanols</td>
<td>3 weeks</td>
<td>No alterations of markers of liver and kidney function in healthy men</td>
<td>Frank et al., 2009 [60]</td>
</tr>
<tr>
<td>625 catechins and 39 caffeine</td>
<td>12 weeks</td>
<td>No liver toxicity</td>
<td>Maki et al., 2009 [52]</td>
</tr>
<tr>
<td>666 catechins</td>
<td></td>
<td></td>
<td>Kajimoto et al., 2005 [49]</td>
</tr>
<tr>
<td>800EGCG</td>
<td>4 weeks</td>
<td>No significant changes in blood counts and blood chemistry profiles</td>
<td>Chow et al., 2003 [57]</td>
</tr>
<tr>
<td>300EGCG</td>
<td>12 weeks</td>
<td>No adverse effects</td>
<td>Hill et al., 2007 [47]</td>
</tr>
<tr>
<td>583 catechins</td>
<td>12 weeks</td>
<td>No significant association between liver cancer risk and green tea consumption</td>
<td>Inoue et al., 2009 [61]</td>
</tr>
<tr>
<td>Population based study, Japan</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased consumption of green tea, meta analysis</td>
<td></td>
<td>Reduce the risk of liver disease</td>
<td>Jin et al., 2008 [62]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Sing et al., 2011 [63]</td>
</tr>
</tbody>
</table>

Green tea-based supplements, histological examination revealed inflammatory, cholestatic or necrotic liver damage depending on the subject (2). In ~20% of case reports, additional liver damage following re-challenge with the same preparation was observed (2). However, no clear determinants for the type of pathology observed have been reported (2). Oral bolus dosing results in greatly increased $C_{\text{max}}$ of EGCG compared with dietary administration and divided doses of the same total daily dose (2, 57). Caffeine content, presence of aluminum, and the affinity of catechins on iron are the major harmful effects of over consumption of tea (5). Green tea extracts may exert diuresis, excess gas, nausea, heartburn, stomachache, abdominal pain, diarrhea, dizziness, headache, muscle pain, increased levels of transaminases and serum bilirubin, blood pressure elevation and decreased dietary iron absorption (2, 5, 33, 46, 57). The incidence of gastrointestinal adverse events increased at higher doses under fasting conditions and with bolus dosing (41, 57). Green tea consumption is not advisable in cases of special sensitiveness to xanthic bases (5). Negative effects produced by caffeine are nervousness, sleep disorders, vomiting, headache, epigastric pain, tachycardia, palpitation, anxiety, restlessness, dizziness and high blood pressure (5, 39). Even though, acute caffeine consumption may alter some cardiovascular variables, chronic ingestion of caffeine has little or no health consequences (39).

Supplements of green tea contain much higher catechin and caffeine doses than green tea beverages, in different dosage forms and may cause harmful effects (2). Oral bolus dosing results in greatly increased $C_{\text{max}}$ of EGCG compared with dietary administration and divided doses of the same total daily dose (2, 57). Caffeine content, presence of aluminum, and the affinity of catechins on iron are the major harmful effects of over consumption of tea (5). Green tea extracts may exert diuresis, excess gas, nausea, heartburn, stomachache, abdominal pain, diarrhea, dizziness, headache, muscle pain, increased levels of transaminases and serum bilirubin, blood pressure elevation and decreased dietary iron absorption (2, 5, 33, 46, 57). The incidence of gastrointestinal adverse events increased at higher doses under fasting conditions and with bolus dosing (41, 57). Green tea consumption is not advisable in cases of special sensitiveness to xanthic bases (5). Negative effects produced by caffeine are nervousness, sleep disorders, vomiting, headache, epigastric pain, tachycardia, palpitation, anxiety, restlessness, dizziness and high blood pressure (5, 39). Even though, acute caffeine consumption may alter some cardiovascular variables, chronic ingestion of caffeine has little or no health consequences (39).

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Green tea and transient ischemic attack

A meta analysis from nine studies involving 4378
Anti-obesity effects of green tea extracts on humans

Table 4. Hepatotoxicity of green tea extract

<table>
<thead>
<tr>
<th>Composition</th>
<th>Age/year</th>
<th>Gender</th>
<th>Time duration of intake/Month</th>
<th>Harmful effect</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>720 mg/day green tea extract</td>
<td>44</td>
<td>Female</td>
<td>6</td>
<td>Acute liver toxicity with hepatitis</td>
<td>Molinari et al., 2006 [66]</td>
</tr>
<tr>
<td>Green tea extract</td>
<td>37</td>
<td>Female</td>
<td>4</td>
<td>Nausea, abdominal pain and jaundice</td>
<td>Bonkovsky, 2006 [67]</td>
</tr>
<tr>
<td>‘Hydroxycut’; green tea extract</td>
<td>27</td>
<td>Male</td>
<td>1</td>
<td>Fatigue and jaundice</td>
<td>Stevens et al., 2005 [68]</td>
</tr>
<tr>
<td>‘Euphoria’; herbal product</td>
<td>45</td>
<td>Female</td>
<td>1</td>
<td>Jaundice</td>
<td>Jimenez-Encarnacion et al., 2012 [69]</td>
</tr>
<tr>
<td>including green tea</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>‘SlimQuick’; herbal product</td>
<td>24</td>
<td>Female</td>
<td>3</td>
<td>Jaundice</td>
<td>Weinstein et al., 2012 [70]</td>
</tr>
<tr>
<td>including green tea</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>‘Fat burners’; green tea</td>
<td>28</td>
<td>Female</td>
<td>1</td>
<td>Jaundice</td>
<td>Krishna et al., 2011 [71]</td>
</tr>
<tr>
<td>‘Hydroxycut’ or Herbalife products; green tea extract</td>
<td>31</td>
<td>Female</td>
<td>3</td>
<td>Jaundice</td>
<td>Chen et al., 2010 [72]</td>
</tr>
<tr>
<td>‘Herbalife’ products; green tea</td>
<td>37</td>
<td>Female</td>
<td>4</td>
<td>Jaundice</td>
<td></td>
</tr>
<tr>
<td>extract</td>
<td>53</td>
<td></td>
<td>12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>‘Hydroxycut’; green tea extract</td>
<td>23</td>
<td>Female</td>
<td>2</td>
<td>Jaundice</td>
<td>Rashid and Grant, 2010 [73]</td>
</tr>
</tbody>
</table>

strokes among 194,965 individuals has revealed that daily consumption of either green or black tea equaling three cup per day could prevent the onset of ischemic stroke (64). Furthermore, regardless of their country of origin, individuals consuming ≥3 cups of tea per day had a 21% lower risk of stroke than those consuming <1 cup per day (absolute risk reduction, 0.79; CI, 0.73 to 0.85) (64).

However, according to a case report, transient ischemic attack-like symptoms could possibly be attributed to one or more components of oolong tea, especially when consumed in large quantities (65).

Conclusions

Catechins render a very modest effect on reducing body weight and waist circumference when combined with dietary control, physical activity and caffeine intake than ingesting catechins alone. However, 300 mg/d of Monoselect Camellia® is the only preparation that showed a clinically and statistically significant weight loss (14.3%). Nevertheless, this study was conducted with hypocaloric diet. Except very few studies most have been conducted for twelve week duration. Hence, further large randomized, long term studies are needed to determine whether this product demonstrates an anti-obesity effect with or without hypocaloric diet. Contrasting results have been found when green tea is used to maintain weight following weight loss. Current evidence on green tea does not support the use of it as an anti-obesity agent. There are several reports of side effects. The liver side effects are a cause for concern. Therefore long term use of green tea as over the counter supplement should not be encouraged. Rather it should be considered a drink, very much like any other tea or coffee, till further evidence of efficacy and safety are proven.

References

2. Grove KA, Lambert JD. Laboratory, epidemiological, and human intervention studies show that tea (Camellia sinensis) may be useful in the prevention of obesity. Journal of Nutrition 2010; 140: 446-51.


Anti-obesity effects of green tea extracts on humans


Prevalence and patterns of hirsutism among Sri Lankan females

N P Somasundaram¹, D J S Fernando², S Kamaladasa³, W K M G Amarawardena⁴


Abstract

Objectives: In order to describe the prevalence of hirsutism in young female population of Sri Lanka, we studied a group of young females to determine the pattern of body hair distribution and grade it according to the modified Ferriman-Gallwey score (mFG).

Method: A descriptive cross sectional study was conducted in the year 2000 with eighty-five female medical students who entered the Sri Jayawardenapura University that year. After consent, each subject was interviewed by a medical officer and an interviewer-administered questionnaire was utilized. The body hair distribution was recorded using the mFG score.

Results: Age of the study population ranged from 21 to 24 years. None of them have used steroids or psoralens prior to study. Only 3 (3.5%) had menstrual irregularity. The mode, Mean and the Median of the total MFG score were 5.0, 8.9 and 9.0 (IQR- 5 to 11) respectively. The prevalence of hirsutism was 56.5% (CI from 45.96 to 67.04) among the study population. Lower limb score had the highest mean value of 1.80 while Lip score had the lowest mean value of 0.31. All the 09 variables had statistically significant correlations with the total score while “lower abdomen score” had the strongest correlation of 0.82.

Conclusion: The prevalence of hirsutism among this young female population was relatively high (56.5%). They were seen to have a high degree of hair growth in all the areas tested on mFG score. The lower abdominal area had the strongest correlation with the mFG score. As many factors including genetic predisposition determine hirsutism this has to be considered when evaluation of young females for hirsutism.

Introduction

Hirsutism is defined as the presence of excessive terminal (coarse) hair in androgen-dependent areas of the female. It has been found that hirsutism negatively influences psychological well-being (2). Hirsutism is usually caused by benign functional conditions (idiopathic hirsutism), polycystic ovary syndrome, but may be the presenting symptom of a malignant tumor requiring immediate intervention. The prevalence of hirsutism is around 10% in most populations (3). The prevalence of hirsutism among Sri Lankan females is unknown. Studies demonstrate racial and genetic variation of hair distribution in females; Sri Lankan and Middle Eastern ethnic being hairier. Several hirsutism scores for women have been proposed based on visual assessment of hair type and growth (4-8).

Out of these methods, the modified Ferriman-Gallwey score (mFG) proposed by Hatch et al. is considered as the gold standard for the evaluation of hirsutism (9). This method uses 9 body areas. If there is no terminal hair growth a score of zero is given. Minimally visible terminal hair growth is given a score of 1, score of 2 is given if hair growth is more than minimal, a score of 3 is that of a not very hairy male while a score of 4 is what’s typically observed in well-virilized healthy adult male. A recommended cut-off value to define hirsutism is the 95th percentile of the mFG score of the relevant general population ethnicity (3). When this value is unavailable, a cut-off value of 8 or above is applied to White and Black women, while for Far East and South East Asian women this is decreased to three or above.

However modified Ferriman-Gallwey score (mFG) was not validated locally for the evaluation of hirsutism. It should also be noted that the mFG scoring system gives an estimation of the total amount of body hair, and not that of the regional distribution of the excessive hair growth. The validity of this system on Sri Lankan population has not been fully evaluated.

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Brief Research Communication

**Justification**

Detecting hirsutism with a cost-effective method yield physiological as well as psychological benefits for women. It helps early identification of treatable conditions. As documented local literature is not common, this study evaluates the burden of hirsutism in relation to local context. Several previous observational studies have suggested that specific body areas may be more related to total body hirsutism than others (9,10). Therefore evaluation of individual parameters of mFG score and their correlation would enable the future researches to decide on required modifications for a locally validated tool to screen for hirsutism.

**Objectives**

The objectives were to determine the prevalence of hirsutism among a group of young females, to determine the pattern of body hair distribution and grade them on mFG system and to describe correlation between individual parameters in the mFG with the total mFG score.

**Methods**

A descriptive cross sectional study was done after obtaining the ethical approval from the ethical review committee of University of Sri Jawardenapura. Study population was female medical students who entered the Sri Jayawardenepura University in the year 2000. Study setting was the routine medical screening that is performed for the entrants at the university medical centre. The total population of female medical students in that particular batch was taken to the study. Therefore eighty five female medical students participated in the study. Each subject was interviewed by a medical officer and an interviewer-administered questionnaire was utilized. The data collection tool comprised of a past medical history component and an examination component. The former included details about the use of long-term drug therapy (steroids, psorielens), and menstrual pattern. Irregular cycles were defined when the cycle length is more than 35 days. The latter component included the BMI calculation and the 09 parameters to calculate the mFG score. For detailed analysis, BMI cut off values suggested by Sri Lanka Endocrine Society based on Asian data were used. The participants were asked about their practices on cosmetic removal of body hair. The parameters for modified FG score included the grading of hirsutism of lip, chin, chest, upper abdomen, lower abdomen, upper limb, lower limb, upper back and of the lower back. The standard methodology mentioned in the section 1.1 was used in grading.

Data was entered in to a database and analysis was conducted in Statistical Package for Social Sciences (SPSS) version 16. The cutoff of mFG score was taken as 08 and the prevalence was expressed as a percentage. Descriptive analysis was done on the numerical score variables for each parameter and the total FG score. Correlation analysis was done using Spearman correlation coefficient. Significance of the mean scores of the groups with and without hirsutism (as detected by the modified FG score) was evaluated by Mann-Whitney U test.

**Results**

A total of eighty five female medical students were included in the survey. Age of the study population ranged from 21 to 24 years. Among them 84 students were unmarried and one student was married.

Table 1 summarizes the findings for the variables of past medical history. None of them have used steroids or psorielens prior to study. Only 3.5% (n=3) had menstrual irregularity.

Table 1. Distribution of parameters in past medical history

<table>
<thead>
<tr>
<th>Variable</th>
<th>Yes</th>
<th>No</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Used steroids or psorielens</td>
<td>00(0)</td>
<td>85(100)</td>
<td>85(100)</td>
</tr>
<tr>
<td>Irregular menstruation</td>
<td>03(3.5)</td>
<td>82(96.5)</td>
<td>85(100)</td>
</tr>
</tbody>
</table>

Table 2 shows the distribution of BMI. Total of 57 students participated for BMI assessment, out of which only 3 were obese. (5.3%) (Table 2). None of the obese females had menstrual irregularities. Four participants were using hair removing methods for cosmetic purposes. The minimum value of modified Ferriman-Gallwey score (mFG) was 2 and the maximum was 21. The Mode, Mean and the Median of the total score were 5, 8.9, and 9.0 respectively. (IQR- 5 to 11) Figure 1 depicts the distribution of mFG scores. The distribution curve was skewed to the right with 56.5% having a score ≥ 8.

Table 2. Distribution of BMI

<table>
<thead>
<tr>
<th>BMI category</th>
<th>Frequency</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Underweight (&lt;18.5)</td>
<td>5</td>
<td>8.8</td>
</tr>
<tr>
<td>Normal (18.5 - 22.9)</td>
<td>26</td>
<td>45.6</td>
</tr>
<tr>
<td>Overweight (23 - 24.9)</td>
<td>23</td>
<td>40.4</td>
</tr>
<tr>
<td>Obese (equal or &gt; 25)</td>
<td>3</td>
<td>5.3</td>
</tr>
<tr>
<td>Total</td>
<td>57*</td>
<td>100.0</td>
</tr>
</tbody>
</table>

*Missing data in BMI assessment was 29
Fourty eight students had score of 8 or more in modified Ferriman-Gallwey score (mFG), giving a hirsutism prevalence of 56.5% (CI from 45.96 to 67.04) amongst the study population. None of them had other features of virilization on physical examination.

Table 3. Descriptives of individual mFG parameters and their correlation with total mFG score

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean</th>
<th>Median</th>
<th>Spearman Correlation</th>
<th>Significance</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upper Lip</td>
<td>0.31</td>
<td>0</td>
<td>0.49</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Chin</td>
<td>0.35</td>
<td>0</td>
<td>0.40</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Chest</td>
<td>1.18</td>
<td>1</td>
<td>0.77</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Upper abdomen</td>
<td>1.18</td>
<td>1</td>
<td>0.77</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Lower Abdomen</td>
<td>1.46</td>
<td>1</td>
<td>0.82</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Upper limb</td>
<td>1.53</td>
<td>1</td>
<td>0.49</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Lower limb</td>
<td>1.80</td>
<td>2</td>
<td>0.70</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Upper back</td>
<td>0.34</td>
<td>0</td>
<td>0.53</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Lower back</td>
<td>0.47</td>
<td>0</td>
<td>0.54</td>
<td>&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>

Table 3 summarizes the means, medians and correlations with total score, of the 09 variables of mFG score. Lower limb score had the highest mean value of 1.80 while Lip score had the lowest mean value of 0.31. All the 09 variables had statistically significant correlations with the total score while “lower abdomen score” had the strongest correlation of 0.82. Chin score had the lowest correlation with the total score.

All the parameters of the mFG score had a significant association with the hirsutism status (either presence or absence).

Table 4. Association between hirsutism status and parameters of mFG score

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean rank</th>
<th>Significance*</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upper Lip</td>
<td>48.38</td>
<td>36.03</td>
<td>0.002</td>
</tr>
<tr>
<td>Chin</td>
<td>47.43</td>
<td>37.26</td>
<td>0.020</td>
</tr>
<tr>
<td>Chest</td>
<td>55.18</td>
<td>25.91</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Upper abdomen</td>
<td>56.18</td>
<td>25.91</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Lower Abdomen</td>
<td>57.32</td>
<td>24.42</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Upper limb</td>
<td>50.83</td>
<td>32.84</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Lower limb</td>
<td>55.49</td>
<td>26.80</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Upper back</td>
<td>50.56</td>
<td>33.19</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Lower back</td>
<td>51.51</td>
<td>31.96</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*Using Mann Whitney U test

Figure 1. Distribution of mFG scores
Discussion

In our study only 3 students were found to have obesity according to the revised Sri Lankan obesity guideline cutoff, and only 3 students had menstrual irregularities. None of the obese females had menstrual irregularities. Therefore the study population was considered as a relatively healthy population and further investigations for PCOD and other rare causes for hirsutism was not carried out. However, not continuing with tests to exclude an underlying pathology is a short coming of this study.

Most studies reveal the prevalence of hirsutism around 10% in most populations. Indian study by Zargar et al. (2002) showed a prevalence of 10.5%(11). A Spanish study by Asuncion et al. (2000), Turkish study by Sagsoz et al. (2004), USA study by DeUgarte et al. (2006), Iran study by Noorbala and Kefai (2010) described a prevalence of 7.1%, 8.3%, 5.4%, 10.8% respectively (12-15). An Australian study done by March et al. (2010) showed a higher prevalence of 21.2% in a white Caucasian population (16). All the studies have used mFG score to assess hirsutism.

In our study, the strength of correlation between the total score and the individual nine parameters showed diversity from 0.40 to 0.82. But the abdominal score had the strongest correlation with the total mFG score. In a similar study by Homeira Rashidi et al showed that evaluation of terminal hair growth on the chin or lower abdomen has a high sensitivity for predicting hirsutism. (18). Knochenhauer ES et al also found that hair growth score of 2 or more on the chin or lower abdomen only was found to be a highly sensitive predictor for hirsutism in high-risk populations with an expected hirsutism prevalence of >20% (10).

Our study showed a higher prevalence of 56.5%. Racial difference in prevalence of hirsutism as well as inter observer variability in recording the mFG score can be contributing factors for this difference. Poor validity of the cut off used can be another cause for this higher value of hirsutism. Therefore it highlights the importance of a locally validated cut off for the mFG for Sri Lanka rather than using a blanket cut off of 8.

In our study subjects had mFG scores ranging from 2 to 21. The most frequently affected site was the lower limb, but the most densely affected area was also found to be the lower limb. In a study on assessment of hirsutism among Korean women showed that the most frequently affected site was the upper back, but the most densely affected area was the lower abdomen (17).

Our study also showed a statistically significant association between hirsutism score and the individual means of nine body sites.

In our study, the strength of correlation between the total score and the individual nine parameters showed diversity from 0.40 to 0.82. But the abdominal score had the strongest correlation with the total mFG score. In a similar study by Homeira Rashidi et al showed that evaluation of terminal hair growth on the chin or lower abdomen has a high sensitivity for predicting hirsutism. (18). Knochenhauer ES et al also found that hair growth score of 2 or more on the chin or lower abdomen only was found to be a highly sensitive predictor for hirsutism in high-risk populations with an expected hirsutism prevalence of >20% (10).

Conclusions

The prevalence of hirsutism among a group of female university entrants to Sri Jayawardenapura University was 56.5% (CI from 45.96 to 67.04). All the nine parameters of the mFG score are significantly associated with the final hirsutism score (p < 0.05). Out of them strongest correlation was observed with the lower abdominal score (Spearman correlation coefficient – 0.82).

Recommendations

A larger population based study to determine the normative data for Sri Lankan women is a priority and will help develop age standardized data. Minimizing the number of examiners and training examiners prior to evaluation of the score will be helpful to minimize inter-observer variation. Use of photographic representation of mFG scoring system will also be helpful to reduce inter-observer variation.

References


Images in Endocrinology

Pituitary stalk interruption syndrome (PSIS) – a rare cause of short stature

M S A Cooray1, N P Somasundaram1, T Rajapakse2, S Dayaratne2, H Chandrasena3


A 16 year old girl was evaluated for short stature and delayed puberty. She was noted to be shorter than her twin sister since infancy. Her parents, twin and two other siblings had normal growth and development. Although her twin went through puberty at 12 years of age, she failed to develop any sign of puberty. There were no symptoms of hypothyroidism, adrenal insufficiency, polydipsia or polyuria.

The patient was a product of non-consanguineous marriage and the first born of twins, delivered with breech presentation. Although there was a history of early neonatal seizures with prolonged ICU stay and delayed developmental milestones compared to her twin, there had been no chronic medical problems later on and she performed well at school. The social, family and peer interactions were normal with no behavioural problems. There was no history of short stature or primary amenorrhoea in the family.

On examination her height and weight were less than the 3rd percentile and she was pre pubertal (Tanner stage 1). White blood count (WBC), erythrocyte sedimentation rate (ESR), urinalysis (UA), and serum electrolytes were normal. Her hormone analysis is shown in table 1.

The X ray hand showed the bone age to be 6 years (Pyle and Greulich).

MRI brain revealed an absent anterior pituitary, performed well at school. The social, family and peer interactions were normal with no behavioural problems. There was no history of short stature or primary amenorrhoea in the family.

MRI brain revealed an absent anterior pituitary, ectopic posterior pituitary located in the region of the hypothalamus with absent pituitary stalk.

Figure 1. MRI brain (a) sagittal and (b) axial images showing an absent anterior pituitary and ectopic posterior pituitary located in the region of the hypothalamus with absent pituitary stalk.

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Pituitary stalk interruption syndrome (PSIS) – a rare cause of short stature

A diagnosis of panhypopituitarism with intact posterior pituitary function was made and she was treated with thyroxine, hydrocortisone and growth hormone replacement therapy as well as low dose oestrogen therapy to induce puberty.

<table>
<thead>
<tr>
<th>Table 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thyroid stimulating hormone</td>
</tr>
<tr>
<td>FreeT4</td>
</tr>
<tr>
<td>Follicle-stimulating hormone</td>
</tr>
<tr>
<td>Luteinizing hormone</td>
</tr>
<tr>
<td>Prolactin</td>
</tr>
<tr>
<td>Peak growth hormone (GH) response</td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

Discussion

PSIS is a rare disorder of which the exact aetiology is uncertain. It is characterised by the absence of the pituitary stalk, anterior pituitary hypoplasia, and an ectopically located posterior pituitary. The clinical syndrome may be one of isolated GH deficiency or multiple anterior pituitary hormone deficiencies. The posterior pituitary function has been shown to be normal in these patients (1). A study of 55 patients with PSIS revealed documented breech delivery in 88.9% of the patients and the prevalence of deficiencies in growth hormone, gonadotropins, corticotropin, and thyrotropin were 100%, 95.8%, 81.8% and 76.3%, respectively (2). Timely diagnosis and replacement of the deficient hormones is the key to the management of these patients.

References

Endocrine similes in public speech

S Kalra¹, Y Gupta², S Julka³


Introduction

Endocrinology is a vast subject, full of uncharted dimensions and unexpected vistas. A relatively young specialty, endocrinology is at centre stage of scientific attention today. The ever-increasing number of Nobel prizes awarded to endocrine discoveries (1), approvals given to endocrine drugs (2), and grants awarded for endocrine research bear testimony to this. In parallel, endocrinology has made great inroads into popular culture, with hormones becoming an integral part of modern communication and social media.

Endocrinology is a field which can be exapted (3), or utilized, for multiple purposes. Endocrine terminology lends itself to both scientific as well as colloquial use. Though the endocrine profession is probably incapable of regulating or “policing” the use of endocrine words as nouns and adjectives, it should take the onus of educating the public about appropriate meanings and connotations of various hormones.

Quality of speech

Public speech, for example, can be described in terms of endocrine similes. We are all familiar with melatoninergic speakers who put us to sleep. While other medical specialties may prefer to use the descriptive ‘somniferous’ or sedative’, melatoninergic provides a more vivid picture of the effect a boring speaker can have on an unsuspecting audience.

Just as endocrinology is a multifaceted subject, there are multiple ways of describing unappetizing lectures. A lecture delivered at hypothalamic level, for example, would not be understood by the intended audience. A speech full of flattery and sycophancy could be called a glucotoxic delivery, while one with unnecessary padding may be termed lipotoxic. An overloaded talk may deserve the adjective of maladaptive anabolism, while an extremely long speech which causes starvation-induced weight loss can be called catabolic, cachexic, or a verbal bariatric surgery.

Duration of speech

The ideal length of a public discourse varies from speaker to speaker, topic to topic, and listener to listener. An ideal oration, however, can be likened to insulin: it should have a short half life (intravenous insulin t½: 3-5 minutes) but should pack a powerful punch. (Insulin: the most potent anabolic hormone in the body). A similar analogy can be drawn with incretins: an audience-friendly talk should be short like GLP-1’s half-life, but long enough to have an impact, like GLP-1 receptor agonists (GLP1RAs). Another comparison would be with insulin analogues: the ideal address should have the length of an ultra-fast acting as part, and the retention quality of ultra-long acting degludec.

Impact of speech

Metabolic memory or glycemic legacy is a phrase which deserves a place in the endocrine lexicon of rhetoric: the best oratory is one that is remembered long after it is delivered, and which leaves a legacy for future generations. While some talks have an impact as short as the half-life (in minutes) or amino-acid chain length of oxytocin [n=3 and 9, respectively], others last as long as the duration of action of zoledronic acid (1 year).

Quality of speaker

Just as endocrinology moves from a glucocentric to a comprehensive approach in diabetes management, the endocrine description of rhetoric includes terminology beyond that of diabetes pathophysiology and pharmacotherapy.

Some authors are known for the instant connect they build with the audience: perhaps they can be described as oxytocin-rich or oxytocinergic speakers. They are able to create a positive feedback with the audience, in contrast to the negative feedback pathways normally associated with endocrine physiology. It must be noted, here, that oxytocin is perhaps the only hormone which is able to kick-start a positive feedback loop with uterine contractions.

Yet other orators bring a relaxed old world charm to their public interactions. Speaking in an unhurried manner, perhaps estrogen dominates their hormonal landscape. Whether a distinguished male speaker would appreciate

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being identified as an estrogenic orator is open to debate, though.

The other glands, too, add hormonal spice to the adjectives that define public speech. An adrenergic speaker is one who exudes energy in his verbal and non verbal language, while an Addisonian orator would imply the opposite. The term dopaminergic can also be utilized to present an educated, intelligent, and energetic speaker who needs no rest: dopamine is the predominant catecholamine in the brain.

The phrase ‘thyrotoxic speaker’ world conjure a mental picture of a fast-speaking orator, with excessive hand, ocular, and facial gestures, while a hypothyroid orator would make use of long, unnecessary pauses. A “speech full of testosterone” or an androgenic delivery would qualify an oration marked by bravado and “machismo” talk, while a hypogonadal debate would suggest a weak-kneed response. The descriptor ‘hypercalcemic speaker’ may be interpreted by hard core endocrinologists to mean a “constipated” speaker full of attitude and airs.

**The audience**

Endocrine similes are not limited to speaking; they can be used to paint word-pictures of the audience as well. A hypoglycemic audience would be one which was disinterested in a programme, looking forward to the cocktail or dinner instead. An audience full of glucagon may imply one which has no appetite for learning. The paradox of hypoglycemia and hyperglucagonemia describing a similar set of listeners will not be lost upon the endocrinology reader of this article. NASH (non-academic silent honchos) is an acronym that can be used to describe a disinterested audience as well.

It needs mention here that melatoninergic effects, including yawning and power-naps, can be contagious. This conjures the para-endocrine concept of pheromones, or external neurotransmitters, which mediate inter-individual communication.

Paracrine effects, such as one member of the audience taking a neighbor out of the hall, are all too frequent today. These are an extension of the apoptosis (vacant chairs) seen in empty auditoria. Of course, the endo-literate delegate will always have a suitable excuse – he may blame his dihydrotestosterone for causing prostatomegaly, while she may invoke a high progesterone phase to explain her disinterest. Neuro-endocrinologically minded colleagues may wish to assess vasopressin (antidiuretic hormone) secretion before sitting to attend long sessions.

A Grave audience may not necessarily be grave and serious: a talkative group will leave the impression of a collective Graves’disease, with the modern triad of silent eye gestures, conversations, and mobile texting, during an unsuspecting speaker’s talk.

**Conclusion**

Endocrinology has contributed significantly to the advancement of basic and clinical science. These in turn, have helped enhance our understanding and management of hormonal disease. This mutually beneficial bidirectional relationship helps spawn original ideas, which in turn facilitate discovery of newer innovations that expand the borders of science. Similarly, the use of endocrine similes in speech in scientifically correct and literally apt manner should help both endocrinology and communication grow in tandem with each other.

**References**

Instructions to Authors


Purpose and Scope

The Sri Lanka Journal of Diabetes, Endocrinology and Metabolism (SJDEM) publishes original research articles, reviews, and other special features related to diabetes, endocrinology and metabolism in humans and human tissue.

General Information

Manuscripts must be written in fluent English and conform to the specifications described below. Manuscripts submitted to SJDEM are evaluated by peer reviewers. Authors of manuscripts requiring modifications have two (2) months to resubmit a revision of their paper. Manuscripts returned after more than two (2) months will be treated as new submissions. An unsolicited revision of a rejected manuscript will either be returned or treated as a new submission, at the editor’s discretion.

Manuscript Categories

All manuscripts must adhere to the word count limitations, as specified below, for text only; the word count does not include the abstract, references, or figure/table legends. The word count must be noted on the title page, along with the number of figures and tables.

- **Original Articles** – Word count 3600 and include a maximum of six figures and tables and 40 references.

- **Brief Reports** must include focused studies with important, but very straightforward, negative or confirmatory results. Word count 1800 with maximum of two figures and tables and 20 references.

- **Clinical Reviews** and other **Reviews** should address topics of importance to clinical endocrinologists, researchers and clinicians. Word count 4000 with maximum four figures and tables and 60 references. A brief section describing the search strategies used to obtain information is required.

- **Case Report** must describe a single case or small series that reveals a novel and important insight into a condition’s pathogenesis, presentation, and/or management. The case report must include a concise scholarly review of relevant literature pertaining to the disorder. Word count 2400 with maximum four figures and tables and 20 references.

- **Extensive Clinical Experiences** are learned descriptions of substantial clinical experience with a specific endocrine or metabolic disorder, or class of disorders, by a single clinical endocrinologist or facility. Word count 3600 and maximum four figures and tables and 40 references.

Position and Consensus Statements related to the endocrine and metabolic health standards and healthcare practices may be submitted by professional societies, task forces, and other consortia. All such submissions will be subjected to peer review, must be modifiable in response to criticisms, and will be published only if they meet the Journal’s usual editorial standards. Word count 3600 with maximum six figures and tables and 120 references.

Controversies in Clinical Endocrinology must describe and justify different approaches to diagnosis and/or management of patients with an endocrine or metabolic condition. This is ideally authored by two individuals who thoughtfully describe their respective clinical perspectives on a clinical problem, practice that must include the rationale and evidence. Word count 2400 with maximum two figures and tables and 20 references.

Images in Endocrinology require a single figure or two closely related figures that illustrate the value of visual information in clinical diagnosis of endocrine and metabolic disorders, with a caption that is 50 words or less, and a commentary of 250 words or less, and five or fewer references.

Commentaries are essentially uninvited editorials, which should concisely address and take a well-reasoned position on a timely issue of importance to clinical endocrinologists and/or investigators. Word count 1200 with maximum 10 references; no figures or tables are permitted.

Letters to the Editor may be submitted in response to work that has been published in the Journal. Letters should be short commentaries related to specific points of agreement or disagreement with the published work. Letters are not intended for presentation of original data unrelated to a published article. Word count 500 with maximum five complete references and no figures or tables.

Manuscript Submission Procedures

SJDEM only uses electronic manuscript submission. Please email to endocrinesl@gmail.com

All submissions must include:

- A cover letter requesting that the manuscript be evaluated for publication in SJDEM and any information relevant to your manuscript.
- Completed Copyright Assignment and Affirmation of Originality form.
- Completed Disclosure of Potential Conflict of Interest form.
**Manuscript Preparation**

**General Format**

The Journal requires that all manuscripts be submitted in a single-column format that follows these guidelines:

- All text should be double-spaced with 1-inch margins on both sides using 11-point type in Times Roman font.
- All tables and figures must be placed after the text and must be labeled. Submitted papers must be complete, including the title page, abstract, figures, and tables. Papers submitted without all of these components will be placed on hold until the manuscript is complete.
- Authors are encouraged to cite primary literature rather than review articles in order to give credit to those who have done the original work.
- Any supplemental data intended for publication must meet the same criteria for originality as the data presented in the manuscript.

**Title Page**

The title page should include the following:

- Full title (a concise statement of the article’s major contents)
- Authors’ names and institutions. At least one person must be listed as an author; no group authorship without a responsible party is allowed. A group can be listed in the authorship line, but only on behalf of a person or persons. All group members not listed in the authorship line must be listed in the Acknowledgments.
- Abbreviated title of not more than 40 characters for page headings
- At least three key terms for indexing and information retrieval
- Word count (excluding abstract, figure captions, and references)
- Corresponding author’s e-mail and ground mail addresses, telephone and fax numbers
- Name and address of person to whom reprint requests should be addressed
- Any grants or fellowships supporting the writing of the paper
- Disclosure summary (see Disclosure of Potential Conflict of Interest form for instructions)
- Clinical Trial Registration Number, if applicable

**Structured Abstracts**

All Original Articles, Brief Reports, Clinical Reviews, Case Reports, Consensus and Position Statements, Controversies in Endocrinology, and Extensive Clinical Experiences should be submitted with structured abstracts of no more than 250 words. All information reported in the abstract must appear in the manuscript. The abstract should not include references. Write the abstract with a general medical audience in mind. Please use complete sentences for all sections of the abstract.

**Introduction**

The article should begin with a brief introductory statement that places the work to follow in historical perspective and explains its intent and significance.

**Materials and Methods**

These should be described and referenced in sufficient detail for other investigators to repeat the work.

**Results and Discussion**

The Results section should briefly present the experimental data in text, tables, and/or figures. The Discussion should focus on the interpretation and significance of the findings with concise objective comments that describe their relation to other work in that area.

**Acknowledgments**

The Acknowledgments section should include the names of those people who contributed to a study but did not meet the requirements for authorship. Each person listed in the acknowledgments must give permission for the use of his or her name.

**References**

References to the literature should be cited in numerical order (in parentheses) in the text and listed in the same numerical order at the end of the manuscript on a separate page or pages. Examples of the reference style that should be used are given below. For further examples refer Ann Intern Med. 1988; 108: 258-265 and Br Med J. 1988; 296: 401-405.

**Journal articles and abstracts:** List all authors when six or less; when seven or more, list only first three and add et al. If it is necessary to cite an abstract because it contains substantive data not published elsewhere, it must be designated at the end of the reference [e.g., 68:313 (Abstract)].

**Books:** List all authors or editors.

**Sample References**


Instructions to authors

Tables

Tables must be constructed as simply as possible and be intelligible without reference to the text. Each table must have a concise heading. A description of experimental conditions may appear together with footnotes at the foot of the table. Tables must not simply duplicate the text or figures. The width of the table must be designed to occupy one or two journal columns.

Figures and Legends

Sizing the figure: The author is responsible for providing digital art that has been properly sized, cropped, and has adequate space between images. Plan the size of the figure to fill 1, 1.5, or 2 columns in the printed journal. In most cases, figures should be prepared for 1-column width. Produce original art at the size it should appear in the printed journal. On the submission page, check boxes to indicate that the figures are the correct size and resolution.

Units of Measure

Results should be expressed in metric units. Systeme Internationale (SI units) must be added in parentheses. Temperature should be expressed in degrees Celsius (e.g., 28°C) and time of day using the 24-hour clock (e.g., 0800 h, 1500 h).

Standard Abbreviations

All nonstandard abbreviations in the text must be defined immediately after the first use of the abbreviation.

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Prior Publication

The journal publishes original research and review material. Material previously published in whole or in part shall not be considered for publication. At the time of submission, authors must divulge in their cover letter all prior publications or postings of the material in any form of media. Abstracts or posters displayed for colleagues at scientific meetings need not be reported.

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An author should have participated in either the conception, planning, or execution of the work, the interpretation of the results and the writing of the paper. An acknowledgment accompanying the paper is appropriate recognition for others who have contributed to a lesser extent.

Experimental Subjects

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Experimental Animals

A statement confirming that all animal experimentation described in the submitted manuscript was conducted in accord with accepted standards of humane animal care should be included in the manuscript.

Clinical Trials Registration

Clinical trials require their prospective registration. The Clinical Trial Registration number should be provided clearly on the title page of the manuscript.

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Best practice guidelines for ASEANPlus

Management of diabetic foot wounds

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Preface

While there are several clinical practice guidelines for managing diabetic foot problems, none have yet been developed for ASEAN. The ASEAN Plus Expert Group Forum has been formed in November 2012 to address this issue. Its objective is to develop clinical guidelines to raise the standard of health care provided to patients with diabetic foot wounds in ASEAN Plus countries. Such best practices will benefit healthcare professionals treating such individuals. Two experts have been invited from each member country, namely Indonesia, Malaysia, Philippines, Singapore, Sri Lanka and Thailand to serve a term of 2 years. Members include orthopaedic surgeons, vascular surgeons, a general surgeon, a plastic surgeon and endocrinologists. We would like to thank Smith & Nephew Singapore Pte Ltd for their educational support and sponsorship.

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Annexures 1: Assessment Form
**Quick Reference Guide**  
**Best Practice Recommendations**

### Section 1: Prevention of Foot Ulcer and Amputation
- Prevent development of diabetic neuropathy.
- Prevent ulcer development by promoting good care of feet by patients.
- Encourage patients to go for regular foot screening.
- Offer early intervention or refer to a specialist when foot problems develop.
- Prevent below-knee amputation by good control of diabetes and good care of the feet to prevent early foot complications.

### Section 2: Assessment and Investigation
- Perform a thorough assessment of a patient with a diabetic foot problem.
- Perform general laboratory investigations.
- Send material for culture.
- Perform Radiological tests.

### Section 3: Medical Treatment
- Aim for good glycaemic control in all patients with diabetic foot ulcer.
- Nutrition should be individualized.
- Improve the nutritional status in malnourished patients.
- When patients are kept fasting provide carbohydrate.
- Prepare the wound bed to facilitate wound healing.
- Infection should be identified early and managed appropriately to avoid limb loss.
- Antibiotics should be used appropriately.
- Antibiotics should be used in conjunction with other treatments.
- Look for underlying osteomyelitis in all wounds.
- Use the TIME guide to guide aim of care and dressing selection.
- Choose the appropriate wound dressing based on wound characteristics.
- Use alternative technology where appropriate to aid wound healing.

### Section 4: Surgical Treatment
- Perform adequate debridement to remove all devitalised or infected tissue.
- Perform split skin graft for large granulating wound.
- Perform minor (distal) amputation where possible.
- Perform amputations if indicated.
- Perform rehabilitation early.
- Perform limb salvage when possible by carrying out revascularisation.
- Perform primary proximal amputation when limb salvage is not possible.

### Introduction
Diabetes currently affects 366 million people worldwide or 8.3% of the world's adult population. This figure is expected to increase to 9.9% by 2030 (Table 1), owing to environmental factors such as sedentary lifestyles and changing dietary patterns. Now the fourth leading cause of death in most developed countries, diabetes has been considered as the "global epidemic of the 21st century".
Foot wounds are very common among diabetic patients, affecting about 15% of all diabetic patients in developed countries. They are a major cause of amputations. Approximately 85% of all amputations begin with a wound. A diabetic patient is up to 40 times more likely to receive a lower limb amputation. Currently, it is estimated that every 20 seconds a leg is lost due to diabetes globally. Lower limb amputations often cause mortality in diabetic patients: 70% of them die within five years after an amputation.

Nomenclature: In this guideline the term ‘diabetic foot wound’ is synonymous with ‘diabetic foot ulcer.’

Pathogenesis
To manage Diabetic Foot wounds, one must first understand their pathogenesis – the “Diabetic Foot Triad” (Figure 1). 3 risk factors – Neuropathy, Vasculopathy and Immunopathy – contribute to varying degrees in different patients.

Types of wounds

Infective wounds
Usually found on the dorsum of the foot or in the web space.
**Ischaemic wounds**

Result from diabetic vasculopathy. Signs of chronic ischaemia are shininess of the skin, loss of hair, increased skin pigmentation and trophic nail changes. However in most diabetic foot ulcers there is a degree of ischemia, which is not severe enough to be apparent but promotes infection and causes delay in healing and increases risk of amputation.

**Both infective and ischaemic**

Some wounds have features of both infection and ischaemia.

**Neuropathic wounds**

Usually occur in weight bearing areas as a result of loss of protective sensation and high pressure points from changes in the mechanics of the foot.

**Decubitus wounds**

Occur when too much pressure is constantly placed on the skin. Common sites include the heel, lateral malleolus and the lateral aspect of the 5th metatarsal.

**Classification Systems**

For our guidelines, we have adopted the Wagner-Meggitt Wound Classification\(^5,6\) for classifying the wounds. In addition, the King’s College Classification\(^7\) is also used.

**Wagner-Meggitt Wound Classification**

This classification (Table 2 and Figure 7) was first described by Meggitt in 1976\(^5\) and popularised by Wagner in 1981\(^6\). It is a six-grade system that classifies ulcers according to the depth and extent of wound. Advantages of the Wagner-Meggitt Wound Classification include its simplicity in usage. It also provides a guide for practitioners to plan treatment. Disadvantages include the fact that infection is only taken into account in Grade 3 and ischaemia in Grades 4 and 5.
Table 2. Wagner-Meggitt Wound Classification

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description of ulcer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 0</td>
<td>Pre- or post-ulcerative lesion completely epithelialized</td>
</tr>
<tr>
<td>Grade 1</td>
<td>Partial/ full-thickness ulcer confined to the dermis, not extending to the subcutis</td>
</tr>
<tr>
<td>Grade 2</td>
<td>Ulcer of the skin extending through the subcutis with exposed tendon or bone. No abscess formation or osteomyelitis</td>
</tr>
<tr>
<td>Grade 3</td>
<td>Deep ulcer with abscess formation or osteomyelitis</td>
</tr>
<tr>
<td>Grade 4</td>
<td>Localised gangrene of the toes or partial foot gangrene</td>
</tr>
<tr>
<td>Grade 5</td>
<td>Whole foot gangrene</td>
</tr>
</tbody>
</table>

![Figure 2. Wagner-Meggitt Wound Classification](image)

King’s College Classification

The King’s College Classification (Table 3) is a simple staging system. It is based on the types of clinical presentation of the diabetic foot – ulcer, cellulitis, gangrene and amputation. The advantage of this system is that it is simple to use and is useful for planning the appropriate treatment for each stage. Its disadvantage is that it has not been well validated.

Table 3. King’s College classification

<table>
<thead>
<tr>
<th>Stage 1. Normal foot</th>
</tr>
</thead>
<tbody>
<tr>
<td>There is no risk factor in the normal foot (Figure 1). There is no neuropathy. Both foot pulses are palpable. There is no deformity, callosity or swelling.</td>
</tr>
</tbody>
</table>
Stage 2. High-risk foot
One or more risk factors for ulceration are present – namely sensory neuropathy or ischaemia. In the latter, one or both distal pulses are not palpable. There may be deformity, callosity, previous ulceration or previous amputation in the foot.

Stage 3. Ulcerated foot
This stage presents with skin breakdown or an ulcer. Ulceration usually occurs on the plantar surface in the neuropathic foot and on the dorsum of the foot in infection.

Stage 4. Cellulitic foot
There is cellulitis with infection of the skin and subcutaneous tissue.

Stage 5: Necrotic foot
This is characterized by the presence of necrosis or gangrene (Figure 5). Common sites of involvement are toes (one or more) and heel of the foot. They present as dry gangrene (no superimposed infection) or as wet gangrene (with superimposed infection).

Stage 6. Major amputation
Major amputation is defined as one taking place above the ankle joint – namely below knee, through knee and above knee amputation. Causes of below knee amputation include agonising pain in the foot, overwhelming infection in the foot and extreme necrosis or gangrene involving the foot.
References

Prevention of foot ulcer and amputation

70% of all amputations happen to patients with diabetes mellitus. 85% of the amputations in diabetes patients can be prevented by prevention, organized care given by multi-disciplinary teams, close monitoring, and education of patients.

Recommendation 1: Prevent development of diabetic neuropathy
1. Prevent development of diabetes mellitus in population
2. Achieve early metabolic control in those who have developed diabetes. This encompasses
   i. good glycemic control
   ii. keeping blood pressure under control
   iii. avoidance of smoking and excessive alcohol

Recommendation 2: Prevent development of ulcers by promoting good care of feet by patients
1. Motivate patients to take care of their feet
2. Educate patients on
   a. Importance of appropriate footwear and choosing footwear/socks
   b. Daily inspection of feet and footwear
   c. Application of moisturizer
   d. Identifying problems in the feet such as infection, blisters, callus

Recommendation 3: Encourage patients to go for regular foot screening
1. Offer annual comprehensive foot examination for all patients with diabetes.
2. More frequent examination will be required for those who have problems.
3. The foot examination should include:
   a. Inspection (footwear, dry skin, callus, fissures, amputations, ulcers, deformities)
   b. Assessment of vascularity
      i. Palpation of dorsalis pedis and posterior tibial pulses are most reliable
      ii. History of claudication may be absent due to neuropathy or patient not walking
      iii. Ankle-Brachial-Pressure Index (ABPI) <0.9. This may be elevated despite poor flow.
c. Testing for loss of protective sensation (LOPS). This is determined by >1 of the following
   i. Lack of sensation
   ii. Sensory loss on testing (10-g monofilament plus testing any one of the following: vibration using 128-Hz tuning fork, pinprick sensation, or vibration perception threshold)
   iii. Loss of ankle reflexes

4. Risk stratify based on findings (see Table 4 and Figure 3)
   a. Risk factors that are used for risk stratification include:
      i. Previous ulcer or amputation
      ii. Sensory neuropathy
      iii. Peripheral vascular disease
      iv. Deformity or callus
   b. Risk stratification enables patients to be managed in a cost effective manner, with more frequent follow up and more aggressive management for patients with increased risk.

<table>
<thead>
<tr>
<th>Risk category</th>
<th>Definition</th>
<th>Recommended action</th>
<th>Review</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low risk foot</td>
<td>No risk factors</td>
<td>Foot care education</td>
<td>Annually</td>
</tr>
<tr>
<td></td>
<td>No previous ulceration</td>
<td>Optimize metabolic control</td>
<td></td>
</tr>
<tr>
<td>High risk foot</td>
<td>One Risk Factor</td>
<td>Special footwear</td>
<td>Every 3-6 months</td>
</tr>
<tr>
<td></td>
<td>No previous ulcer</td>
<td>Offer intervention</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Optimize control</td>
<td></td>
</tr>
<tr>
<td>Super high risk foot</td>
<td>Previous Ulceration/Amputation</td>
<td>Special footwear</td>
<td>Every 2-3 months</td>
</tr>
<tr>
<td></td>
<td>or Two of the risk factors</td>
<td>Offer intervention</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Optimize control</td>
<td></td>
</tr>
<tr>
<td>Foot emergencies</td>
<td>Ulcer, injury, infection</td>
<td>Assess depth and VIP</td>
<td>Every 1-2 months</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(Vascular, infection, pressure)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Manage as appropriate</td>
<td></td>
</tr>
</tbody>
</table>

Table 4. Risk classification of diabetic foot

Recommendation 4: Offer early intervention or refer to a specialist when foot problems develop

1. If there is LOPS or deformities: Provide special foot wear and monitor closely
2. Shave callus
3. Clip nails
4. If the pulses are not normal evaluate further or refer to vascular specialists

Recommendation 5: Prevent below-knee amputation by good control of diabetes and good care of the feet to prevent early foot complications
Figure 3. Flowchart of diabetic foot management

Figure 4. The stairway to amputation\(^2\). Prevent and treat risk factors for ulceration and amputation.

References

Assessment and investigation

Recommendation 6: Perform a thorough assessment of a patient with a diabetic foot problem

In all patients with DFU perform a three-step assessment¹:

- the patient for general status
- the affected leg
- the ulcer

**Step 1. Assess and document diabetes, its complications and comorbidities¹,²**

- Type and duration of diabetes
- Medications used
- Degree of metabolic control
- Look for complications: renal disease, cardiovascular disease (hypertension, dyslipidemia, smoking, angina, myocardial infarction, revascularization, transient ischemic attack, strokes and peripheral vascular disease) or heart failure.

**Step 2. Assess and document status of the diabetic foot¹,²**

- presence or absence of sensory symptoms
- rest pain or claudication
- type of foot wear
- foot care habits
- callous or deformities
- previous foot ulcers or infections
- previous surgery including revascularization or amputation
- Evaluate the DFU:
  - Initial wounding event,
  - History of recurrent wounding,
  - Previous wound healing problems,
  - Prior diagnostic tests,
  - Prior therapies and response to them,
  - Functional impact of the wound on the patient,
  - Social history to determine potential adverse impact on wound healing.

Examine the feet and document²,³

**Inspection**

*Dermatologic*

- Skin status: color, thickness, dryness, cracking
- Sweating
- Infection: check between toes for fungal infection
- Ulceration
- Calluses/blistering: hemorrhage into callus?
Management of diabetic foot wounds

Musculoskeletal
- Deformity, e.g., claw toes, prominent metatarsal heads, Charcot joint (Figure 5)
- Muscle wasting (guttering between metatarsals) (Figure 6)

Neurological assessment
10-g monofilament + 1 of the following 4 (Figure 7)
- Vibration using 128-Hz tuning fork
- Pinprick sensation
- Ankle reflexes
- Vibration Perception Threshold

Vascular assessment
Foot pulses (Figure 8)
- Femoral
- Popliteal
- Dorsalis Pedis
- Posterior Tibial

Ankle Brachial Index (ABI)
\[
ABI = \frac{\text{Ankle systolic pressure (highest)}}{\text{Brachial systolic pressure (highest)}}
\]
- Ankle pressures are taken at the Dorsal Pedis and Posterior Tibial.
- Use the highest of the two ankle pressures and brachial pressures

<table>
<thead>
<tr>
<th></th>
<th>Normal</th>
<th>Ischaemia</th>
<th>Critical ischaemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.8 to 1.2</td>
<td>Normal</td>
<td>Ischaemia</td>
<td>Critical ischaemia</td>
</tr>
<tr>
<td>&lt;0.8</td>
<td>Ischaemia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;0.5</td>
<td>Critical ischaemia</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Figure 6. Clawing of toes
Figure 7. Ten grams of force applied until filament bends
Figure 8. Sites for palpating foot pulses
Figure 9a. Dorsalis pedis artery

Figure 9b. Posterior tibial artery

Figure 10. Measuring toe brachial index

Toe Brachial Index (TBI) when ABI is high (>0.9)

40% of all diabetic patients with an ulcer present falsely high ABI values (ABI>1.3) because of vessel wall calcification

Table 4. Severity of peripheral artery disease (PAD)

<table>
<thead>
<tr>
<th>Type/Severity</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mild PAD</strong></td>
<td>Palpable foot pulses/ absent foot pulses with <strong>ABI &gt; 0.6</strong>*, (TBI&gt;0.7 TcPO2 &gt; 50 of healing mmHg)</td>
</tr>
<tr>
<td>o High probability</td>
<td>o Evaluate the effect of maximal 6-week optimal wound care.</td>
</tr>
<tr>
<td></td>
<td>o Reassess perfusion and consider revascularization when wound healing response is poor.</td>
</tr>
<tr>
<td></td>
<td>*Note: ABI &gt; 0.6 has less predictive value, and in these patients, TCPO2 or toe pressure should be measured.</td>
</tr>
<tr>
<td><strong>Severe PAD</strong></td>
<td>Absent foot pulses, <strong>ABI &lt; 0.6</strong></td>
</tr>
<tr>
<td>o Low probability of healing</td>
<td>(optional Toe pressure &lt; 50 mmHg, TcPO2 &lt; 30 mmHg).</td>
</tr>
</tbody>
</table>
Step 3. Examine the DFU and document

Document ulcer characteristics

In assessing a diabetic foot wound, one must describe the characteristics of the wound:

- Site of wound: dorsum / sole / heel / web space
- Size of wound
- Edge of wound: clean-cut / inverted / everted
- Floor of wound: slough / granulation tissue
- Content of wound: exudate / pus

(Contd.)
Investigations

Recommendation 7: Perform general laboratory investigations

1. Screen for anemia and malnutrition (albumin or prealbumin) as they may impair wound healing\(^1\)\(^2\).

2. If infection is suspected consider: C reactive protein, erythrocyte sedimentation rate, cultures (deep tissue cultures including bone fragments/biopsy in the case of osteomyelitis and blood cultures)

3. Assess and optimize metabolic profile: Glycosylated hemoglobin, lipid profile, cardiac and renal evaluation.

\[ \text{Do not withhold antibiotics till cultures become available} \]

\[ \text{Use clinical judgment} \]

Recommendation 8: Send material for culture

- A culture must be taken before starting antibiotics
- First clean the ulcer and surrounding skin with normal saline
- Press the wound at the edges to squeeze pus from the center portion
- Collect pus from the deepest portion of the wound to avoid contamination
- Send the swab for culture and sensitivity for aerobic and anaerobic organisms

Recommendation 9: Perform radiological tests

1. Plain radiography (of the affected foot and if necessary both sides for comparison) is useful to evaluate for infection, foreign bodies, and deformity including Charcot arthropathy.

2. Look for osteomyelitis.
   - Radiologic changes may lag behind by two weeks in the presence of osteomyelitis\(^1\)\(^2\).
II. MRI may be indicated if there is positive probe-to-bone test\textsuperscript{1,2}.

III. Other methods to diagnose early osteomyelitis are radioactive labeled scans such as Tc99m exametazime or Indium WBC labeled scans.

\textbf{Suspect osteomyelitis early and refer to specialist}

**Multidisciplinary foot care team** \textsuperscript{4,5}

Each hospital should have a multidisciplinary foot team.

The members of the team should consist of:

- surgeon with expertise in managing diabetic foot problems
- diabetologist
- diabetes specialist nurse
- podiatrist
- tissue viability nurse
- specialist services such as vascular surgery, radiology, clinical microbiology, nephrology and cardiology

**References**


Medical treatment

Endocrine control
Poor glycemic control is common among patients with diabetic foot ulcers. The factors that disrupt glucose control include:
- Infection
- Surgical trauma
- Stress
Recommendation 10: Aim for Good glycemic control in all patients with diabetic foot ulcer.

Glycemic Targets:

In critically ill patients:
- Target: 140 – 180 mg/dL (7.8 – 10 mmol/L).
- Method: Use intravenous insulin infusion

In other hospitalized patients:
- Target: a premeal glucose less than 140 mg/dL (7.8 mmol/L)
- Method: basal insulin, and bolus doses for mealtimes

In relatively well patients:
- Target: a premeal glucose less than 130 mg/dl (7.2 mmol/l) if this can be done without increasing hypoglycaemia. HbA1C target of 7% is recommended for most home managed patients provided this could be achieved safely.
- Method: If the patient is stable on oral drugs these may be continued. If the glycaemic control is poor optimize, preferably with insulin.

Medical Nutrition Therapy

Recommendation 11: Nutrition should be individualized.

Factors such as body weight, current medical status, and other comorbid conditions, such as obesity, hyperlipidemia, and hypertension should be taken into account when planning a diet. Involve a nutritionist if possible.

Recommendation 12: Improve the nutritional status in malnourished patients.

Recommendation 13: When patients are kept fasting provide carbohydrate.
- Method: Use 5% dextrose or Dextrose saline infusion

Wound Bed Preparation

Recommendation 14: Prepare the wound bed to facilitate wound healing.

The wound bed should be prepared for healing to occur effectively. Wound bed preparation is considered to accelerate endogenous healing and increase effectiveness of other therapeutic measures. Important aspects include debridement, management of bacterial burden and exudate management.
The TIME acronym\(^3\) provides a framework for a structured approach to wound bed preparation.

<table>
<thead>
<tr>
<th>Clinical Observations</th>
<th>Proposed Pathophysiology</th>
<th>WBP Clinical Actions</th>
<th>Effect of WBP Actions</th>
<th>Clinical Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tissue Non-Viable or Deficient</td>
<td>Defective matrix and cell debris impair healing</td>
<td>Debridement (episodic or continuous)</td>
<td>Restoration of wound base and functional extra-cellular matrix proteins</td>
<td>Viable wound base</td>
</tr>
<tr>
<td>Infection or Inflammation</td>
<td>High bacterial counts or prolonged inflammation</td>
<td>remove infected foci</td>
<td>Low bacterial counts or controlled inflammation</td>
<td>Bacterial balance and reduced inflammation</td>
</tr>
<tr>
<td>Moisture Imbalance</td>
<td>Desiccation slows epithelial cell migration</td>
<td>Apply moisture balancing dressings</td>
<td>Restored epithelial cell migration, desiccation avoided</td>
<td>Moisture balance</td>
</tr>
<tr>
<td>Epidermal Margin – Non Advancing or Undermined</td>
<td>Non migrating keratinocytes</td>
<td>Re-assess cause or consider corrective therapies</td>
<td>Migrating keratinocytes and responsive wound cells, Restoration of appropriate protease profile</td>
<td>Advancing epidermal margin</td>
</tr>
</tbody>
</table>

Redrawn from Schultz et al, 2003

---

1 Sibbald, 2000  
2 Paris Advisory Board, June 2002  
3 Schultz et al, 2003

**Wound Infection**

**Recommendation 15: Infection should be identified early and managed appropriately to avoid limb loss.**

Diabetic foot wounds often become infected – approximately 60% are infected with anaerobic bacteria. Appropriate treatment varies based on the degree of bacterial growth.

**Table 5. Stages of infection and appropriate treatment.**

<table>
<thead>
<tr>
<th>Infection Stage</th>
<th>Appropriate Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Contaminated Wound</td>
<td>No need for antibiotics</td>
</tr>
<tr>
<td>- Bacteria present in wound</td>
<td></td>
</tr>
<tr>
<td>- No clinical reaction</td>
<td></td>
</tr>
<tr>
<td>Colonised Wound</td>
<td>Apply local antimicrobial dressing</td>
</tr>
<tr>
<td>------------------------------------------------------</td>
<td>-----------------------------------</td>
</tr>
<tr>
<td>o Bacteria multiplying in wound</td>
<td></td>
</tr>
<tr>
<td>o No adverse clinical reaction</td>
<td></td>
</tr>
<tr>
<td><img src="image1" alt="Colonised Wound Image" /></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Critically Colonised Wound</th>
<th>Apply local antimicrobial dressing</th>
</tr>
</thead>
<tbody>
<tr>
<td>o Heavy bacterial load</td>
<td></td>
</tr>
<tr>
<td>o Delayed healing, Change in wound bed colour, Absent / abnormal granulation tissue, Increased / abnormal odour, Increased serous discharge, Increased pain at wound site</td>
<td></td>
</tr>
<tr>
<td>o No signs of inflammation/cellulitis</td>
<td></td>
</tr>
<tr>
<td><img src="image2" alt="Critically Colonised Wound Image" /></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Overt Infection</th>
<th>Start intravenous antibiotics</th>
</tr>
</thead>
<tbody>
<tr>
<td>o Very heavy bacterial load</td>
<td></td>
</tr>
<tr>
<td>o Clear signs of infection</td>
<td></td>
</tr>
<tr>
<td><img src="image3" alt="Overt Infection Image" /></td>
<td></td>
</tr>
</tbody>
</table>
Antibiotic Usage

**Recommendation 16: Antibiotics should be used appropriately.**

Antibiotic treatment risks inducing the development of antibiotic-resistant bacteria. Thus, antibiotics should be used appropriately:

- Local antibiotic creams and pastes are inadvisable as the risk of developing antibiotic-resistant bacteria is high
- Antibiotics choice should be based on culture and sensitivity results
- Osteomyelitis requires high-bone-penetration antibiotics for at least 6 weeks
- Follow up with blood and radiological investigations is important

**Recommendation 17: Antibiotics should be used in conjunction with other treatments.**

Where necessary, antibiotics should be used together with surgical methods and antimicrobial dressings for greater effect:

- Abscesses must be surgically drained
- Osteomyelitis must be managed by excision of infected bone
- Local antimicrobial dressings (e.g. silver) help to combat multi-drug resistant strains

Osteomyelitis

**Recommendation 18: Look for underlying osteomyelitis in all wounds.**

Osteomyelitis is infection of the bone, which occurs commonly in patients with diabetic foot problems.

**Diagnosis**

Osteomyelitis should be assumed to be present when a sterile metal probe or a gloved finger on palpation reaches the bone.

**Suspect osteomyelitis early and refer to specialist**

**Treatment**

Osteomyelitis is difficult to treat and usually requires:

- long-term antibiotic treatment
- surgery to remove the infected bone

**Dressing Selection According to TIME Guide**

**Recommendation 19: Use the TIME Guide to guide aim of care and dressing selection.**
<table>
<thead>
<tr>
<th>Tissue</th>
<th>Aim of care</th>
<th>Exudate</th>
<th>Dressing</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Dry or low</td>
<td>hydrogel</td>
</tr>
<tr>
<td>Necrotic</td>
<td>If vascular supply is good, debride eschar and promote moisture balance</td>
<td>Moderate</td>
<td>hydrocolloid or foam</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Heavy</td>
<td>Alginate, foam or hydrofiber</td>
</tr>
<tr>
<td></td>
<td></td>
<td>If vascular supply is compromised, keep dry eschar</td>
<td>Gauze or foam with pad</td>
</tr>
<tr>
<td>Sloughy</td>
<td>Deslough, provide moisture balance</td>
<td>Low</td>
<td>Hydrocolloid, hydrogel</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Moderate</td>
<td>Alginate</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Heavy</td>
<td>Foam, hydrofiber</td>
</tr>
<tr>
<td>Granulating</td>
<td>Provide moisture balance</td>
<td>Low</td>
<td>Non adherence material</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Moderate</td>
<td>Hydrocolloid, foam</td>
</tr>
<tr>
<td>Epithelializing</td>
<td>Provide moisture balance</td>
<td>Low</td>
<td>Non adherence material</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Moderate</td>
<td>Hydrocolloid or foam</td>
</tr>
<tr>
<td>Infection</td>
<td>Get rid of infection (biofilm)</td>
<td>Low</td>
<td>Nano-crystalline or ion silver containing material, iodine cream</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Moderate</td>
<td>Silver containing, iodine containing material</td>
</tr>
<tr>
<td>Moisture balance</td>
<td>Maintain moist environment</td>
<td>Low</td>
<td>Film, hydrogel</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Moderate</td>
<td>Hydrocolloid, Alginate</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Heavy</td>
<td>Foam, hydrofiber, NPWT</td>
</tr>
<tr>
<td>Edge</td>
<td>Promote advance of wound edge</td>
<td>Low</td>
<td>Film, hydrogel</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Moderate</td>
<td>Hydrocolloid, Alginate, NPWT</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Heavy</td>
<td>Foam, hydrofiber, NPWT</td>
</tr>
</tbody>
</table>

4 Caputo et al 1994
Categories of Wound Dressings
Recommendation 20: Choose the appropriate wound dressing based on wound characteristics.

<table>
<thead>
<tr>
<th>Category</th>
<th>Characteristics</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Film</td>
<td>Sterile, thin, waterproof, breathable, self-adhesive polyurethane film</td>
<td>Suitable for flat/shallow low exudate wounds</td>
</tr>
<tr>
<td>Tulle dressing</td>
<td>Non-adherent dressing</td>
<td>Epithelialized low-exudate wound</td>
</tr>
<tr>
<td>Hydrocolloid</td>
<td>Adhesive dressing made of natural or synthetic polymer e.g. gelatine, pectin.</td>
<td>Suitable for flat/shallow low- to medium-exudate wounds</td>
</tr>
<tr>
<td>Hydrogel</td>
<td>Amorphous, water-based gels or sheets rehydrates dry necrotic tissue</td>
<td>Suitable for dry, necrotic wounds</td>
</tr>
<tr>
<td>Alginate</td>
<td>Forms a soft flexible gel</td>
<td>Suitable for moderately exudative lesions</td>
</tr>
<tr>
<td>Hydrofibre</td>
<td>Retains fluid within the structure of the fibre forming a soft gel</td>
<td>Suitable for cavity, deep or superficial wounds with slough or eschar and medium to heavy exudate e.g. leg ulcers, pressure ulcers</td>
</tr>
<tr>
<td>Polyurethane foam</td>
<td>Available with or without an adhesive border</td>
<td>Suitable for granulating or epithelialising wounds with moderate to heavy exudate</td>
</tr>
<tr>
<td>Silver dressing</td>
<td>Silver nano-particle or ion impregnated in a non-woven material that releases silver ion slowly</td>
<td>Suitable for critically colonised or infected wounds</td>
</tr>
<tr>
<td>Iodine dressing</td>
<td>Providone iodine impregnated in a non woven material that releases iodine slowly</td>
<td>Suitable for critically colonised or infected wounds</td>
</tr>
</tbody>
</table>

Other methods of treatments
Recommendation 21: Use alternative technologies where appropriate to aid in wound healing.

<table>
<thead>
<tr>
<th>Technology</th>
<th>Mechanism</th>
<th>Indication</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative Pressure Wound</td>
<td>Application of negative pressure to a wound in a closed environment.</td>
<td>Open wound with high exudate</td>
<td>Reduces frequency of dressing changes.</td>
</tr>
<tr>
<td>Wound Therapy</td>
<td>Maintains moist environment and prevents desiccation. Promotes formation of granulation tissue</td>
<td></td>
<td>Offers temporary wound closure.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Cannot be used in infected wound.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Necrotic tissue should be debrided first.</td>
</tr>
</tbody>
</table>
Hyperbaric Oxygen | Provides 100% oxygen to the wound tissue | For wounds with inadequate perfusion | Vascular supply is inadequate
---|---|---|---
Maggot debridement therapy: Common green bottle fly (*Lucilia cuprina*) | Digestion of slough by secreting enzymes that dissolve the necrotic tissue and the biofilm | For wounds with slough and necrotic tissue | For patients too ill to undergo surgical debridement
Hydrosurgery | Ultra-thin, high-velocity stream of saline to debride with fine precision | For wounds with slough or necrotic tissue | Useful for wound bed preparation

References
2. Paris Advisory Board, June 2002

---

**Surgical treatment**

**Debridement**

It is the most common operation performed for diabetic foot. Debridement is often left to the residents to perform. However, a good debridement can only be performed by a surgeon experienced in diabetic foot surgery.

**Recommendation 22: Perform adequate debridement to remove all devitalised or infected tissue.**

**Definition**

Debridement is the excision of necrotic, devitalised or infected tissue from a wound, leaving healthy and vascularised tissue behind.¹

**Indications**

- Discharge
- Necrotic tissue
- Slough

**Why Debridement?**

- Devitalised tissue in wound floor harbours bacteria
- Necrotic tissue masks underlying infection
Always assess vascularity before attempting debridement  
Absence of both foot pulses or ABPI <0.6 should trigger vascular referral

Types of Surgical Debridement

**Sharp debridement**

Figure 13a and 13b. Using scalpel or scissors to remove devitalised tissue

**Ultrasonic debridement**

Figure 14. Using low-frequency ultrasound (25 – 42 Hz) and normal saline to remove devitalised tissue

**Hydrosurgery debridement**

Figure 15. Using high-pressure saline jet to remove devitalised tissue.
Management of diabetic foot wounds

**Procedure for Surgical Debridement**

- **First stage**
  - Excise edge of wound
  - Excise floor of wound

- **Second stage**
  - Flush with normal saline
  - Use new blade to trim edge of wound
  - Excise another thin layer of floor
  - Leave healthy bleeding tissue behind

- **Apply dressing to wound**

**Tips for Debridement**

- Do not leave exposed fascia behind
- Do not leave exposed tendon behind
  - Fascia or tendon will later form slough
- Do not leave exposed bone
  - See negative pressure dressing or
  - Cover with flap

**Consent for Procedure**

- Patient may need a second debridement
- Patient may need a split skin graft for a large wound

**Split Skin Grafting (SSG)**

Following adequate debridement, diabetic wounds heal. Small wounds heal via secondary closure. Large wounds require split skin grafting. In performing split skin grafting, donor skin is usually taken from the thigh of the patient on the same limb.

**Recommendation 23: Perform split skin graft for large granulating wound.**

**Definition**

Application of a skin graft including the epidermis and part of the dermis. Figures 17 and 18.
Osteomyelitis

Prolonged antibiotic therapy of 6 weeks is needed. A peripherally inserted central catheter (PICC) must be inserted for delivery. The type of surgery performed is shown in Table 6.

Table 6. Types of Surgery for OM

<table>
<thead>
<tr>
<th>Site of Osteomyelitis</th>
<th>Surgical Procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Distal / middle phalanx</td>
<td>Toe disarticulation</td>
</tr>
<tr>
<td>Metatarsal</td>
<td>Ray amputation</td>
</tr>
<tr>
<td>MTPJ (septic arthritis)</td>
<td>Excision of MTPJ</td>
</tr>
<tr>
<td>Lateral malleolus</td>
<td>Ankle fusion</td>
</tr>
<tr>
<td></td>
<td>Below knee amputation</td>
</tr>
<tr>
<td>Calcaneum</td>
<td>Partial/total calcaneotomy</td>
</tr>
<tr>
<td></td>
<td>Below knee amputation</td>
</tr>
</tbody>
</table>

* MTPJ – Metatarsophalangeal Joint

Amputation

Indications

Amputation is performed for:
  - Gangrene or necrotic tissue
  - Osteomyelitis or septic arthritis

Types of Amputations

- Minor (distal) or
- Major (proximal)
Table 7. Classification of Amputations (Nather and Wong 2013)³

<table>
<thead>
<tr>
<th>Amputation Level</th>
<th>Distal (minor)</th>
<th>Proximal (major)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Forefoot</td>
<td>Toe disarticulation</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ray</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Transmetatarsal</td>
<td></td>
</tr>
<tr>
<td>Midfoot</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Through tarso-metatarsal joint</td>
<td>Lisfranc</td>
<td></td>
</tr>
<tr>
<td>Through tarso-metatarsal joint</td>
<td>Chopart</td>
<td></td>
</tr>
<tr>
<td>Hindfoot</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Syme</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Boyd</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pirogoff</td>
<td></td>
</tr>
<tr>
<td>Trans-tibial</td>
<td></td>
<td>Below-knee</td>
</tr>
<tr>
<td>Through knee</td>
<td></td>
<td>Gritti Stokes</td>
</tr>
<tr>
<td>Trans-femoral</td>
<td></td>
<td>Above-knee</td>
</tr>
<tr>
<td>Hip</td>
<td></td>
<td>Hip disarticulation</td>
</tr>
</tbody>
</table>

Recommendation 24: Perform minor (distal) amputation where possible.

Minor (Distal) Amputation

The first amputation should preferably be minor or distal. The mortality rate is significantly higher when a major amputation is performed.4,5

Minor amputations allow tibial weight-bearing.

Pre-Requisites for Minor Amputation

- Must have at least one palpable pulse
- ABI: more than 0.7
- TBI: more than 0.7
Ray amputation
The ray amputation is the most common amputation performed. It is a more viable option of ensuring adequate surgical debridement of the septic margin than a toe disarticulation (through metatarso-phalangeal joint).

Recommendation 25: Perform ray amputation if indicated.

Definition
Amputation through the metatarsal bone removing part of metatarsal and corresponding toe. More than one ray may need to be removed.

Indications
- Wet gangrene of toe
- Osteomyelitis of proximal phalanx or metatarsal head
- Septic arthritis of metatarso-phalangeal head

Informed Consent
- Patient may need more proximal amputation
- Patient may need amputation of adjacent ray(s)

Trans-Metatarsal Amputation

Recommendation 26: Perform transmetatarsal amputation if indicated

Definition
Amputation through all 5 metatarsal bones of forefoot.

Indication
- Forefoot gangrene
Informed Consent

- Lisfranc’s Amputation\(^7\) – amputation through tarso-metatarsal joints (Lisfranc joint) or
- Chopart’s Amputation\(^7\) – amputation through calcaneo-cuboid and talo-navicular joints (Chopart’s joint)
  May be performed instead of trans-metatarsal amputation, depending on availability of flaps.
- Patient may need below-knee amputation if operation fails

Syme or Pirogoff amputation

Nather et al\(^6\) considered the Syme or Pirogoff the most proximal amputation that can achieve successful limb salvage. It can be fitted with prosthetic shoes and is end-weight bearing.

Recommendation 27: Perform Syme / Pirogoff amputation if indicated.

Definition

Syme
Trans-malleolar amputation of foot through ankle joint.

Boyd
Amputation at the ankle with removal of the talus and fusion of the tibia and horizontal cut surface of calcaneus.

Pirogoff
Trans-malleolar amputation of foot through ankle joint and fusion of the tibia and distal cut surface of calcaneus.
Indications
- Gangrene of forefoot
- Infection of forefoot

Discussion
Syme Amputation has been advocated for trauma.\(^8\) However, Syme Amputation can also give good results in patients with diabetic foot infections.\(^9\) It is well-known that Syme Amputation should be reserved for patients with at least a palpable posterior tibial pulse and an ankle-brachial index of more than 0.5.\(^8,9,10\) However, it has several disadvantages, including instability of the calcaneal flap to the tibial surface due to poor adherence of the soft tissue to the tibial surface.\(^3\) Also, the dissection of calcaneum from the underlying flap in a Syme may lead to devascularisation of the flap.\(^11\) A third disadvantage is that with excision of the calcaneum, a shorter stump is produced, making walking barefoot difficult.\(^12\)

With Boyd and Pirogoff Amputation, the tibio-calcaneal bony fusion gives added stability to the flap. The shortening of the stump is also minimised. The additional length makes it easier for the patient to walk without prosthesis. Nather et al\(^13\) reported good outcome in all 6 cases undergoing Pirogoff amputation.
Informed Consent

- Patient may need below-knee amputation if amputation fails.

Below Knee Amputation (BKA)

This amputation is universally accepted as a failure of limb salvage. A BKA is life-threatening. The peri-operative mortality for BKA is about 10%. It is 30% at one year, 50% at 3 years and 70% at 5 years.\textsuperscript{14}

Recommendation 28: Perform below-knee amputation (BKA) if indicated

**Definition**

Trans-tibial amputation.

**Indications**

- Infection up to ankle
- Severe ischaemia/gangrene of whole foot
- Dorsalis pedis and posterior tibial pulses both not palpable
- ABI < 0.5, TBI < 0.5
- Rest pain in foot
- Gangrene or ulcer in heel, not salvageable by a flap

Rehabilitation

**Recommendation 29: Perform rehabilitation early.**

**Rehabilitation:**

- Start on first post-operative day:
  - Straight leg raising exercises
  - Chest physiotherapy

Informed Consent

- Patient may need revision BKA or above-knee amputation (AKA) if amputation fails.
And progress to:
- Hip abduction
- Isometric quadriceps exercises
- Isometric gastrocnemius exercises
- Stump exercises
- Standing with walking frame
- Walking / balancing with walking frame
- Balancing across parallel bars
- Figure of eight stump bandaging three times a day

Above Knee Amputation (AKA)

Recommendation 30: Perform above-knee amputation if indicated

Definition
Trans-femoral amputation. Figure 38 and 39

Indications
- Failed below knee amputation
- Infection up to middle of leg
- Ischaemia up to middle of leg
- Flexion contracture of knee in a patient requiring BKA
Informed Consent

- Patient may need revision AKA if amputation fails

Limb Salvage

Recommendation 31: Perform limb salvage when possible by carrying out revascularization.

Definition

Increasing blood flow and blood supply

Factors to consider when deciding on vascularisation options

- General condition of the patient
  - Renal function
  - Cardiac function
- Site and diameter of the vessel affected, length and severity of occlusion
- Availability of suitable length of autogenous venous conduit, i.e. saphenous vein, cephalic vein
- Outflow to the foot and patency of the pedal arch
- Severity of soft tissue necrosis and infection

Revascularisation Options

Balloon Angioplasty

Bypass Grafting
Recommendation 32: Perform primary proximal amputation when limb salvage is not possible.

Indications
Patients who:

- Are immobile or bedridden
- Have infected ankle joint

Flow chart for Revascularisation

References
Management of diabetic foot wounds

### Assessment Form

<table>
<thead>
<tr>
<th>LAST:</th>
<th>FIRST:</th>
<th>MIDDLE:</th>
<th>PIN:</th>
</tr>
</thead>
<tbody>
<tr>
<td>DATE:</td>
<td>SEX:</td>
<td>AGE:</td>
<td>BIRTH DATE:</td>
</tr>
<tr>
<td>ATTENDING MD:</td>
<td>OUT(   ) IN(   ) ROOM #:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>WCC MD:</td>
<td>CONTACT #:</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### MEDICAL HISTORY

<table>
<thead>
<tr>
<th>Diabetic History:</th>
<th># of years</th>
<th>Insulin Dependent</th>
<th>Medications:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Type 1</td>
<td>Type 2</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Other Illnesses:</th>
<th>HTN</th>
<th>Venous Insufficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAD</td>
<td></td>
<td>Renal Disease</td>
</tr>
<tr>
<td>CVA</td>
<td></td>
<td>PADD</td>
</tr>
<tr>
<td>Others</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| Personal History: | Smoking | Alcohol Drinker | Living Alone | Activity: |
|-------------------|---------|----------------|--------------|
|                   |         |                |              |

<table>
<thead>
<tr>
<th>BMI-</th>
<th>Ht-</th>
<th>Wt-</th>
<th>Normal</th>
<th>Overweight</th>
<th>Obese</th>
<th>Malnourished</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### GENERAL FOOT CARE

<table>
<thead>
<tr>
<th>Right</th>
<th>Left</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Feet Clean
- Socks/ Hose
- Foot wear (appropriate)
- Interdigital Area-Dry
- Macerated

### Nail and Skin Conditions

| Nails | Thickened
|-------|---------|
| Fungal Infection
| Ingrown Toenail

| Skin | Dry and Scaly
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td></td>
</tr>
</tbody>
</table>

#### BIOMECHANICAL

<table>
<thead>
<tr>
<th>Callus Formation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corn</td>
</tr>
<tr>
<td>Bunion</td>
</tr>
<tr>
<td>Charcot</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>LAST:</td>
</tr>
<tr>
<td>------</td>
</tr>
</tbody>
</table>

### NEUROLOGICAL ASSESSMENT

<table>
<thead>
<tr>
<th></th>
<th>Right</th>
<th>Left</th>
</tr>
</thead>
<tbody>
<tr>
<td>Burning Sensation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pins &amp; Needles Sensation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Numbness</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leg Pain</td>
<td>Right</td>
<td>Left</td>
</tr>
<tr>
<td>Intact Protective Sensation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vibration Sense</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reflexes</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**MONOFILAMENT TEST**

Note: (+) if patient can feel the filament (-) if not.

### CIRCULATORY ASSESSMENT

<table>
<thead>
<tr>
<th></th>
<th>Right</th>
<th>Left</th>
<th></th>
<th>Right</th>
<th>Left</th>
<th>Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intermittent Claudication</td>
<td></td>
<td></td>
<td>Leg Ache/ Heaviness</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rest Pain</td>
<td></td>
<td></td>
<td>Swelling</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leg Wound/ Ulcer</td>
<td></td>
<td></td>
<td>Bulging/ Spider Vein</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Capillary Refills (Seconds)</td>
<td></td>
<td></td>
<td>Hyperpigmentation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Arterial Pulses (0,+,++)</strong></td>
<td></td>
<td></td>
<td><strong>ANKLE-BRACHIAL INDEX</strong></td>
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<td>Posterior Tibial Artery</td>
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<td><strong>ABI (normal/ Abnormal)</strong></td>
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**FINDINGS:**

**RECOMMENDATION:**