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Managing cardiovascular risk in type 2 diabetes


Diabetes is associated with a marked increase (by a factor of two to four) in the risk of coronary heart disease (1-3). Clinically established coronary heart disease itself is associated with an increase in mortality from coronary heart disease by a factor of three to seven, depending on the mode of presentation (4,5). Among patients with type 2 diabetes, the seven year risk of suffering a first myocardial infarction (MI) is similar to that of recurrent MI in non diabetic persons who have had a previous MI (6).

The presence of coronary artery disease is 10 times greater among patients with type 1 diabetes than age and gender matched persons without diabetes (7). Cardio-metabolic risk factors, including insulin resistance and associated manifestations, predispose to increased cardiovascular disease (CVD) in type 2 diabetes.

Glycaemic control with HbA1c targets of less than 7 resulted in 50% reduction in the incidence of CVD in patients with type 1 diabetes enrolled in the DCCT/EDIC study (8). The UKPDS post-trial monitoring results showed continuing benefit of earlier intensive glycaemic control with maintenance of the relative risk reductions for any diabetes related endpoint (21%, P=0.013), myocardial infarction (33%, P=0.005) and all-cause mortality (27%, P=0.002), despite loss of within trial blood glucose and antihyperglycaemic therapy differences – a legacy effect of type 2 diabetes (9).

In contrast, several recent studies (ACCORD (10), VADT (11), ADVANCE (12)) have failed to demonstrate CVD risk reduction through intensive glycaemic control in patients with type 2 diabetes. Therefore, the comprehensive approach that recognizes and controls multiple CVD risk factors is the most effective management strategy in patients with diabetes (13).

In all patients with diabetes, cardiovascular risk factors should be assessed at least annually. The risk factors include dyslipidaemia, hypertension, smoking, positive family history of premature coronary disease and the presence of micro or macroalbuminuria. Abnormal risk factors should be treated to recommended targets (14).

Effective life style intervention improves glycaemic control, blood pressure, lipids and associated cardio metabolic risk factors. Preliminary data of the Look AHEAD Study indicate benefits in CVD risk markers associated with weight loss (15). Smoking cessation should be promoted for all patients who are smoking in order to reduce the CVD risk. Patients with diabetes should achieve target lipid levels. In the lipid arm of the ACCORD (10) trial, addition of fenofibrate to raise HDL and decrease triglycerides in patients taking simvastatin did not reduce the rate of fatal cardiovascular events, non fatal MI or non fatal stroke as compared with simvastatin alone. These results do not support the routine use of combination therapy with fenofibrate and simvastation to reduce the CVD risk in the majority of high risk patients with type 2 diabetes.

In the patients with type 2 diabetes at high risk for CVD, targeting a systolic blood pressure of less than 120 mmHg, as compared with less than 140 mmHg, did not reduce the rate of a composite primary outcome of fatal and non fatal major CVD events [ACCORD study (10)]. Therefore, patients with diabetes blood pressure target of 130/80 mmHg should be achieved to reduce the CVD risk in diabetes until further evidence is available.

Recent randomised controlled trials have failed to show CVD benefits of aspirin use for primary prevention in patients with diabetes (15). Low dose aspirin for primary prevention is reasonable for adults with diabetes and no previous history of vascular disease who are at increased CVD risk (10 year risk of CVD events more than 10%) and who have no known risk for bleeding. Appropriate candidates include most men over 50 years of age and women aged over 60 years with major risk factors (15). Aspirin is recommended in secondary prevention of diabetes patients with documented CVD events. In patients with known CVD, ACE inhibitor, aspirin and statin therapy should be used to reduce the cardiovascular events.

In conclusion, a comprehensive approach to the prevention and management of heart disease in diabetes patients is advocated. This is best accomplished through a combination of life style modification and targeting of the multiple cardio metabolic risk factors and co morbidities.

– Dr. Uditha Bulugahapitiya

References


Assessment of adiposity by bio impedance analysis: developing a population specific equation for Sri Lankan adolescents

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(Index words: adiposity, fat mass, adolescents)

Abstract

Objective: Adiposity in adolescence is associated with chronic disease in adulthood, and assessment of body fat mass is vital for screening at risk populations. Adiposity is measured in many ways including bio impedance analysis. The objective of this study was to validate existing bio impedance analysis (BIA) equations on 15-19 year old adolescent girls and to derive a population specific equation for the prediction of percentage fat mass (%FM) for adolescent girls.

Methods: Body composition of 15 - 19 year old, adolescent girls was assessed by the deuterium dilution method and BIA. Validity of existing equations for the prediction of %FM of Sri Lankan adolescent girls were assessed prior to the derivation and validation of a new %FM equation. The new equation was derived using linear regression analysis against the reference method, deuterium dilution.

Results: Existing BIA equations significantly (p< 0.001) overestimated %FM. The new equation derived for the prediction of %FM of Sri Lankan adolescent girls significantly correlated with the reference method. There was no significant difference in %FM obtained by the reference method (%FM: 24.67 ± 9.2) and the derived equation (%FM: 24.9 ± 6.3).

Conclusions: The new equation; %FM = -74.065 + 0.671 (height² / resistance) + 0.049 (resistance) + 2.080 (BMI), is appropriate for the prediction of %FM in Sri Lankan post pubertal adolescent girls, and may be validated for use on other South Asian populations.

Introduction

Adiposity in childhood and adolescence is one of the main determinants of insulin resistance, representing the metabolic basis for development of future chronic disease (1). Identification of at risk individuals during their adolescent years is essential in prevention, but many difficulties are encountered in assessing adiposity in adolescents due to variability in muscle mass, maturation and growth rates. Body mass index (BMI) is often used to assess adiposity, but does not differentiate between fat and non-fat components of body mass, resulting in inaccuracies in classification of individuals as overweight or obese (2). Other techniques of body fat assessment, such as densitometry and stable isotope methods are accurate, but expensive and impractical for routine screening. Bio impedance analysis (BIA) is based on applying a low level current through the body and measuring the impedance of tissues. These values are applied to an equation which is already programmed into the machine for the calculation of fat mass (3). The low cost and simplicity of assessment has popularized this method.

However, most BIA prediction equations programmed into bio impedance analysers are derived for Western populations and have poor validity in other populations (4, 5), with %FM being overestimated in lean subjects and underestimated in obese individuals (5, 6). There are no published BIA equations for South Asian adolescents, with the few available equations being derived for the prediction of total body water (TBW), and through it, fat mass (7-9). Ideally, the available %FM prediction equations should be validated in the population being assessed prior to use, or population specific prediction equations should be derived against a reference method to improve accuracy of BIA analysis (10).

While values of TBW, fat free mass (FFM), fat mass (FM) and their percentages can be obtained directly from the BIA instrument; FM can also be calculated using the impedance, resistance and / or reactance values, which may also be obtained from the instrument. Most BIA equations for the prediction of percentage fat mass (%FM) have been derived on Caucasian and African American populations, employing height² / resistance and body weight as the most significant predictors of %FM. There

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are no published population specific BIA equations for post pubertal adolescent girls in Sri Lanka or in other areas of similar ethnicity.

This study aims to validate existing BIA equations on a population of 15-19 year old adolescent girls against a reference method using stable isotopes (deuterium dilution method) and to derive a population specific equation for the prediction of %FM for post pubertal adolescent girls.

Methods

Study participants

Healthy, post pubertal adolescent girls (n = 160) aged 15-19 years, were recruited for a study on body composition assessment. The sample was selected using a convenience sample representing both school going and non-school going adolescent girls living in public health midwife areas in urban and rural sectors of Colombo and Kalutara Districts in Sri Lanka. Ethical approval for this study was obtained from the Ethics Review Committee of the Faculty of Medicine, University of Colombo and written informed consent was obtained from all study participants.

Assessment

All body composition measurements were performed between 0830 and 1300 hours. The participants fasted for two hours from food and drink, did not perform strenuous exercise and emptied their bladders preceding the fat mass assessment by the reference method. The reference method for body composition assessments are densitometry or stable isotope analysis of TBW using deuterium oxide (D2O) which can be measured using an Isotope Ratio Mass Spectrometry (IRMS) or Fourier Transformed Infrared Spectrometry (FTIR) (11). The deuterium dilution technique was used as the criterion method for the estimation of total body water. The reference method used in this study was the two compartment model of assessment of TBW using the stable isotopes of D2O (deuterium dilution method) and measurement using FTIR, a spectroscopic technique that uses the absorption of infrared light to determine the concentration D2O of a sample (12). A single dose of D2O (Cambridge Isotope Laboratories Inc., MA, USA) was ingested by all subjects confirmed by IRMS and further details of this assessment and analysis have been published previously (13).

Bioelectrical impedance analysis (BIA)

Bioelectrical impedance analysis (BIA) was measured using an SFB7 ImpediMed instrument (ImpediMed Limited, Australia). A multiple frequency current was used with four surface electrodes. The girls were asked to lie supine on a non-conductive surface with hands kept in a prone and slightly abducted position away from the trunk. In order to minimise interference, legs were abducted to a minimum of 20 cm between the two medial malleoli and thighs were parted to prevent touching each other. Surface electrodes for the source current were placed on the dorsal side of the third metacarpo-phalangeal joint of the left hand and third metatarsal-phalangeal joint of the left foot. The sensing electrodes were kept at midway between the styloid process of ulna and radius on the posterior surface of the left wrist and midway between medial and lateral malleoli on the anterior surface of the left ankle. A minimum distance of 5 cm was maintained between the source and sensing electrodes to avoid any interference. If the natural distance between the source and sensing electrodes was less than 5 cm, the sensing electrode was moved proximally till the desired distance was achieved (9). Conduction gel coated disposable surface electrodes were used and connected to the BIA machine via crocodile clips. The instrument was routinely checked on each day of sample collection using a test cell. Percentage fat mass values were obtained directly by the BIA instrument; in addition impedance, resistance and reactance values were obtained from the instrument and transformed into a measure of %FM using BIA equations for the prediction of %FM.

Statistical analysis

Statistical analysis was carried out using SPSS version 15 for Windows. Percentage fat mass values were obtained directly by the BIA instrument. Total body water values obtained by the reference method, were divided by the hydration factor (0.73 for adolescent girls), in order to derive the FFM. FM was calculated by subtracting FFM from body weight. Percentage fat mass was calculated as a fraction of body weight. Percentage fat mass by the reference method and BIA were compared using paired samples t-test for over / underestimation.

Assessment of validity of selected BIA equations to predict %FM of the study population by comparison with %FM from the reference method was as follows:

Selected BIA equations derived on adolescents and children, for the prediction of %FM are given in Table 1. While the Kushner (14), Bray (15) and Houtkooper (16)
Table 1. Existing BIA equations for the prediction of %FM

<table>
<thead>
<tr>
<th>Equation</th>
<th>Author</th>
<th>Population for which equation was derived</th>
</tr>
</thead>
<tbody>
<tr>
<td>%FM = (weight - (0.59 × (height × height / R) + 0.065 × weight + 0.04) / (0.754 × weight))</td>
<td>Kushner et al (1992)</td>
<td>0.02 - 66 years, Caucasian and Peruvian</td>
</tr>
<tr>
<td>%FM = (1 - (0.4 × (height × height / R) + 0.148 × weight + 3.32) / (0.76 × weight)) × 100</td>
<td>Bray et al (2002)</td>
<td>10.79 ± 0.05 years, Caucasian; African-American</td>
</tr>
<tr>
<td>%FM = -1.11 × (height × height / R) + 1.04 × weight + 15.16 (height in cm)</td>
<td>Houtkooper et al. (1989)</td>
<td>10 - 14 year old children</td>
</tr>
<tr>
<td>FFM = 0.56 × (height × height/Z) + 0.22 × weight + 1.6 × sex - 0.22 (height in cm, sex: male = 1; female = 0)</td>
<td>Wickramasinghe et al. (2008)</td>
<td>5 - 15 year old, Sri Lankan children</td>
</tr>
<tr>
<td>FFM = 0.299 × (height × height / R) + (0.086 × height) + (0.245 × weight) + 0.260 × age + 0.901 × sex - 0.415 × ethnicity (height in cm; Thai ethnicity = 1, others = 0; sex: male = 1, female = 0)</td>
<td>Liu et al (2011)</td>
<td>8 - 10 year old, Asian children</td>
</tr>
</tbody>
</table>

R: resistance, Z: impedance

Equations were directly applied to the population under study to obtain %FM. The equations of Wickramasinghe (7) and Liu (17) were used to calculate FFM of the population and thereby FM (body weight - FM) and %FM (fat mass × 100 / body weight), based on the assumption that body weight = FM + FFM. Pearson’s rank correlation coefficients were obtained to assess the association between %FM obtained from the reference method (deuterium dilution) and %FM obtained from the selected equations. Mean %FM values by the reference method were compared to values obtained by application of impedance and anthropometric values to existing equations using the paired samples t-test.

Derivation of a new BIA equation to predict %FM was done as shown below:

The data of study participants were divided into cross validation and validation groups by sorting the age of girls in ascending order and including every third girl in the cross validation group. The preliminary prediction equation for %FM was derived for the validation group, by linear regression analysis, using backward likelihood ratio, with %FM (reference method) as the dependant variable, and resistance, height²/resistance, body weight, BMI and age as independent variables. Predictability of the preliminary equation was evaluated using the cross-validation group. The final prediction equation was derived after combining both validation and cross-validation groups, by linear regression analysis using the enter method. The independent variables for the final equation were determined by the preliminary equation. Level of agreement between the %FM values calculated from the final derived prediction equation and the reference method was assessed using Spearman's correlation (r) and Bland Altman plots. Over/underestimation was assessed by Student t-test. High overall percentages of the predictions (> 70%) and significant χ² values (p < 0.001) were taken as indicative of goodness of fit of the models.

Results

Percentage fat mass by the reference method ranged from 9.2 to 49.1 with a mean %FM of 24.7 ± 9.2. Application of fat mass cut-off values by Sun et al (5) for women, classified 54% (n = 86) of the girls as lean (%FM ≤ 25%), while 22% (n = 35) had excess fat mass (%FM ≥ 33%). Percentage fat mass by BIA, when applied to the total population, significantly overestimated (p < 0.001) mean %FM obtained by the reference method (Figure 1). Direct assessment by the BIA underestimated %FM in girls who were classified as lean by deuterium dilution (%FM ≤ 25), and it underestimated %FM in girls who had excess fat by deuterium dilution (%FM ≥ 33) (Table 2).

Applicability of selected BIA equations to predict %FM

All selected BIA equations significantly overestimated body fat when compared to the reference method (Table 3).
Table 2. Percentage FM by deuterium dilution method and BIA

<table>
<thead>
<tr>
<th></th>
<th>Deuterium dilution</th>
<th>BIA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total population (n = 160)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>% FM</td>
<td>24.7 (9.3)</td>
<td>29.5 (6.2)</td>
</tr>
<tr>
<td>%FM (deuterium dilution) ≤ 25 (n = 86)</td>
<td>17.3 (3.9)</td>
<td>29.2 (4.8)</td>
</tr>
<tr>
<td>%FM (deuterium dilution) ≤ 33 (n = 35)</td>
<td>37.9 (4.0)</td>
<td>29.9 (8.1)</td>
</tr>
</tbody>
</table>

1Significant overestimation by BIA, p<0.001
2Significant underestimation by BIA, p<0.001

Table 3. Percentage FM by the reference method (deuterium dilution), compared with %FM calculated using selected BIA equations

<table>
<thead>
<tr>
<th>Method</th>
<th>Mean ± SD</th>
<th>Correlation with deuterium dilution method (Spearman’s correlation coefficient)</th>
</tr>
</thead>
<tbody>
<tr>
<td>%FM (Kusher et al, 1992)</td>
<td>46.7 ± 8.2</td>
<td>0.67²</td>
</tr>
<tr>
<td>%FM (Bray et al, 2002)</td>
<td>33.4 ± 5.6</td>
<td>0.63²</td>
</tr>
<tr>
<td>%FM (Houtkooper et al, 1989)</td>
<td>27.4 ± 6.2</td>
<td>0.63²</td>
</tr>
<tr>
<td>%FM (Wickramasinghe et al, 2008)</td>
<td>38.7 ± 4.6</td>
<td>0.564²</td>
</tr>
<tr>
<td>%FM (Liu et al, 2011)</td>
<td>30.6 ± 5.9</td>
<td>0.658²</td>
</tr>
<tr>
<td>%FM (Deuterium dilution)</td>
<td>24.6 ± 9.2</td>
<td></td>
</tr>
</tbody>
</table>

1Significant overestimation from reference method, p<0.001
2Significant correlation, p<0.001
3FFM equations, which were used to calculate FM and %FM

Table 4. Comparison of anthropometric and impedance variables in validation and cross validation groups

<table>
<thead>
<tr>
<th>Variables</th>
<th>Validation group (mean ± SD)</th>
<th>Cross validation (mean ± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n = 107</td>
<td></td>
<td>n = 53</td>
</tr>
<tr>
<td>Age (years)</td>
<td>17.19 ± 1.5</td>
<td>17.25 ± 1.4</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>19.9 ± 3.5</td>
<td>19.5 ± 3.6</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>47.2 ± 8.3</td>
<td>46.1 ± 8.1</td>
</tr>
<tr>
<td>Height (m)</td>
<td>1.53 ± 0.05</td>
<td>1.53 ± 0.07</td>
</tr>
<tr>
<td>Resistance (Ω)</td>
<td>724.3 ± 79.8</td>
<td>737.4 ± 89.3</td>
</tr>
<tr>
<td>height²/resistance (cm²/Ω)</td>
<td>33.0 ± 3.8</td>
<td>32.5 ± 4.4</td>
</tr>
<tr>
<td>%FM (BIA)</td>
<td>29.4 ± 6.2</td>
<td>29.7 ± 6.3</td>
</tr>
<tr>
<td>%FM (deuterium dilution)</td>
<td>25.1 ± 9.4</td>
<td>23.8 ± 9.0</td>
</tr>
</tbody>
</table>
Table 5. Models of the preliminary and final prediction equation

<table>
<thead>
<tr>
<th></th>
<th>Preliminary equation</th>
<th>Final equation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Equation</td>
<td>(%FM = -93.65 + 0.892 \text{ (height}^2/\text{resistance}) + 0.064 \text{ (resistance)} + 2.161 \text{ (BMI)})</td>
<td>(%FM = -74.065 + 0.671 \text{ (height}^2/\text{resistance}) + 0.049 \text{ (resistance)} + 2.08 \text{ (BMI)})</td>
</tr>
<tr>
<td>Spearman’s (r)</td>
<td>0.7</td>
<td>0.696</td>
</tr>
<tr>
<td>%FM (equation)</td>
<td>24.7 ± 6.4</td>
<td>24.9 ± 6.3</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>%FM (deuterium dilution)</td>
<td>23.8 ± 9.0</td>
<td>24.67 ± 9.2</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Figure 1. Scatter plots indicating \%FM by BIA and the reference method (deuterium dilution).
Derivation of a new BIA equation to predict %FM

Age, anthropometric measurements and impedance variables of the validation and cross validation groups were similar (Table 4). The preliminary prediction equation derived for %FM using the validation group, was derived using %FM by the reference method as the dependent variable and age, BMI, body weight, resistance and height²/resistance as independent variables. While age and body weight were not significant predictors of %FM, BMI, resistance and height²/resistance, were the most reliable independent variables (p < 0.001) for prediction of %FM. The preliminary equation when applied to the cross validation group (n = 53) significantly correlated (r = 0.700, p < 0.001) with %FM (deuterium dilution) (Figure 1a). There was no significant difference between %FM obtained by the reference method (deuterium dilution) and %FM through the preliminary equation (Table 05). Bland Altman plots for plot difference shown in Figure 1(b) gave a mean bias of -0.93 ± 6.9%.

The final equation was derived following the combination of both the validation and cross validation groups (n = 160), linear regression analysis using %FM (deuterium dilution) as the dependent variable and BMI, resistance and height²/resistance (identified as the most reliable variables from the preliminary equation) as the independent variables. While there were no significant differences between %FM obtained by the reference method (deuterium dilution) and the final equation, %FM (final equation) significantly correlated (r = 0.696, p < 0.001) with %FM (deuterium dilution) (Figure 2a) (Table 05). Bland Altman plots used to assess the level of agreement between

![Figure 2. Association between %FM (deuterium dilution) and %FM (preliminary equation).](image)

![Figure 3. Association between %FM (deuterium dilution) and %FM (final equation).](image)
the derived prediction equation and %FM (deuterium dilution) for plot difference shown in Figure 2(b) gave a mean bias of -0.29 ± 6.7%.

Discussion

To our knowledge, this is the first BIA equation for the prediction of %FM in postpubertal girls of Sri Lankan origin and would be of use in screening for excess body fat among adolescent girls in Sri Lanka. The new equation is simple and only includes height²/resistance, which can be obtained from the BIA machine and BMI, easily obtained by height and weight measurements as variables. The inclusion of BMI in the equation indicates that it is a valuable component in body fat assessment, though on its own it may be prone to error. Though previous BIA equations too included height²/resistance as a prediction variable (14-16), body weight and age, which are common variables in other prediction equations (10), body weight may have been eliminated due to the inclusion of BMI into our equation and age, due to the narrow age range of our study population.

The results of this study indicate that direct use of %FM from BIA is inappropriate, and would possibly result in erroneous classification of a majority of adolescent girls as having excess body fat. Direct assessment by the BIA was shown to overestimate %FM in the population, with underestimation of %FM of girls who were classified as having excess fat mass by the reference method. Similar to our results, Sun et al (5), reported that BIA tends to overestimate fat mass when subjects are relatively lean (fat mass <25%) and underestimate fat mass when subjects are overweight or obese (%FM > 33%).

Due to the lack of BIA equations for the prediction of %FM of South Asian adolescent girls, the other equations that we used were those derived on Caucasian or African American children who were younger but of similar weight and height to our population (15, 16). The fact that our study population was postpubertal, despite being the same weight and height, may partly account for the poor validity of such equations when applied to our population. The Kushner equation was selected as its wide age range (0.22 - 66 years) included our age range of 15 - 19 years (14). However, this too was found to be unsuitable. The equation by Wickramasinghe et al was selected as it included children of Sri Lankan origin, and that by Liu et al (17) was selected as it included children of Asian origin. However, both equations were for the calculation of FFM and was based on the assumption that FM may be calculated by the subtraction of fat free mass from bodyweight. Further, both equations were developed on children <15 years of age, while our population was postpubertal adolescents, making these equations unsuitable for our population.

Therefore, we deduce that existing BIA equations for the prediction of %FM were not suitable for postpubertal adolescents, as they overestimated %FM, compared to the reference method. This evidence further supports the consensus that population specific equations are essential in assessing fat mass by BIA.

The new BIA equation for the prediction of %FM of 15 - 19 year old Sri Lankan adolescent girls, significantly correlated with the reference method of deuterium dilution. The Bland Altman plot for comparison of two methods further illustrates accuracy of the new prediction equation. The mean difference between the actual and predicted %FM (mean bias) was close to zero (mean bias: - 0.29%) and had only one individual with residuals exceeding the 95% confidence limits of %FM. In conclusion, the new BIA equation can be used for the estimation of %FM of post pubertal adolescent girls in Sri Lanka and is possibly suitable for other adolescent girls of South Asian origin.

Acknowledgments

The authors thank Thisira Andrahennadhi, Department of Biochemistry and Molecular Biology, Faculty of Medicine, University of Colombo for technical assistance.

References


Screening for gestational diabetes in the Anuradhapura district

T R N Fernando¹, B G S Jayaratna², E C K Lankeshwara²


(Index words: gestational diabetes, screening)

Abstract

Introduction: Gestational diabetes mellitus (GDM) is one of the most common medical complications of pregnancy. GDM is associated with 2-4 times increase in perinatal complications. Asian women are at higher risk of GDM compared to white Caucasians. Only few studies have been done to understand GDM among rural Sri Lankan women.

Objectives: To determine if risk assessment for GDM is conducted at the field antenatal booking and to determine the types of screening methods for GDM applied in the Anuradhapura district (AD).

Method: Cross sectional retrospective analysis of a hospital based sample of pregnant women attending for their delivery.

Study population: Pregnant mothers with period of amenorrhoea (POA) >28 weeks, in the AD.

Results: N = 422. Six out of seven risk factors mentioned in the antenatal record (ANR) were well documented, in >90%. Eight risk factors, not mentioned in the ANR were poorly documented (<22%). Random urine sugar testing was done in 93%, while blood sugar tests were done in <41%.

Conclusion: Screening for GDM in the primary health care of Anuradhapura district is grossly inadequate.

Introduction

Gestational diabetes is defined as glucose intolerance first recognized during pregnancy. This definition includes women with previously undiagnosed diabetes at one end of the spectrum and those with mild disturbances of glucose intolerance resulting from the metabolic changes in late pregnancy at the other end (1). Perinatal mortality remains five times higher in GDM when untreated compared to non diabetic women.

GDM represents 90% of diabetes mellitus diagnosed during pregnancy. Its prevalence doubled in the last 8 years; a 12% increase occurring per year in high risk populations (3). The number of diabetics, is projected to double (during 2000 - 2030), in developing countries, including South Asia, thus posing a huge challenge to health care systems (8, 10).

The first case report of GDM was in 1824, with a description of a mother with thirst, polyuria and glycosuria and the death of a macrosomic infant from shoulder impaction (1). In 1917, Joslin upon observing 1300 pregnant women, published the first report of GDM, recognising adverse outcomes can be prevented by active metabolic control (2).

The pathogenesis of GDM involves insulin resistance (IR) and defective insulin secretion; anti-insulin hormones secreted by the placenta give rise to IR, making pregnancy a diabetogenic state. The onset of IR is usually after 24 weeks of gestation. A normal pancreatic reserve will respond by increasing insulin secretion, although a reduction in the pancreatic β-cell mass results in maternal hyperglycaemia (3). Glucose is transported across the placenta by facilitated diffusion. Therefore maternal hyperglycaemia will cause fetal hyperglycaemia. The fetal pancreas will increase production of insulin in response to hyperglycaemia. Insulin being an anabolic hormone predisposes the fetus to macrosomia. In addition glucose will stimulate insulin like growth factor (IGF) receptors and increase fetal growth rate.

Perinatal complications of untreated GDM include increased perinatal deaths, large for gestational age fetus, shoulder dystocia and neonatal hypoglycaemia. GDM also increases the risk of pre-eclampsia and intra-partum complications in the mother. The long term risk of type 2 diabetes for women with GDM is doubled compared to non GDM women (17). A 10 year multicentre randomised clinical trial found a significant reduction, in serious adverse perinatal outcome in the treatment group with insulin (5).

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In early 1990s studies demonstrated that Asians had the highest risk of developing GDM compared to other ethnecities (4). Cheung and Wasmer examined the records of 2139 Asian women and concluded the prevalence of GDM among women in Sri Lanka is 10.5%, in China 9.2% and Philippines 6.2% (6). In 2004 Seshiah et al reported the prevalence of GDM in South India is as high as 18% (7), while Ginge et al reported this as 10.3% in Homagama in 2003 (19). The International Diabetes Federation states the prevalence of GDM in Sri Lanka stands at 11.5% in its report in 2010 (10). However, in white Caucasians these values are low, about 2-5% (6). The prevalence of GDM depends on: the ethnicity, prevalence of type 2 DM in the population and the type of diagnostic test used.

Assessing high risk women at ante natal booking and testing at 24-28 weeks of pregnancy is the widely accepted screening method for GDM. United Kingdom, NICE Guideline (2008) recommends screening all South Asian women by OGTT, i.e. with or without risk factors. The Sri Lankan Guidelines on Management of Diabetes Mellitus issued in 2007, by the Ceylon College of Physicians, addresses GDM screening (15). This includes 15 risk factors to be assessed at antenatal booking visit and recommends when risk factors are identified, to perform a 2 hour post prandial blood sugar (PPBS) test. If this value is >130 mg/dl, to proceed immediately to a 75g oral glucose tolerance test (OGTT). If 2 hour PPBS is normal, even with one risk factor for GDM, to proceed with 75g OGTT between 24-28 weeks of gestation (15).

National Laboratory Guideline by the Ministry of Health 2007 recommends selective screening for women with risk factors for GDM (18). This identifies 11 risk factors including, glycosuria in the first trimester or glycosuria on two occasions in either 2nd or 3rd trimester (18).

**Objectives**

To determine if risk assessment for GDM is routinely carried out at the field antenatal booking (ANB) and the types of test performed to detect GDM, in primary health care in the Anuradhapura district.

**Methodology**

**Study design:** cross sectional retrospective analysis of a hospital based sample of pregnant women attending for their delivery.

**Study population:** 422 pregnant women with a POA >28weeks from AD, using convenient method of sample selection.

**Study procedure:** ethical clearance was obtained from the Ethics Review Committee of Faculty of Medicine and Allied Sciences, Rajarata University. Data collection was done by using a data extraction sheet. Pilot study was done in April 2011 to pre-test and validate the questionnaire. Verbal consent was taken. Data was collected from the field antenatal records (ANR) of the pregnant women who were >28 weeks, admitted to Teaching Hospital, Anuradhapura (THA). Almost 98% of deliveries of AD take place at the THA.

Data collection was started and completed in June 2011 over 20 days, by a group of medical students of the batch 2005/06 of Rajarata University.

![Figure 1. Risk assessment and documentation at field ante natal booking.](image-url)
Gestational diabetes

Figure 2. Investigations performed to screen for GDM at field clinics.

Figure 3. Investigations carried out following request at field ANC.
Results

The median age of the sample is 27 years with an age range from 17 years to 42 years.

The percentage of primigravida is 44.8%.

Out of 15 risk factors for GDM given in Ceylon College of Physicians Clinical Practice Guidelines, 6 were documented in more than 90% of the field antenatal records at the ANB. Body mass index (BMI) was documented in only 68.2%. Seven risk factors were documented in less than 22% at the ANB (Figure 1). The most frequently done test to detect diabetes in the field ante natal clinics (ANC) was the random Benedict’s test in urine, accounting for 93.4% (Figure 2). Blood glucose testing was done only in 41.9% of women in this study population. The most frequently requested blood sugar test was 2 hour PPBS and 77.7% of the requested PPBS were done (Figure 3). Out of 422 women, 103 (24.5%) ANR had PPBS requested at primary health care in Anuradhapura district. Only 80 (19%) women out of these 103 had the PPBS results documented in the ANR (Figure 2).

The 50 g oral glucose challenge test (GCT) was the 2nd most frequently done test in 68 (16.1%) women (Figure 2). GCT was requested at the field ANCs. 75 g OGTT was done only in 4 (0.9%) women out of 9 requests in the ANRs (Figure 2 and Figure 3).

Discussion

For the past five decades Sri Lanka has focused on maternal mortality and has achieved millennium development goals with distinction. However, the focus on perinatal mortality had not been as good as maternal mortality. Therefore GDM has not been a priority in the preventive arm of primary health care in Sri Lanka.

Only few studies have been done in Sri Lanka on GDM in rural women. Ginige et al studied 1020 pregnant women from Homagama DDHS area in 2003, on community based screening for GDM (16). This study recommends that in primary care, screening for GDM, testing for postprandial glycosuria by enzyme based test strips is a better alternative to the current practice of Benedict’s test of random urine, until our MCH system is able to implement universal screening using capillary blood glucose 2 hours following 75 g glucose loading at 24-28 weeks of pregnancy in the field, following an in depth survey of its cost effectiveness (16).

Nanayakkara K, studied pregnancy outcomes and complications of 200 antenatal mothers diagnosed with GDM at the Teaching Hospital, Kandy, Sri Lanka, and compared these with western data. They showed one in five mothers remained having type 2 diabetes mellitus, in the immediate post-partum: indicating a perilous rise of diabetes in women of reproductive age in this country (9).

Previous research on “screening of GDM” in Sri Lanka, arrived at the following conclusions. One study indicated that traditional risk factors didn’t predict GDM, hence screening for GDM should be performed in all women at 24-28 weeks of pregnancy by using 50 g oral glucose challenge test (11). Another study indicates that, screening methods for GDM practiced in Anuradhapura district are highly unsatisfactory (12).

The significant finding in our study is that the risk factors for GDM that were listed in the field ante natal record (ANR) were assessed and documented in over 90%. However, the risk factors that were not mentioned in the ANR were poorly documented (<20%).

Out of 15 risk factors given in Sri Lankan guidelines for GDM, 7 had been listed in the ANR used by the primary health care in Sri Lanka.

They are: age, BMI, Symphysio fundal height, past history of pregnancy induced hypertension, past history of recurrent miscarriages, previous unexplained still births and previous birth weights.

Six out of the seven risk factors given above were assessed and documented in more than 90% in the ANRs except BMI which was only 68% (Figure 1). Weight of the mother was recorded only in 21.6% of ANRs (Figure 1).

Sri Lankan guidelines for GDM recommends to detect high risk women and then to perform 2 hour PPBS or 75 g OGTT (15,18). Risk factor screening, even in high prevalence populations for GDM, has a sensitivity and specificity of only up to 50% (13).

The test that was commonly used to detect hyperglycaemia in this study population was glycosuria testing by random Benedict’s test at the ANCs. Majority (93%) of women had a glycosuria test done, which is a common practice in our ANCs (Figure 2). Glycosuria has a very poor sensitivity and specificity in pregnancy and is not recommended as a screening test for GDM. However, the blood glucose testing was performed in less than 41% of women in this study.

Post prandial blood sugar (PPBS) was the test commonly done to check the blood glucose level, this too in only 19% of women (Figure 2). 2 hour PPBS has a specificity of 80% and sensitivity of 40%, therefore giving high false negative rates. 2 hour PPBS is not a good screening test for GDM.

50 g oral glucose challenge test (GCT) was done in 16% of women in this study. GCT is recommended as a screening test for GDM by American College of Obstetricians and Gynaecologists. GCT has a specificity of 85% and a sensitivity of 80%. This test has an advantage over 75 g oral glucose tolerance (OGTT) as the patient does not have to be fasting and only one blood sample is tested. Disadvantages of this test are, if screening is positive with GCT then a diagnostic test has
to be performed with OGTT and it will not detect fasting hyperglycaemia.

Fasting blood sugar (FBS) was done in 2% of women in this study. FBS has a sensitivity of 70 - 90% and a specificity of 50 - 75%. The sensitivity and specificity increases with the lower cut off value for the FBS level. FBS is recommended by International Association of Diabetes and Pregnancy Study Groups (IADPSG) as a screening test to detect overt diabetes in the first antenatal clinic visit at 126 mg/dl (14). However, attending the clinic for the first time in a fasting state is impractical in many rural settings of South Asia. Furthermore in most women with GDM the fasting value often does not reflect the post prandial value and ethnicity of Asian Indians who have high insulin resistance (IR) and as a consequence, their PPG is higher compared to Caucasians.

The 75 g OGTT, the gold standard test, was performed only in 0.9% of women in this study. OGTT has a sensitivity of 80% and specificity of 87%. This test is considered the best available screening and diagnostic test for GDM, the disadvantage being the need for 3 blood glucose samples to be taken and the increased burden on local laboratories.

International Association of Diabetes and Pregnancy Study Groups (IADPSG) consensus statement based on HAPO data on the diagnosis of GDM recommends:

- Screening at the first antenatal visit to diagnose overt diabetes (to all women or selected high risk women), to detect overt diabetes at the 1st antenatal visit FBS or HbA1c are recommended. They recommended cut off value for FBS > 5.1 mmol/l with no suggested cut off value for HbA1c.
- Screening by GCT is not recommended, as GCT will not detect women with fasting hyperglycaemia.
- OGTT threshold for GDM, fasting plasma glucose 5.1 mmol/L (92 mg/dl), 1 hour plasma glucose 10 mmol/L (180 mg / dl) and 2 hour plasma glucose 8.5 mmol/L (153 mg / dl). This new criteria may diagnose up to 18% of women with GDM, increase or even doubling the number diagnosed by previous criteria (14). However, the applicability of these criteria is yet not ratified by WHO and has not been tested on the Sri Lankan population at field level.

Conclusions and recommendations

The screening for GDM is unsatisfactory in the Anuradhapura district. This study confirms the previous study done in AD in 2010 on screening for GDM by Dahanayake et al, that screening methods done are highly unsatisfactory (12).

Screening for GDM should be a priority in our primary healthcare. The global studies indicate that Sri Lankan women, being South Asians are at a high risk of developing GDM. A consensus should be arrived at by the experts, to decide on the best cost effective screening strategy for Sri Lanka.

There is a need to change the ante natal record, with changes, to include the risk assessment at booking visits for GDM. In addition, the training of primary health care staff and improve awareness among women regarding GDM too is important.

More research should be encouraged to understand GDM in Sri Lankan women and the cost effectiveness for a universal screening strategy.

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5. Department of Community Medicine, FMAS, RUSL.
6. Students of group 7 of batch 2005/06, of FMAS, RUSL, for collecting data.

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Prevalence of micro and macrovascular complications of diabetes detected at single visit screening

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(Index words: complications, diabetes, prevalence)

Abstract

Objective: To describe the prevalence of complications of diabetes and to study the relationship between the prevalence of complications and the duration of diabetes in a subset of Sri Lankan population

Study design: Cross sectional case analysis of 6765 patients at National Diabetes Centre, Rajagiriya, Sri Lanka.

Data analysis: Data was analyzed with SPSS 11.

Results: The mean duration of diabetes in the study population was 7.9 years (SD=6.7). The results showed that the prevalence of micro vascular complications increased with increasing duration of diabetes. In patients with diabetes mellitus for less than 1 year, retinopathy prevalence was 6.8% and in those with 16-20 years diabetes duration it rose to 52.6%. Neuropathy prevalence at diagnosis was 11% and at 16-20 years it was 54.3%. Nephropathy prevalence at diagnosis and at 16-20 years was 18.8% and 23.8% respectively.

Conclusions: The study has demonstrated high prevalence of complications at the initial diagnosis. Hence, early screening techniques would be beneficial in order to prevent and retard the progression of the disease and to reduce the associated morbidity and mortality.

Introduction

Prevalence of diabetes mellitus particularly type 2 has risen steadily over the past few decades globally. People with diabetes have an increased risk of developing microvascular complications like diabetic retinopathy, diabetic nephropathy and diabetic neuropathy, which, if undetected or left untreated, can have a devastating impact on quality of life and place a significant burden on health care costs.

Diabetic microvascular complications can reduce life expectancy. The strongest risk factors are poor glycaemic control and duration of diabetes. Other modifiable risk factors such as hypertension, dyslipidaemia smoking, as well as non-modifiable risk factors such as age at onset of diabetes and genetic factors all contribute to the progression of complications. Duration of diabetes and poor glycaemic control has been identified as the main factors leading to the development of complications (4).

Evidence is accumulating that complications are common among South Asian diabetic population including Sri Lankans, particularly in terms of cardiovascular and renal disease.

This study is aimed at estimating the prevalence of major micro and macrovascular complications of diabetes among subjects who presented for single visit screening at the National Diabetes Centre, Rajagiriya. We also studied any association between the duration of the disease and prevalence of complications.

Methods

Population characteristics

Study sample consisted of 6765 patients (4121 males and 2629 females) who had at least two screening visits to the National Diabetes Centre at Rajagiriya. Both type 1 and type 2 diabetes patients were included. The mean age of the study group was 51.63 years range. There were 95.5% patients with type 2 diabetes and 4.5% with type 1 diabetes. Study sample represented 14.1% rural and 85.7% urban dwellers. Employment categorisation breakdown shows 46.5% employed (12.9% professionals and 33.6 non professionals), 9.5 retired and 43.1% unemployed people in the study sample.

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Methodology

Electronic medical records of patient data were analysed and results were categorised into major micro and macrovascular complications of diabetes. Screening for diabetic retinopathy was carried out by dilated fundoscopy and a retinal camera (Topcon). All grades of diabetic retinopathy ranging from background retinopathy up to vitreous haemorrhage, in one or both eyes were included as diabetic retinopathy. Diabetic nephropathy included patients who were already diagnosed as having diabetic nephropathy by a physician or those with microalbuminuria above 20 g/dl on early morning spot urine sample (analysed by Daytona analyser) in the presence of a blood glucose level <200 mg/dl and a normal urine full report. Creatinine clearance was calculated by using the Cockcroft Gault formula. Those with nephropathy were further subcategorised into stages of CKD based on estimated GFR.

Patients were considered as having diabetic neuropathy when the clinical examination by a trained medical officer at the National Diabetes Centre showed that the sensory modalities of touch, vibration and pain were either impaired or absent in one or both feet. Touch was tested using cotton wool, pressure was tested with 10 g monofilament (Semmes Weinstein) and vibration was tested by using 128 Hz tuning fork.

Patients were diagnosed as having ischaemic heart disease if they carried a diagnosis. Data on stroke was not systematically captured and hence not analysed in this study. Diagnosis of peripheral vascular disease was made when the ankle brachial pressure index was <0.8. Blood pressure was checked with a standard manual sphygmomanometer and where the pedal pulse was weak or absent Doppler study was used to detect the blood flow in lower limb arteries.

We categorised the duration of diabetes into 6 groups as follows, Group1 (< 1 year), Group 2 (1-5 years), Group 3 (6-10 years), Group 4 (11-15 years), Group 5 (16-20 years), Group 6 (>20 years). There were 690 (10%) subjects in Group 1, 2353 (34.8%) in Group 2, 1710 (25.3%) in Group 3, 1034 (15.2%) in Group 4, 689 (10%) in Group 5, 289 (4.2%) in Group 6.

Data analysis

We analysed the data using SPSS version 11.

Results

The mean duration of diabetes in the study population was 7.9 years (SD = 6.7). There were 95.5% patients with type 2 DM and 4.5% with type 1 DM.

Majority of retinopathy cases were among the type 2 DM patients. Our results show a progressive rise in the number of retinopathy cases as the duration of diabetes increased (Table 1). There were 6.8% (n = 49) in <1 year group, 28.3% (n = 489) < 10 year group, while in those patients with diabetes of > 20 years the figure rose up to 57.8% (n = 175). Even severe degrees of retinopathy was noted among patients with duration of diabetes < 1 year. There were 6.8% patients with established retinopathy and among them 11 (23.3%) had background retinopathy, while 3 (6.2%) had evidence of maculopathy in < 1 year group. Diabetic neuropathy also demonstrated a similar trend with < 1 year group showing a prevalence of 11%, 6 - 10 year group 28.6% and over 20 year group rising to a figure of 65.3%. Table 1 summarizes the prevalence of microvascular complications in each group of patients with diabetes mellitus.

The prevalence of nephropathy (microalbuminuria) in < 1 year group was 18.8%, in 6 - 10 year group 21.2% and in the over 20 year group 25.4%. Those with nephropathy were further subcategorised into stages of CKD based on estimated GFR using the Cockcroft Gault formula. Table 2 shows the prevalence.

Table 1. Prevalence of complications of diabetes mellitus

<table>
<thead>
<tr>
<th>Complications</th>
<th>Duration of diabetes in years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt; 1 year</td>
</tr>
<tr>
<td>Retinopathy (%)</td>
<td>6.8</td>
</tr>
<tr>
<td>Nephropathy (%)</td>
<td>18.8</td>
</tr>
<tr>
<td>Neuropathy (%)</td>
<td>11</td>
</tr>
</tbody>
</table>
Diabetic peripheral neuropathy was observed in 11% (n = 79) patients < 1 year group, 28.6% (n = 493) in 6 - 10 year group, and in 54.3% (n = 344) in 16 - 20 year group (Table 1). Neuropathy was diagnosed if at least one of the above mentioned criteria were present in one or both feet (absence of vibration, touch or positive monofilament test -> 3/10).

Peripheral vascular disease was found in 7 patients (0.1%) in the < 1 year group, 7 (0.1%) in 6 - 10 year group, and in 88 (1.3%) in the 16 - 20 year group. The prevalence of IHD was 2.2% (n = 16) in < year group, 5% in 6 - 10 years and 10.6% in 16 - 20 years. Hypertension was detected in 4106 (60.7%) patients.

Discussion

The chronic complications of diabetes mellitus are important prognostic factors in diabetes and also reflect the standards of care the patients receive. The pathogenic mechanisms are variable and differ according to the race. In general the development of diabetic microangiopathy depends on the duration and the severity of disease while that of macro angiopathy does not. Age and duration of diabetes have been the most frequently mentioned risk factors for new onset type 2 diabetes complications (3, 4). Harris (4) has suggested, the presence of diabetic complications in type 2 DM may be a consequence of untreated hyperglycaemia or other factor while diabetes remain clinically undiagnosed (4). He has also shown that 50% type 2 DM patients in Europe had presence of complications at time of diagnosis. As the incidence of diabetes continues to rise, the burden of diabetic microvascular complications will also increase. To reduce the associated morbidity and mortality it is essential that factors associated with the onset and progression of diabetes-related complications are identified as early as possible.

In our study, we have shown that, even during the first year of diagnosis the prevalence of diabetic retinopathy was 6.8% and diabetic nephropathy prevalence during the first 5 years was as high as 64%. A significant proportion (45%) had evidence of stage 2 diabetic nephropathy during the first year of detection of diabetes. Table 3 compares the results of our study with results from regional countries like India (2) and Korea (1). The prevalence of retinopathy and neuropathy in Sri Lanka is comparable to those in India. However, our figure for diabetic nephropathy is about 4 times higher than that of...
India. The studies quoted are very old ones (1999), and it is better to mention what criteria they have used to diagnose each complication and the observed differences for example higher diabetic retinopathy and neuropathy in Korea is due to this effect.

Randomised intervention trials have shown that intensive treatment (tight control of blood glucose, blood pressure and lipids) delays the onset and slows the progression not only of diabetic retinopathy, but also of diabetic nephropathy in patients with type 1 diabetes (7). In the Diabetes Control Complications Trial intensive therapy reduced the mean adjusted risk of the cumulative incidence of microalbuminuria in the primary prevention cohort by 34% and the albumin excretion rate by 15% following the first year of therapy.

One of the shortcomings of our study is that we did not screen patients routinely for asymptomatic ischaemic heart disease which is common in diabetes mellitus.

We have been able to demonstrate a considerable degree of retinopathy and nephropathy affects the local population within the first year of diagnosis. These findings should be an eye opener to both the clinician as well as the health care planners of the country. Because of the chronic nature, insidious complications, and the means required to control diabetes being costly, diabetes mellitus is a major challenge to the health system. The therapeutic implications are that early detection and effective screening programme is mandatory in this regard as Sri Lanka is already witnessing an upsurge of diabetes.

References
Update on thyroid cancer management and the limitations faced by us

Kanishka de Silva


Magnitude of the problem

Thyroid problems are universal with pockets of high prevalence areas around the world. In United States new thyroid nodules develop at 0.1% per year (2% per year if exposed to head and neck radiation) resulting in palpable nodules which increase with age reaching 5% prevalence at 50 years or older. The magnitude of the problem was even more when thyroid glands were examined at autopsy, surgery or by ultrasound scans with 50% of thyroid glands having nodules which were almost always benign (95%).

Goiters are also very common in Sri Lanka with thyroid malignancies forming a small fraction of thyroid nodules. Unfortunately these may be missed easily in the general pool of benign thyroid enlargement, unless a special effort is made to diagnose and treat these. Missing is something that should be avoided, as most patients with differentiated thyroid cancer, if properly treated by experienced medical personnel have a potentially curable disease. In this scenario, it is always easy to miss and do too little or over react and do too much.

Initial evaluation of a thyroid nodule

Thyroid nodules are generally found by the patient or the clinician on clinical examination but at times may be detected incidentally during neck imaging for other reasons. In a patient with a thyroid nodule, a history and clinical examination must be undertaken to guide further investigations. But in a significant number of patients, the only detected abnormality is the thyroid nodule. The first recommended investigations in nodule evaluation are thyroid stimulating hormone (TSH) level and ultrasound scan (US). The clinical features, TSH measurements and US features are used to determine whether it is necessary to do a fine needle aspiration cytology (FNAC) of the nodule or whether there is a low risk for malignancy (2).

Further analysis based on TSH level

If there is a normal or an elevated TSH, a FNAC (based on clinical and US features) is indicated to exclude malignancy. In addition patients with elevated TSH must be further evaluated and treated for hypothyroidism. Patients with a low TSH would benefit by an isotope scan. Hot (autonomous) nodules are rarely associated malignancy and would require treatment for thyrotoxicosis. Cold or warm nodules require FNAC (based on clinical and US features) and management depending on the FNAC findings.

US features indicating FNAC

Certain US features create a higher degree of suspicion and thereby indicate FNAC. These include hypoechoic nodules, microcalcification, increased central vascularity, infiltrative margins, nodule taller than wide in transverse plane, a solid nodule more than 1.5 cm, a cystic and solid nodule, spongiform nodule more than 2 cm and associated suspicious cervical lymph node enlargement. FNAC is not indicated for simple cysts other than for therapeutic aspiration (4).

FNAC findings

The FNAC results could be reported using different classifications (2,5,6). Two main systems currently used are the USA based NCI / Bethesda and UK based BTA / RCP Thy 1- Thy 5 categories. These parallel system FNAC categories are as follows:

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Management strategies based on FNAC

Based on the FNAC finding following management strategies could be adopted (2,6):

I. Insufficient cytology or a non diagnostic smear [Thy 1 and Thy 1c (cystic lesions)].

II. Benign – includes nodular goiter, colloid nodules, hyperplastic/adenomatoid nodules, Hashimoto’s thyroiditis, granulomatous thyroiditis. [Thy 2 and Thy 2c (cystic lesions)].

III. Atypia of undetermined significance or follicular lesions of undetermined significance (atypical follicular lesions, cellular follicular lesion, neoplasm cannot be ruled out) [Thy 3a (atypia)].

IV. Follicular neoplasm or suspicious of follicular neoplasm and include hurthle neoplasm [Thy 3f (follicular)].

V. Suspicious of malignancy [Thy 4].

VI. Malignant (papillary, medullary, anaplastic, lymphoma, metastatic) [Thy 5].

Extent of surgery for thyroid cancers

Appropriate thyroid resection especially for lower risk papillary cancer is very controversial. Mayo clinic result analysis indicate that in low risk papillary thyroid cancer (MACIS score: 3.99 or less) there is no improvement in survival rates after surgery more extensive than lobectomy. National Comprehensive Cancer Network (NCCN) panelists analyzed large number of studies which showed that lobectomy alone is adequate for unifocal papillary microcarcinoma (less than 1 cm in diameter in patients who have not been previously exposed to radiation and have no other risk factors and whose disease is confined to the thyroid and has no vascular invasion) as well as minimally invasive follicular cancers. Analysis of AMES criteria show that patients offered total thyroidectomy for low risk papillary cancer tend to have lower 20 year local recurrence and neck recurrence (2,7).

Papillary carcinoma has been shown to be multifocal in 30 - 87.5% cases. A large thyroid remnant left behind after unilateral lobectomy may leave a potentially involved lobe behind with the possibility of progression and dissemination. In addition it may complicate long term follow up with serum thyroglobulin (TG) and whole body \(^{131}\)I imaging, as well as \(^{131}\)I treatment for metastatic disease. Total thyroidectomy will also reduce the long term risk of degeneration of differentiated tumours into anaplastic cancer. The long term recurrence rates as high as over 30% have been shown in the lobectomy alone group compared with only 1% after total thyroidectomy and radio I (\(^{131}\)I) ablation. Some studies also show better long term survival in the aggressively treated group. It has also been shown that about 50% of patients with recurrent disease in the central neck die of the disease, whereas about 50% of patients who die of thyroid cancer die of central neck recurrences (2).
Total thyroidectomy is indicated in papillary carcinoma, if age is below 15 or over 45 years, bilateral nodular enlargement, tumour over 4 cm, aggressive variant (tall cell variant, columnar cell, poorly differentiated features), extra thyroidal extension, cervical lymph node metastasis and presence of distant metastasis. In follicular and hurthle cell carcinoma if there is invasion or metastasis and in medullary carcinoma. Anaplastic carcinoma is universally fatal, but if locally resectable disease is encountered, a total or near total thyroidectomy should be offered (2).

Total thyroidectomy increases the risk of recurrent laryngeal nerves and more importantly is associated with long term hypoparathyroidism. But an experienced surgeon recognizing and carefully preserving these structures would minimize these risks. Therefore these aspects should be discussed with the patient and the patient preference must also be taken into account prior to planning the extent of thyroid surgery.

In papillary carcinoma, hurthle cell cancer and medullary carcinoma with node negative (N0) neck, a prophylactic central neck dissection (Level VI) is indicated. Follicular carcinoma with node negative (N0) neck could be spared a neck dissection as lymphatic metastasis is uncommon. If nodes are involved a selective clearance of Levels II, III, IV and V are undertaken in any of these patients (2).

**Post surgical management**

Patients with papillary, follicular and hurthle cell carcinoma must be post surgically evaluated (at 2 - 12 weeks post operatively) with TSH, thyroglobulin (TG) measurement and anti TG - antibody (AB). $^{131}$I Scan after adequate TSH stimulation (thyroid withdrawal / rh TSH ) could be undertaken to assess for completeness of thyroidectomy and presence of residual disease. A phenomenon described as “Stunning effect” where $^{131}$I induced follicular cell death occurs which can reduce uptake of radio iodine to the thyroid remnant and metastasis. Use of $^{123}$I or a small dose of $^{131}$I followed by a uptake of radio iodine to the thyroid remnant and induced follicular cell death occurs which can reduce iodine imaging (2).

Thyroid remnant can be ablated by 30-iodine regime without $^{131}$I scan or dosimetry to reduce the significant number of centres rely on fixed dose radio.

**Chemo therapy (chemo) and other treatment**

Chemo has a limited role in thyroid cancer. In radioiodine non responsive metastasis of differentiated carcinoma chemo has been tried (doxorubicin, bisphosphonate for bone metastasis). Other novel treatments include kinase inhibitors (motesanib, sunitanib, axitinib, vandetanib), histone deacetylase inhibitors (virinostat, depsipeptide), DNA methylation inhibitor (decitabine), heat shock protein 90 inhibitor (17 AAG), proteaosome inhibitor (bortezomib), selective cyclooxygenase 2 inhibitor (celecoxib) and derivative of thalidomide (lenalidomide) (2).

**Post treatment surveillance**

Patients with papillary, follicular and hurthle cell carcinoma – physical examination, TSH, TG and anti TG-AB at 6 months, 1 year, and annually as well as periodic US scan of the neck are used if patient is disease free. TSH stimulated TG is useful in previously radioiodine treated patients (with negative TSH suppressed TG and anti TG-AB). TSH stimulated radioiodine imaging is useful for patients with advanced disease (T 3 - 4, M1), abnormal TG (either TSH suppressed or stimulated), abnormal anti TG-AB, abnormal US in the follow up. Non radioiodine imaging (CT, MRI, PET CT) can be used if radioiodine imaging is negative with stimulated TG over 2 - 5 ng/ml.
In medullary carcinoma the recommendation is to check calcitonin and CEA at two months after surgery and thereafter annually for calcitonin, CEA, US neck, pheochromocytoma (MEN 2 A or B patients) and hyperparathyroidism (MEN 2A patients) (2,7).

Limitations faced in Sri Lanka

Majority of our patients undergo treatment for thyroid problems in non fee levying government hospitals, where TSH, TG, anti TG-AB and other serum markers are not freely available. It also takes a long time to get a report from another distant major hospital even if it is available. Long dates may be given for US scans, and also the experience of radiologists on thyroid scanning could vary. Isotopes are brought in batches and can be out of stock for varying periods of time, leading to long waiting lists. Cyto-pathologists are not available in all hospitals and the experience levels also vary on thyroid FNAC reporting. A uniform classification for thyroid FNAC reporting is not followed in Sri Lanka leading to difficulties in decision making. Most of the surgeons overcome these problems by, routinely offering a lobectomy with a follow up completion total thyroidectomy in suspected cases of cancer or by offering a subtotal thyroidectomy if they don’t suspect one. Isolation facilities for radioiodine treated patients are only available at Cancer Institute, Maharagama. Patients requiring therapeutic doses need to be transferred to this institution creating a long waiting list. There could be many more problems related to patient tracking, report tracking as well as difficulties encountered in offering a rational management discussion with our patients. Therefore decision making as described in this article, may not be possible in a large number of hospitals in Sri Lanka. International guidelines must be respected, but practical realities in our country need to be taken into account, in managing our patients.

References

Glucocorticoid induced hyperglycaemia

M I Weerakkody¹, N P Somasundaram²


Abstract

Modern medicine has discovered numerous benefits of supra-physiological doses of glucocorticoids, both as immunosuppressive as well as anti inflammatory agents. Hyperglycaemia is one important side effect of steroids, with a number of unresolved issues on its diagnosis and management. This article describes important points regarding the pathophysiology and diagnosis of steroid induced hyperglycaemia. It also discusses a practical approach to its management.

Introduction

The use of glucocorticoids as anti inflammatory and immunosuppressive agents are on the rise, with a parallel increase of the adverse effects of prolonged and supra-physiological dose medications. Glucocorticoids exacerbate hyperglycaemia in almost all patients with diabetes mellitus, but it is also responsible for the development of diabetes mellitus in previously normoglycaemic individuals.

In a nested case control study using the Health Improvement Network in the United Kingdom, oral glucocorticoid therapy was associated with an odds ratio of 1.36 for the development of new onset diabetes (1). Other studies have recorded odds ratios for new onset diabetes due to exogenous steroids between 1.7 to 2.31 (2). In all these studies the total glucocorticoid dose and the duration of therapy were strong predictors of the induction of diabetes. This is substantiated by evidence that patients with decreased insulin secretory reserve are more likely to develop diabetes (3). Other risk factors are older age and higher body mass index, both of which are known risk factors for the development of insulin resistance and type 2 diabetes mellitus.

The occurrence of hyperglycaemia with glucocorticoids may remain undetected in a proportion of patients as glucocorticoids are more likely to increase post prandial blood glucose than fasting blood glucose. In a study among patients with primary renal disease treated with prednisolone, 40% developed 2 hour post prandial blood glucose values exceeding 200 mg/dl but with normal fasting blood glucose (4). In a cohort of patients with various neurological diseases receiving prednisolone, corticosteroid related diabetes developed in 50%. These patients also had a similar pattern of abnormally high post prandial blood glucose with normal fasting values (5).

Mechanisms of glucocorticoid induced hyperglycaemia

The predominant mechanism responsible for glucose intolerance associated with glucocorticoid therapy is reduced insulin sensitivity. This impairment in insulin action has been demonstrated in both liver and skeletal muscle. The ability to compensate for this decrease in insulin sensitivity, by an increase in insulin secretion, determines the extent of the rise in plasma glucose with glucocorticoids (6). A reduction in insulin secretory capacity has also been observed at higher doses of corticosteroids (7). Calcineurin inhibitors such as cyclosporine and tacrolimus are known to induce glucose intolerance through a direct effect on insulin synthesis and release. Toxic levels of the drugs have also been shown to induce islet cell apoptosis (8). Due to the dual effects of glucocorticoids and calcineurin inhibitors, the incidence of new onset diabetes in patients undergoing organ transplantation is quite high; the incidence ranging from 10% to 50% being reported (2). In addition hyperglycaemia induced by glucocorticoids is known to be associated with reduced glucose transporter 2 (GLUT2) receptor expression and decreased glucose transport of glucose into pancreatic beta cells (9).

The pharmacokinetic properties of most glucocorticoids are short lasting; but their pharmacodynamic properties with respect to glucose tolerance are prolonged, as there are genomic effects of the drugs on mediating gluconeogenesis and peripheral insulin sensitivity. Although the plasma half life of prednisolone and dexamethasone are about 2.5 hours, in a recent study insulin concentrations were significantly elevated even after 20 hours of administration of dexamethasone to normal volunteers suggesting that the hyperglycaemic effect is longlasting (10).

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Management of glucocorticoid induced hyperglycaemia

The detection of glucocorticoid induced hyperglycaemia requires frequent monitoring of blood glucose levels; self monitoring of blood glucose would therefore play an important role. As the typical pattern of hyperglycaemia with steroids is minimally elevated fasting blood glucose levels with exaggerated post prandial hyperglycaemia, measurement of post prandial blood glucose should be the key screening tool (11).

Treatment of glucocorticoid induced hyperglycaemia, even in the short term, is important. Studies show that even short term post prandial hyperglycaemia is associated with acute inflammation and endothelial dysfunction in patients with and without type 2 diabetes mellitus (12). Reduction of fluctuations in glucose levels with administration of insulin decreases these defects. Although evidence from randomised trials testing this hypothesis in glucocorticoid treated patients is lacking, this phenomenon could be extrapolated as a likely occurrence with glucocorticoid treatment. Healthy dietary practices with avoidance of overeating and the consumption of concentrated simple carbohydrates, regular exercise and regular monitoring of blood glucose levels play an important role in the prevention and treatment of steroid induced hyperglycaemia.

All currently available drugs for the treatment of type 2 diabetes mellitus could also be used to treat glucocorticoid induced hyperglycaemia, but there are only a few published studies regarding the efficacy of these agents in glucocorticoid induced hyperglycaemia. However, few key principles should be employed in choosing glucose lowering drugs in patients. Metformin could be considered as one of the agents of choice in these patients, as it increases insulin sensitivity and counteracts the chief mechanism of pathogenesis of glucocorticoid induced hyperglycaemia. However, as some of the patients on long term glucocorticoids are either hypoxic or have renal insufficiency, metformin may not be the suitable option for them due to increased risk of lactic acidosis. Long acting sulfonyleureas were first used in renal transplant patients with achievement of good blood glucose control in about 25% of the patients (2). The relatively low cost and prompt insulin secretory action are some of their benefits. The presence of drugs that are metabolised mainly by the liver (e.g. glypizide) are advantageous in advanced liver or renal failure. However, long acting sulfonyleureas may increase the risk of hypoglycaemia, especially in patients with deteriorating renal function (13). Thiazolidinediones (glitazones) are also a treatment option. They have been used successfully in post transplant diabetes mellitus patients, either alone or in combination with other oral agents (14, 15). However there is increasing concern regarding oedema, congestive cardiac failure and risk of cardiovascular disease with their use (16). This may be detrimental for patients on glucocorticoids, which by themselves are associated with other metabolic complications like hyperlipidaemia, that have an additional detrimental effect on co-existing compromised renal function, which by itself is a risk factor for cardiac disease. There is emerging evidence of increasing fracture risk for women on long term glitazones (17), and with the increased risk of osteoporosis with glucocorticoid use, the combined risks would actually preclude their use in this specific group of patients.

In view of high doses of steroids being required to induce a therapeutic response in most diseases, they generally induce very severe insulin resistance, which may not be controlled adequately with non insulin therapy (11). Therefore insulin treatment would be necessary in most patients with glucocorticoid induced hyperglycaemia, except for the few who are on small doses of steroids. Insulin can be used safely and effectively in most patients. There are several options for treatment such as using basal insulin, prandial insulin or a pre mixed regime. There is a paucity of randomised clinical trials on the best insulin regime for patients with glucocorticoid induced hyperglycaemia. However, a recently concluded study comparing prandial, basal and pre mixed insulin in type 2 diabetes mellitus demonstrated that each regime reduces the HbA1C values significantly, but the blood sugar control was slightly better with prandial or pre mixed insulin regimes (18). These results could possibly be extrapolated to the steroid induced hyperglycaemia patients. But prandial and pre mixed insulin regimes have the disadvantage of being multiple, and complex which can reduce patient compliance with a higher risk of hypoglycaemia (1).

As patients treated with once daily glucocorticoids typically have normal fasting glucose levels with elevated post prandial values, a prandial insulin regime that is calculated according to the patient’s body weight, meal pattern and caloric consumption, has been used as one appropriate strategy (11). Basal insulin would only be added to those on higher doses or multiple daily doses of glucocorticoids, or to those with pre-existing diabetes. However, frequent insulin injections, especially for patients who are already burdened by another chronic illness may actually reduce compliance. It can also be argued that the normal fasting blood glucose levels with gradual elevation of blood glucose throughout the day, resulting in post prandial hyperglycaemia, is related to the time course of insulin resistance induced by glucocorticoids rather than due to a specific defect in post prandial insulin secretion (2). In pregnancy, which is also a state of insulin resistance, the requirement of basal insulin increases with advancing pregnancy but the prandial insulin requirement remain stable (2).
Therefore the best approach to ensure patient compliance and adequate control of blood glucose is basal insulin in the morning, calculated according to the body weight and the glucocorticoid dose (1). Since isophane insulin has a peak action after 4 - 8 hours of administration with a duration of action for 12 to 16 hours, which mirrors the peak and duration of action of the prednisolone, the preference would be to use isophane insulin as the basal insulin type. The substitution of insulin glargine or detemir would be appropriate when dexamethasone is used as it has even longer hyperglycaemic effects (2). Prandial insulin could be added if blood glucose fails to be controlled with the above regime, or, if the patient has pre-existing diabetes. Patient compliance with this treatment would be better, as it involves just a single dose of insulin in the morning and the patient can adjust the dose according to his/her steroid intake.

Conclusion
Glucocorticoids are the treatment of choice for numerous conditions, often used long term, with a clear therapeutic benefit. However, it is often associated with a number of adverse events, with glucocorticoid induced insulin resistance leading to hyperglycaemia being a common problem. It is important to treat this hyperglycaemia as if uncontrolled is associated with acute inflammation and endothelial dysfunction. Glucocorticoid induced hyperglycaemia can be treated with either oral hypoglycaemic agents or insulin, but insulin is the more suitable treatment option.

References
New drugs in diabetes

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(Index words: Colesevelam, Bromocriptine mesylate, Dapagliflozin)

Abstract

The field of diabetes has witnessed the development of new therapeutic agents with novel mechanisms of action. This article describes four drugs which have the potential for revolutionizing the management of type 2 diabetes in the future.

Colesevelam is a bile acid sequestrant, which is unique in reducing both LDL cholesterol and hyperglycaemia, when used in combination with metformin, sulphonylurea and insulin. Additionally, it is effective in patients with prediabetes and hypercholesterolaemia. Hypoglycaemia and weight gain are not observed with colesevelam.

Bromocriptine mesylate is a timed release dopamine D2 receptor agonist which restores the dopaminergic tone within the central nervous system (CNS). It reduces plasma glucose, triglyceride and free fatty acid (FFA) levels. Additionally, cycloset decreased the cardiovascular composite end point by 40%. The drug has to be taken within 2 hours of awakening.

Dapagliflozin is a selective sodium-glucose co-transporter 2 (SGLT2) inhibitor which increases urinary glucose excretion resulting in net caloric loss. It reduces both weight and blood pressure. But dapagliflozin-treated patients reported an increase in events suggestive of genital infections and lower urinary tract infections (UTIs), which needs further evaluation.

Glucokinase (GK) which is involved in the first step in glycolysis, exhibits two different actions in pancreas and liver leading to increased insulin secretion and glycogen synthesis respectively. Glucokinase activators (GKAs) increase the affinity of GK for glucose by ten fold. Long term clinical trials are needed to evaluate the safety of this novel drug.

Introduction

Type 2 diabetes is characterised by elevated blood glucose levels resulting from a pancreatic β−cells secretory insufficiency combined with insulin resistance (1). The disease has a polygenic basis because numerous genes (the latest count exceeding 20) participate in its pathogenesis. But modern lifestyle characterised by limited physical activity and excessive caloric intake are critical precipitating factors for the current epidemic of type 2 diabetes worldwide (2).

Desirable properties of an ideal antidiabetic drug should include effective and sustainable blood glucose reduction, minimal risk of hypoglycaemia, reduction in cardiovascular risk factors and cardiovascular events, weight reduction, safety in the presence of hepatic, renal and cardiac failure, ability to use in combination with existing drugs and cost effectiveness. It appears that existing antidiabetic drugs in use need considerable improvement in their properties, if they are to be compared with the ideal antidiabetic drug. This deficiency has lead to the development of new therapeutic agents which have the capacity, in some aspects, to match the ideal antidiabetic drug.

This article describes four such new antidiabetic drugs (Colesevelam, Bromocriptine, Dapagliflozin and Glucokinase activators) which have the potential for revolutionising the management of type 2 diabetes.

Colesevelam

Bile acid sequestrants (BASs) were developed as lipid lowering agents for the treatment of hypercholesterolaemia. BASs also improve glycaemic control which provides the basis for the use in patients with type 2 diabetes. Colesevelam hydrochloride is the only BAS which was approved by Food and Drug Administration (FDA) for both lipid and glycaemic control (3).

Mechanism of action

Bile acid sequestrants remove bile acid from the intestine, which prevents hepatic recycling required for
cholesterol synthesis. But the exact mode of glycaemic control remains unexplained. Possible mechanisms include the reduction of endogenous glucose production by the effects on the farnesoid X receptor (bile acid receptor) within the intestine and liver (4). Furthermore BASs may have effects on the farnesoid X receptor (bile acid receptor) within the intestine and liver (4). Furthermore BASs may have effects on the farnesoid X receptor (bile acid receptor) within the intestine and liver (4). Furthermore BASs may have effects on the farnesoid X receptor (bile acid receptor) within the intestine and liver (4). Furthermore BASs may have effects on the farnesoid X receptor (bile acid receptor) within the intestine and liver (4).

**Efficacy**

In three double blinded studies, the addition of colesevelam (3.75 g / day) to existing antidiabetes therapy resulted in a significant reduction in HbA1c. Placebo-corrected reductions in HbA1c ranged from 0.5% (at 16 weeks on background insulin therapy) to 0.54% (at 26 weeks on background metformin or sulphonylurea therapy). In addition, colesevelam reduced plasma fasting glucose (FBG reduction > 30 mg / dL) relative to the placebo in all three studies (5-7).

Apart from glycaemic benefit, colesevelam resulted in a significant LDL cholesterol reduction (ranging from 12.8% to 16.7%) in patients with type 2 diabetes (5-7). This effect was present even when colesevelam was added to existing statin therapy. HDL cholesterol did not significantly change from baseline. However, triglyceride level increased significantly (18%), when colesevelam was added to sulphonylurea or insulin based therapy. The lipid and apolipoprotein ratios (LDL / HDL cholesterol and apoB / apoA1) indicative of cardiovascular risk were significantly reduced with colesevelam (5-7).

**Safety and tolerability**

Compliance with colesevelam was 93% in the three double blind studies (5-7), suggesting that it was well tolerated. The most common drug related adverse effects were gastrointestinal in nature (mainly constipation), since these agents bind to bile acids in the intestine. Incidence of hypoglycaemia was similar with colesevelam and placebo. Weight management is an important component of antidiabetic therapy and colesevelam was shown to be weight neutral (3).

Colesevelam is contraindicated in patients with a history of bowel obstruction, serum triglyceride concentration more than 500 mg / dL and with a history of hypertryglyceridaemia induced pancreatitis.

**Colesevelam in prediabetes**

Individuals with prediabetes are at an increased risk of developing type 2 diabetes and cardiovascular disease. One study showed that colesevelam reduced LDL cholesterol and fasting plasma glucose significantly in patients with hypercholesterolaemia and prediabetes (8). Therefore colesevelam may represent a novel treatment strategy for this population. However, additional research is needed to evaluate whether colesevelam prevents conversion from prediabetes to type 2 diabetes.

**Colesevelam in established type 2 diabetes**

Many hypoglycaemic agents have reduced efficacy when added as a third or fourth line agent to existing treatment. However, colesevelam has been demonstrated to maintain its efficacy as an add-on therapy (5-7), suggesting this agent provides an added glycaemic benefit regardless of existing diabetes therapy and duration of disease.

Colesevelam is not contraindicated in patients with renal, hepatic or cardiac failure, because it is not systemically absorbed (3). This finding is particularly important in patients with long standing type 2 diabetes who may have either renal or cardiac failure and cannot take medications such as metformin and thiazolidinediones.

**Bromocriptine mesylate**

In 2009, bromocriptine mesylate, a sympatholytic dopamine D2 receptor agonist was approved by the FDA for the treatment of type 2 diabetes. This centrally acting antidiabetic agent has a novel mechanism of action. It reduces plasma glucose, triglyceride and FFA levels. Additionally, a one year prospective study showed a reduction in cardiovascular events in patients treated with bromocriptine mesylate (9).

**Mechanism of action**

Bromocriptine is unique in that it does not have a specific receptor that mediates its action on glucose and lipid metabolism. Rather its effects are mediated via resetting of dopaminergic and sympathetic tone within the CNS (10).

As explained by the thrifty gene hypothesis, mammalian species living in the wild have an incredible ability to switch the metabolism from insulin sensitive state to insulin resistant state when food is sparse. This switch provides a survival advantage (11). Insulin resistant state is brought about by decreasing dopamine levels within the ventromedial hypothalamus. Restoration of dopamine leads to an insulin sensitive state (9). This mechanism provides the basis for the use of bromocriptine in type 2 diabetes.

Type 2 diabetic patients are believed to have an early morning dip in dopaminergic tone. Restoration of this deficiency by early morning bromocriptine administration leads to a decline in hepatic gluconeogenesis, reduced adipose tissue lipolysis and improved insulin sensitivity (9). Three clinical trials (12-14) proved that bromocriptine mesylate significantly reduced fasting and postprandial glucose concentrations without a change in serum insulin concentration or body weight. Bromocriptine mesylate has demonstrated a 0.5-0.7% reduction in HbA1c. It also significantly reduced serum FFA and triglyceride concentrations.
Pharmacokinetics and dose

Bromocriptine mesylate tablets are rapidly dissolved and absorbed within 30 minutes (12). But only 5 - 10% of the ingested dose reaches systemic circulation due to extensive hepatic first pass metabolism (15). Bromocriptine mesylate differs from traditional bromocriptine formulations in its quick release that provides maximum plasma concentration within 60 minutes. The drug is available as 0.8 mg tablets. The starting dose is 0.8 - 1.6 mg / day and the maximum dose is 4.8 mg/day. It is administered as a once daily dose within 2 hours of awakening (9).

Safety and tolerability

The common side effects are nausea (26%), asthenia (15%), constipation, dizziness and rhinitis. There was no significant increase in the incidence of hypoglycaemia, because insulin secretion is not stimulated (12).

Cardiovascular benefits

Bromocriptine mesylate decreased the cardiovascular composite end point by 40% (14), i.e. 79 diabetic patients need to be treated for 1 year to avoid one cardiovascular event. The mechanisms via which bromocriptine mesylate reduce cardiovascular events remains to be identified. The possible mechanisms are its inhibitory effect of CNS sympathetic over-activity on the vasculature and reduction of HbA1c, blood pressure, triglycerides and postprandial FFA levels.

Dapagliflozin

Dapagliflozin is the first in a novel class of glucose-lowering medications, the selective sodium-glucose cotransporter 2 (SGLT2) inhibitors (16). The Food and Drug Administration (FDA) Advisory Committee has not approved dapagliflozin for clinical use due to safety concerns regarding the risk of bladder and breast carcinoma.

Mechanism of action

SGLT2 is expressed in the proximal renal tubule and accounts for about 90% of the reabsorption of glucose from tubular fluid. Dapagliflozin is a selective SGLT2 inhibitor. Therefore these agents increase urinary glucose excretion with resulting net caloric loss (17).

This effect depends on baseline glycaemic control and glomerular filtration rate, but is independent of insulin. Consequently, reduction in plasma glucose with dapagliflozin reduces the glucose load filtered by the kidney and limits further glucose excretion, suggesting that dapagliflozin may possess a low intrinsic propensity for hypoglycaemia (18).

Efficacy

A 52-week duration study revealed that dapagliflozin produced a mean reduction of HbA1c that was statistically non-inferior to the sulfonylurea (glipizide), in patients poorly controlled with metformin monotherapy. This glycaemic control was achieved with 10-fold fewer hypoglycaemic episodes. Weight loss with dapagliflozin was progressive during the first 6 months and stabilized during the latter half of the study (19). This may have resulted from glucosuria induced caloric loss, fluid loss associated with osmotic diuresis, or a combination of both.

Dapagliflozin also reduced blood pressure. The exact mechanism for this effect is unclear, but may involve osmotic diuresis or sodium loss (19).

Adverse effects

Increased urine volume (up to 400 ml) with slight volume depletion was observed in clinical studies with dapagliflozin. But no meaningful changes were noted in electrolytes, serum creatinine or proportions of patients experiencing orthostatic hypotension to indicate dehydration or renal impairment.

Another important question is whether increased glucosuria would predispose to UTIs or genital fungal infections. Dapagliflozin treated patients, especially women, reported an increase in events suggestive of genital infections and lower UTIs (19). But this finding may be due to increased surveillance and anticipation. Hence further studies are needed to better evaluate this potential risk.

Glucokinase activators (GKAs)

Glucokinase, a unique isoform of the hexokinase enzymes, which plays a critical role in glucose homeostasis, was identified during the past three to four decades as a new, promising drug target for type 2 diabetes.

Glucokinase catalyzes the transfer of phosphate from ATP to glucose, generating glucose-6-phosphate. This reaction is the first, rate-limiting step in glucose metabolism (20).

Glucokinase (GK) exhibits two different actions in pancreatic islet β−cells (insulin independent) and hepatocytes (insulin independent). Glucokinase serves as a glucose sensor of the insulin producing pancreatic islet β−cells. In the liver, it controls the conversion of glucose to glycogen and regulates hepatic glucose production (21).

Diseases caused by GK gene mutations provide the best evidence regarding the importance of GK in glucose homeostasis. Activating GK mutations cause hyperinsulinenic hypoglycaemia whereas inactivating mutations cause maturity onset diabetes of the young (MODY - 2)(22).
Glucokinase activators (GKAs) increase the affinity of GK for glucose by as much as ten-fold, which in turn potentiates insulin biosynthesis and release. The published results of treating type 2 diabetic patients with GKAs for 1 week demonstrate that these agents lower blood glucose effectively in a dose-dependent manner without medically significant side effects except moderate hypoglycemia at higher doses (23). However, a recent study demonstrated that GKA (MK 0941) was associated with elevations in triglycerides and blood pressure (24).

Conclusion

Intensive research and development has succeeded in producing antidiabetic drugs with new mechanisms of action. It remains to be seen whether these new drugs withstand the test of time and secure a significant place among approved antidiabetic medications. However, it should be appreciated that the discovery of these new agents made a remarkable improvement in our understanding of glucose homeostasis with potential for further advances.

References

Interpretation of fine needle aspiration cytology of thyroid: do we need a better classification?

Bimalka Seneviratne


Fine needle aspiration cytology technique (FNAC) is a very popular first line investigation for disorders of the thyroid gland. It is a rapid and cost effective technique that can be easily performed in any category of patients. This technique provides useful information for the clinician to plan out the strategy for management of patients.

It is critical therefore that the cytopathologist communicate thyroid FNA interpretations to the referring physician in terms that are unambiguous and clinically useful.

The currently used classification for thyroid FNAC includes the following categories.

- Thy 01 – Inadequate
- Thy 02 – Benign (colloid goiter, thyroiditis, toxic goiter)
- Thy 03 – Follicular proliferation (follicular neoplasm, hurthle cell neoplasm, adenomatoid nodule)
- Thy 04 – Suspicious for malignancy
- Thy 05 – Malignant (papillary, medullary, anaplastic carcinoma)

Lesions are classified as “Thy 01” when the cellular yield is inadequate. This is often encountered following the aspiration of highly vascular nodules and cystic lesions. One of the main advantages of this cost effective technique is that it can be easily repeated within a short time.

When there is unequivocal evidence of a benign condition such as colloid goiter, thyroiditis and hyperplastic nodule the lesion will be classified as “Thy 02”.

“Thy 03/follicular proliferation” category of the above classification includes a significant number of pathological entities with different clinical outcomes. Conditions that qualify to be included within the “Thy 03” category are hyperplastic nodules with highly cellular smears, florid thyroiditis, neoplastic lesions such as follicular adenoma/carcinoma, hurthle cell tumours (hurthle cell adenoma/carcinoma) and certain types of papillary carcinoma, such as follicular variant of papillary carcinoma when the cytological findings are equivocal. Hence the spectrum of diseases within the “Thy 03” group is comparatively wide.

As such, from clinician’s point of view a cytological diagnosis of “Thy 03” in the current classification provides little information to plan out the management. Some of the pathological conditions within “Thy 03” do not require surgery and can be managed effectively by medical intervention. Conditions that require surgery need a further qualification as to the precise nature of the lesion. A significant number of “Thy 03” lesions end up with lobectomies as this category does not separate neoplastic from non-neoplastic lesions and benign from malignant conditions. Hence a cytological diagnosis of “Thy 03/follicular proliferation” fails to provide clinically useful information in most of the cases with regard to the management of the patient.

Thyroid lesions that have some but not all the features of malignancy are included in “Thy 04” category. The “Thy 05” category includes lesions having unequivocal cytological features of malignancy.

Time has arrived to change to a better classification that provides useful information to the clinician enabling him to decide the treatment option. By this means the number of unnecessary thyroid surgery for patients with thyroid disorders can be effectively reduced.

The Bethesda system for reporting thyroid cytology (BSRTC) consists of six diagnostic categories. It provides the definitions and morphologic criteria for the different categories. For clarity of communication, the Bethesda system for reporting thyroid cytopathology recommends that each thyroid FNA report begin with one of the diagnostic categories.

The BSRTC diagnostic categories are shown in Table 1.

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The Bethesda system provides definitions and morphologic criteria for the different categories. For the general categories, some degree of subcategorization which is appropriate has been allowed. Recommended terminology for subcategorization is shown in Table 2.

Table 1. The BSRTC diagnostic categories

I. Non diagnostic or unsatisfactory
II. Benign
III. Atypia of undetermined significance or follicular lesion of undetermined significance
IV. Follicular neoplasm or suspicious for a follicular neoplasm
V. Suspicious for malignancy
VI. Malignant

Table 2. Recommended terminology for subcategorization in the BSRTC

I. Non diagnostic or unsatisfactory
   Cyst fluid only, acellular, obscuring blood
II. Benign
   Colloid goiter, adenomatoid nodule, Hashimoto's thyroiditis, granulomatous thyroiditis
III. Atypia of undetermined significance or follicular lesion of undetermined significance
IV. Follicular neoplasm or suspicious for a follicular neoplasm
   Specify if Hurthle cell (oncocytic) type
V. Suspicious for malignancy
   Suspicious for papillary carcinoma
   Suspicious for medullary carcinoma
   Suspicious for metastatic carcinoma
   Suspicious for lymphoma
   Other
VI. Malignant
   Papillary carcinoma
   Medullary carcinoma
   Poorly differentiated carcinoma
   Anaplastic carcinoma
   Metastatic carcinoma
   Lymphoma
   Other

Each diagnostic category has an implied risk of malignancy. In addition to that useful information, in the Bethesda system of classification of thyroid cytopathology each category has been linked to evidence based clinical management guidelines as shown in Table 3.
Clinical update

The Bethesda system for reporting of thyroid cytology provides clinically useful information as each diagnostic category is linked to a management option.

Time has arrived for a change in the reporting of thyroid cytopathology. Advantages of the proposed Bethesda system for reporting thyroid cytology has to be understood. It is of paramount importance for the clinicians to be aware of the diagnostic categories and the appropriate management options of the BSRTC. Consensus opinion with regard to the application of BSRTC can be arrived by clinicopathological discussions and collaborative meetings involving the specialists of clinical and paraclinical fields.

References


Table 3. Risk of malignancy in the BSRTC categories

<table>
<thead>
<tr>
<th>Diagnostic category</th>
<th>Risk of malignancy (%)</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non- diagnostic or unsatisfactory</td>
<td>_</td>
<td>Repeat FNA with ultrasound guidance</td>
</tr>
<tr>
<td>Benign</td>
<td>0 - 3</td>
<td>Clinical follow up</td>
</tr>
<tr>
<td>Atypia of undetermined significance or follicular lesion of undetermined significance</td>
<td>5 - 15</td>
<td>Repeat FNAC</td>
</tr>
<tr>
<td>Follicular neoplasm or suspicious for a follicular neoplasm</td>
<td>15 - 30</td>
<td>Surgical lobectomy</td>
</tr>
<tr>
<td>Suspicious for malignancy</td>
<td>60 - 75</td>
<td>Near total thyroidectomy or surgical lobectomy</td>
</tr>
<tr>
<td>Malignancy</td>
<td>97 - 99</td>
<td>Near total thyroidectomy</td>
</tr>
</tbody>
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Improving diabetes care in Sri Lankan children: the way forward

Navoda Atapattu¹, K S H de Silva²


(Index words: Type 1 diabetes mellitus, children, management)

Abstract

Type 1 diabetes mellitus (T1DM) is an autoimmune disease. The incidence of T1DM is on the increase worldwide. The incidence in Sri Lanka is yet to be determined but there has been a definite increase in its occurrence in the recent past. Uncontrolled diabetes gives rise to microvascular and macrovascular complications. Various strategies are being implemented to improve care for children with T1DM worldwide. Intensive blood glucose control, regular blood glucose monitoring, screening for complications are prerequisites for better diabetes management. The diabetic care of Sri Lankan children needs to be optimised. Compared to the West we do encounter many practical difficulties. This article discusses the facilities that we have compared to other countries who have achieved good glycaemic control in children and the way forward for the Sri Lankan paediatric population.

Introduction

The incidence of type 1 diabetes mellitus (T1DM) is on the increase especially in the <5 year age group (1). Even though there are geographical differences in the trends, the overall annual incidence is estimated to be around 3%. The incidence of T1DM in Sri Lanka is yet to be determined but over the past few years there has been a definite increase in the number of children affected.

Molecular genetic basis of T1DM

T1DM is an autoimmune disease which results from destruction of pancreatic beta cells. Eighty five to ninety percent (85% - 90%) of patients with T1DM will have islet cell, GAD, IA-2, IA-2β or insulin auto antibodies by the time they develop fasting hyperglycaemia (2). The susceptibility to develop T1DM is determined by more than 40 different genomic loci, HLA having the strongest association (3). HLA - DQB1, DQA1 and DRB1 loci are major determinants.

T1DM can be associated with other autoimmune diseases. One third of patients with T1DM who have the HLA genotype HLA-DR3-DQ2/HLA-DR3-DQ2 have transglutaminase autoantibodies (4). The highest risk for the development of both Addison disease and T1DM is associated with a heterozygous HLA-DR4-DQ8/HLA-DR3-DQ2 genotype (5). Environmental triggers involved in beta cell destruction are largely unknown except for an association with enteroviral infection.

Neonatal diabetes

Neonatal diabetes is defined as insulin sensitive hyperglycaemia diagnosed within the first 6 months of life. The incidence is 1 in 400,000 live births. It could be transient or permanent. Permanent neonatal diabetes is found to be associated with mutations in several different genes, namely KCNJ11 gene which encodes ATP-sensitive K+ channel subunit Kir 6.2 (6), glucokinase (GCK) (7), and transcription factors insulin promoter factor (IPF) (8).

KCNJ 11 mutation reduces the ability for ATP to close the ATP - sensitive K+ channel. Consequently, the mutated KATP channels stay open in spite of an increase in intracellular ATP concentration, preventing insulin release in response to high blood glucose levels. It is the commonest cause of permanent neonatal diabetes. Sulfonyureas stimulate insulin secretion by binding to the beta cell’s high affinity sulfonylurea receptor and closes the ATP - sensitive K+ channels by an ATP independent mechanism. According to recent research it has been suggested that neonatal diabetes diagnosed within 24 weeks after birth who are negative for type 5 diabetes associated antibodies warrant screening for this mutation as these children could be managed effectively with oral medication (6). A proportion of these patients can have associated developmental delay, muscle weakness or epilepsy.

GCK and IPF related neonatal diabetes need lifelong insulin treatment and IPF related patients have both exocrine and endocrine defects. GCK mutation positive

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patients generally have intrauterine growth retardation and glucose intolerant parents.

Permanent neonatal diabetes can occur as part of IPEX syndrome (immunodysregulation, polyendocrinopathy, and enteropathy, X-linked) (9) associated with mutation in FOXP3 or the Wolcott-Rallison Syndrome (10) which is the result of mutation in eukaryotic transcription factor-2α kinase 3 (EIF2AK3).

Wolcott-Rallison syndrome has associated epiphyseal dysplasia, osteoporosis and growth retardation occurring at a later age. Other frequent multisystem manifestations include hepatic and renal dysfunction, mental retardation and cardiovascular abnormalities.

Both these conditions are inherited in an autosomal recessive manner and have a poor prognosis. It is important to make the diagnosis in order to counsel families regarding the future and the risk of recurrence.

Insulin therapy and blood glucose monitoring

Lifelong insulin replacement is needed in T1DM. The Diabetes Control and Complications Trial (DCCT) and its follow up Epidemiology of Diabetes Interventions and Complications (EDIC) study confirmed that intensive glucose control reduce the long term complications and delay the progression of existing complications in T1DM in children (11,12). Continuous subcutaneous insulin infusion (CSII) has become the best insulin delivery system as it simulates the physiological insulin secretion in the body. Other than this basal bolus therapy is widely used as it is much cheaper than CSII but gives the patient a good glycaemic control. In basal bolus regimens and CSII insulin analogues are used. Therapy with insulin analogues is associated with less risk of hypoglycaemia but is expensive. Basal bolus therapy allows flexible meal patterns, insulin administration just after finishing the meal in toddlers, exercise related titration of insulin doses and more effective sick day management. At present the only method of delivery of insulin is via an injection. Although various child friendly devices with small needles, covers to hide needles are available, only the insulin pens are available in Sri Lanka

Methods of blood glucose monitoring have improved and currently continuous glucose monitoring (CGMS) is being used in developed countries to optimise the glucose control.

In addition there are newer glucometers which could be downloaded to a computer. Some glucometers have facilities to calculate correction bolus of insulin at meal time once the meter is programmed for the patient’s needs. Some have the facility to check blood ketone levels which is very useful for sick day management.

In Sri Lanka twice daily insulin regime is used which is the cheapest available method. This regime has an increased risk of hypoglycaemia given the profile of action of intermediate acting insulin. In addition it is necessary to give two injections and meals and snacks taken at the same time of the day which would be difficult at times especially for school children. Also it is quite difficult to adjust insulin to cover physical activity.

Ideally at least 4 blood glucose measurements should be done with twice daily or multiple daily insulin therapy optimise the glucose control. In Sri Lanka patients have to bear the cost of the glucometer and the strips unlike in some western countries, which is a major financial burden for most of our parents. Facilities for meticulous blood glucose monitoring must be available for better insulin delivery methods to be instituted. Glycosylated haemoglobin (HbA1c) should be done every 3 months to check the long term diabetes control. Ideally it has to be kept <7.5% in all children and adolescents according to ISPAD (International Society of Paediatric and Adolescent Diabetes) Guideline 2009.

Complication screening is done annually after 5 years of diagnosis or after 12 years of age whichever comes earlier. In the West screening is done for celiac disease at diagnosis and every 3 years thereafter. We do the annual screening according to the suggested international guidelines however, the non-availability of HbA1c in the state sector hospitals is a major drawback. We do not routinely screen for celiac disease as it is uncommon in Sri Lanka. However, it could be important that we do screen our children for celiac disease at the diagnosis as the dietary advices need to be given accordingly. Untreated celiac disease not only results in poor glycaemic control but also other long term complications like intestinal malignancies may be over looked.

Nutrition and growth

Nutrition is an important aspect in children as it is necessary to maintain a normal body mass index (BMI). The paediatric dietician gets involved in the care of these children from the time of diagnosis. In the West after the initial counselling the dietician does a home visit and the patients and their parents are educated on a healthy diet, how to calculate the amount of carbohydrate in different food items and food items that could be used to treat hypoglycaemia. Following this they provide constant evaluation and help for these young patients and their families. Carbohydrate counting is very important in multiple daily injection regimes or for those who are on insulin pumps. It is the trained paediatric dietician who is capable of supporting the children and families with the diet taking in to account the child’s weight, eating pattern and activity level. Our parents are advised on a “portion diet” by the paediatrician or the diabetes educator nurse based on body weight and caloric requirement.

Hypoglycaemia

With newer insulin analogues the risk of hypoglycaemia is less but some patients do experience it.
Diabetes care in children

This is a very traumatic experience for both the parents and patients. The fear of hypoglycaemia adversely affects diabetes control. Constant advice and support for these children and families is important to overcome this common problem. The school teachers also need to be educated on this matter. In the West a nurse would visit the school and educate the staff. This improves the support and the care they receive at the school. In future we would be able to get the help of diabetes educator nurses to take part in educating not only families of diabetic patients but also the school teachers.

Exercise and sick day management

Hypoglycaemia is commonly seen during or after exercise. Help of a trained dietician and frequent monitoring of blood glucose are important aspects in the management. It is important to check blood glucose more frequently during sick days and to check ketone bodies when blood glucose is more than 15 mmol/l. We do not have facilities to check blood ketone levels with the available glucometers. Parents are advised to keep a constant contact with the diabetes educator nurses or medical professionals during this time. Non availability of these resources increases the risk of admissions with DKA during an illness. However, we do not have the necessary data to assess whether this is true in Sri Lanka.

Psychological support

The diagnosis of diabetes in a child is a very distressing event for the entire family. The feeling of guilt, denial, blaming each other within the family should be addressed at the very beginning. The psychological well being of the child is important to avoid anxiety, conduct disorders, eating disorders, and depression which could affect the long term diabetes control. Constant assessment by a paediatric psychologist during follow up will help to identify these problems early.

The various myths related to the management of these children in Sri Lanka also need to be addressed. Some families believe that indigenous medicine and or religious activities would cure diabetes. At times it has been very challenging to overcome these deep rooted myths and beliefs. It should be emphasised to the parents that management of diabetes in children is different to that of adults. As childhood diabetes was not common in our society in the past adults with diabetes have become their role models which could at times be dangerous. The diabetes educator nurse will be of great help in this situation.

Support groups

Diabetes support groups could organise constant educational programmes and camps for young patients. It will also provide a platform to share the experience, worries about diabetes with peers. These support groups offer an invaluable service for the patients and their parents in Western countries. Time has come for us to initiate support groups for chronic conditions like diabetes in Sri Lanka.

How could we overcome the challenges in the management of T1DM in children?

1. There is a need to identify the incidence and disease burden of T1DM in Sri Lanka.
2. Make newer insulin products available at a reasonable price or provide these from the state hospitals.
3. Have better insulin delivery devices, needles and blood glucose monitoring facilities available for children.
4. Improve the facilities for screening of complications of diabetes.
5. Develop multidisciplinary dedicated clinics.
6. Have a trained nurse available for 24 hours to help patients and families. These nurses need to be available in all parts of the country.
7. Paediatric dieticians who are trained on carbohydrate counting, management of hypoglycaemia during exercise should be made available at least in the main teaching hospitals.
8. Ongoing educational programmes with the use of media, seminars, diabetic camps for young children and their families.
9. Child friendly informational leaflets, videos to help them understand what is happening in their body, why they need insulin.
10. Practical sessions on carbohydrate counting or selecting the appropriate portion diet for the individual patient.
11. Educate school teachers.
12. Make available the services of a psychiatrist on a regular basis even if the child or the family members do not show signs of psychological problems.
13. Have separate clinics for adolescents with diabetes to cater for their specific problems.
14. Public awareness programmes regarding occurrence and treatment of T1DM to overcome deep rooted myths.
15. Have national guidelines for investigation of a child with diabetes at presentation, management of T1DM, management of diabetic ketoacidosis, subsequent care and follow up screening of a child with diabetes, management of hypoglycaemia, management of sick days and exercise.
17. Initiate support groups for patients and parents.

Improperly managed diabetes in children is a silent debilitating condition which would reduce the life expectancy and increase the morbidity making them a burden to the country. Time has come for us as health care professionals to speak up on behalf of our future generation to make a difference.

References


Premature ovarian insufficiency: evaluation and management

Karuppiah Dharshini¹, Noel P Somasundaram²


Abstract

Impairment of ovarian function before the age of 40 years is defined as premature ovarian insufficiency (POI). Alteration of normal menstrual pattern is the commonest presentation of POI and two serum follicle stimulating hormone (FSH) measurements in the menopausal range at least a month apart is diagnostic. Once the possibility of pregnancy is excluded, evaluation of POI should include initial laboratory evaluation of FSH, leutinizing hormone (LH), estradiol, serum prolactin and thyroid status. A possible etiology should be determined by karyotyping, screening for FMR1 premutations, testing autoimmune markers such as anti-21 hydroxylase antibodies and imaging with pelvic ultrasonography. Management should address psychological well being, ovarian hormone replacement, and restoration of fertility. Management of associated endocrinopathies, co-morbidity and genetic counseling are also of great relevance.

Introduction

Premature ovarian insufficiency (POI) is defined as impaired ovarian function before the age of 40 years which is more than 2 standard deviations below the mean age of normal menopause. It is characterized by amenorrhea for 6 months or more with an elevation of gonadotropin (FSH) levels in two serum samples obtained a month apart (1). Early diagnosis and treatment are the keys to preventing the complications of POI (2). Hence, in patients who present with menstrual irregularity, which may be the first indication of ovarian insufficiency, deserve appropriate evaluation at the first clinic visit (3). However, the diagnosis is usually delayed in most patients.

Clinical evaluation

Menstrual irregularity has been the commonest presentation of POI. It can vary from amenorrhea, period of oligomenorrhoea to dysfunctional uterine bleeding. POI can also occur following delivery and after stopping oral contraceptives. However, there is no typical menstrual pattern that could suggest the onset of spontaneous premature ovarian insufficiency.

Once the possibility of a pregnancy is excluded, the clinical evaluation must be aimed at establishing the diagnosis of POI, clarifying its etiology and screening for associated complications. Although vasomotor symptoms and vaginal dryness are common due to estrogen deficiency, 50% of women may produce estrogen and ovulate intermittently. Nevertheless, approximately 5-10 percent of women affected by POI can even conceive and have a normal pregnancy (4, 5). During patient evaluation, it is important to address the details of any chronic illness, adequacy of caloric intake, exercise, emotional stress, prior radiation and chemotherapy, features of autoimmune disorders and family history (Table 1) that might have contributed to the problem. Approximately 10% of women with premature ovarian failure have a familial basis (6) and therefore assessment of family history is important in all subjects.

The initial laboratory evaluation should include FSH, LH, estradiol, serum prolactin and thyroid status (7). Two FSH levels more than 40 mIU/mL by radio immune assay, measured at least one month apart, confirms the diagnosis of POI. In most women with spontaneous POI, FSH is higher than LH, whereas in autoimmune oophoritis LH is markedly elevated (8). Early follicular phase estradiol will be less than the concentrations of women with normal cycles. Serum prolactin should be measured to determine whether the symptoms are caused by hyperprolactinemia.

Karyotyping should be performed in all the patients irrespective of the absence of stigmata of Turner syndrome. FMR1 premutation has been described to be responsible for 14% of familial cases of POI and 2% of spontaneous POI (9). When there is no apparent cause for the POI, many health professionals recommend FMR1 premutation screening (10).

Nearly 3% of women with POI will have positive anti-adrenal antibodies (11); therefore measurement of serum anti-adrenal and anti-21 hydroxylase antibodies should be considered in patients with POI. Careful evaluation for adrenal insufficiency is required for those with positive antibodies. Currently, ovarian antibody assays that are available commercially are of little diagnostic value because of problems with specificity and sensitivity (12).
Pelvic ultrasound examination is useful to identify multifollicular ovaries, which would suggest either autoimmune oophoritis or 17-20 desmolase deficiency. Ovarian biopsy has no proven clinical benefit in managing premature ovarian failure and is not recommended. Bone density scan (DEXA) to evaluate bone mineral density must be performed routinely. Fasting blood glucose, antinuclear antibody, rheumatoid factor, liver and renal profile tests are required if clinically indicated.

Management

The diagnosis of POI is disturbing for the individual patient and therefore management must address the psychological well being, ovarian hormone replacement, and restoration of fertility. In addition, management of associated endocrinopathies and related diseases, coupled with genetic counselling in those with abnormal karyotype and FMR1 premutations need to be addressed (Table 1).

Psychological support

Most women are not prepared for the diagnosis of POI and therefore this should be divulged in a sensitive and caring manner. Accurate information regarding the diagnosis, nature of the disease and available sources for information and support should be provided. Physician must allow the patient enough time to accept the diagnosis and explain that POI is not menopause, but spontaneous ovarian activity and pregnancies are yet possible. Decisions regarding family planning can be made once the patient has had some time to come to terms with her condition.

Ovarian hormone replacement

Women with premature ovarian failure are at an increased risk of developing osteoporosis (13) and coronary heart disease. They have significant vascular endothelial dysfunction, which is restored to normal by estrogen therapy (14, 15). Cyclical hormonal therapy with estrogens and progestins is considered necessary in all women with POI to relieve the symptoms of estrogen deficiency and to maintain bone mineral density. The functioning premenopausal ovary produces 17β-estradiol as the principal estrogen and maintains an average serum estradiol concentration of about 100 pg/mL (16). Estrogen replacement should be physiological and mimic normal ovarian function. Currently, this is available as oral and transdermal preparations, while the latter are more physiological with several advantages over the oral preparations (Table 2).

Bone mineral density (BMD) should be routinely measured and bone protection measures such as weight bearing exercises, a healthy diet, adequate calcium and vitamin D intake and avoiding smoking should be emphasized. Bisphophonates are not recommended due to its long skeletal half life and uncertain effects on fetus (17). Preventing and managing obesity and other cardiovascular risk factors are also important in these patients.

Table 1. Clinical indicators for evaluating causes of POI and its associations

<table>
<thead>
<tr>
<th>Condition</th>
<th>Clinical features</th>
<th>Tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chromosomal defects (Turner syndrome and x chromosomal abnormalities)</td>
<td>Short stature, low posterior hairline, shield chest with widely spaced nipples, wide carrying angle</td>
<td>Karyotype</td>
</tr>
<tr>
<td>Autoimmune disorders</td>
<td>Goiter, features of hypothyroidism, Increased skin pigmentation, orthostatic hypotension consistent with Addison disease.</td>
<td>TSH, FT4, and anti-TPO antibodies, Serum anti-adrenal and anti-21 hydroxylase antibodies, ACTH stimulation test</td>
</tr>
<tr>
<td>Fragile X syndrome</td>
<td>Family history, intellectual disability, dementia, tremor or ataxia</td>
<td>FMR1 premutations</td>
</tr>
<tr>
<td>Ovarian toxins</td>
<td>History of radio and chemo therapy, Viral infections, Galactosemia, cataracts</td>
<td>Galactose-1-phosphate uridyl transferase activity</td>
</tr>
</tbody>
</table>

TSH – thyroid stimulating hormone; FT4 – free thyroxine; TPO – thyroid peroxidase; ACTH – adreno cortico hormone
Table 2. Pharmacological agents used in the management of POI

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estradiol</td>
<td>100 μg/day</td>
<td>Provides 17β-estradiol</td>
</tr>
<tr>
<td>Transdermal patch</td>
<td></td>
<td>Avoids the first pass effect on the liver</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lower risk of venous thrombo embolism than oral estrogen</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Patch may fall off or cause skin irritation</td>
</tr>
<tr>
<td>Oral estradiol</td>
<td>2 - 4 μg/day</td>
<td>Variable bio availability</td>
</tr>
<tr>
<td>Conjugated equine estrogens</td>
<td>1.25 μg/day</td>
<td></td>
</tr>
<tr>
<td>[CEE]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Progestins</td>
<td>10 mg daily</td>
<td></td>
</tr>
<tr>
<td></td>
<td>for 10-12 days</td>
<td></td>
</tr>
<tr>
<td>Medroxyprogesterone acetate</td>
<td>each month</td>
<td></td>
</tr>
<tr>
<td>Micronized progesterone</td>
<td>200 mg daily</td>
<td></td>
</tr>
<tr>
<td></td>
<td>for 10-12 days</td>
<td></td>
</tr>
<tr>
<td></td>
<td>each month</td>
<td></td>
</tr>
<tr>
<td>Elemental calcium</td>
<td>1200 mg/day</td>
<td></td>
</tr>
<tr>
<td>Vitamin D3</td>
<td>800-1000 IU/day</td>
<td>Maintain adequate vitamin D status</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(25 hydroxy vitamin D level of 30ng/mL)</td>
</tr>
</tbody>
</table>

Family planning and fertility

Although the rate of conception is very low, they still have a remote chance of spontaneous ovulation and natural conception. Estrogen replacement therapy can improve the chances of pregnancy by theoretically lowering the LH levels to normal range and preventing premature luteinization of the remaining follicles. Estrogen hormone replacement treatment does not prevent ovulation and conception in these patients and pregnancy test needs to be performed if they fail to menstruate when expected. Effectiveness of oral contraceptives has not been demonstrated in this population and another form of contraceptive method (barrier method or intra uterine device) is advised if contraception is desired (18).

Nevertheless, the potentially beneficial effect of estrogens on fertility yields very low pregnancy rates. There is no established treatment to restore ovulation and fertility in women with POF. Attempts to treat with exogenous gonadotropins could theoretically exacerbate unrecognized autoimmune ovarian failure (19) and currently available options to resolve infertility include change of family building plans, such as adoption, ovum donation or embryo donation. Success rate of in-vitro fertilization with donor oocytes depend primarily on the age of the oocyte donor and the pregnancy rates are similar irrespective of the age of the women with POI.

Autoimmune disorders

Patients with POI are at a greater risk of developing other autoimmune disorders. All patients with POI should be educated regarding the symptoms of adrenal insufficiency and the importance of adrenal evaluation (18). Those with positive adrenal antibodies should undergo an annual evaluation for adrenal insufficiency by the corticotrophin stimulation testing. These patients are also at a high risk of developing autoimmune hypothyroidism and have to be screened for this condition. Several other autoimmune disorders such as polyglandular syndrome, myasthenia gravis, rheumatoid arthritis, systemic lupus erythematosus and dry eye syndrome are associated with spontaneous POI and need evaluation if clinically indicated.

References


Virilization in a pregnancy

M W S Niranjala¹, C N Wijeyaratne², G K C Jayalath³


Abstract

We describe a 29-year old pregnant woman with history of primary hypothyroidism and impaired glucose tolerance presenting in her third trimester with preeclampsia and virilization. Initial investigations revealed markedly elevated serum testosterone, 17 hydroxy-progesterone and a non-suppressed serum cortisol following overnight dexamethasone. Imaging of the adrenals proved normal. At lower segment caesarean section, she had markedly enlarged ovaries with multiple haemorrhagic cysts; compatible with hyperreactio luteinalis. At two months postpartum, there was complete resolution of biochemical hyperandrogenemia, Cushing’s syndrome and placental aromatase deficiency were excluded.

Introduction

Virilization during pregnancy is uncommon. This can manifest as clitoral enlargement, increased muscle strength, acne, hirsutism, frontal hair thinning and deepening of voice. Possible causes include the polycystic ovary syndrome (PCOS), androgen-producing tumours of the ovaries and adrenal glands, hypothyroidism, anabolic steroid exposure, late-onset congenital adrenal hyperplasia due to 21-hydroxylase deficiency and Cushing’s syndrome. Aromatase deficiency, luteoma and hyperreactio luteinalis are rare conditions that can cause virilization during pregnancy (1).

Case report

A 29-year old nursing officer was transferred from a regional hospital at 31 weeks of gestation for investigation and management of high blood pressure and marked virilization. She noticed deepening of her voice and increased hair growth of her body since 20 weeks. On examination, she had excessive body hair with Ferriman Gallway score of 32/36, increased pigmentation and a deep husky voice. Her clitoris was markedly enlarged with a clitoral index of 49 mm² (normal < 35 mm²). She had facial acne and acanthosis nigricans. There was no proximal muscle weakness, wasting, thin skin or easy bruising. She had striae gravidarum. She was clinically euthyroid with no features of acromegaly.

She had a first trimester spontaneous miscarriage in 2006. During next 3 years, she failed to conceive and was managed as for PCOS and had undergone 6 cycles of ovulation induction with clomiphene citrate although her current pregnancy was a spontaneous conception. She did not develop any features of virilization during clomiphene citrate treatment. She also had primary hypothyroidism and impaired fasting plasma glucose for which she was on treatment. Biochemistry revealed elevated plasma testosterone 16 ng / mL (normal 0.15 - 0.8 ng / ml), non suppressed overnight dexamethasone test (cortisol 6 micg / dL), suboptimal thyroid function when taking thyroxine 150 microgram daily (TSH 4.05 mIU / mL (0.4 - 4.5 mIU/ml) Free T3 5.5 pg/mL (1.4 - 4.4 pg/mL) Free T4 0.76 ng/dL (0.8 - 1.8 ng/dL), markedly elevated basal 17 OHP (58.5 ng / mL – normal 2-12 ng /mL) and impaired fasting plasma glucose (5.9 mmol/L). Ultrasound scan showed normal adrenal glands and a date compatible live fetus. Magnetic resonance imaging (MRI) of abdomen and pelvis was normal, but the adrenal glands were poorly visualized due to gravid uterus.

Possible aetiologies considered for hyperandrogenemia at this stage were late onset congenital adrenal hyperplasia, Cushing’s syndrome, androgen secreting neoplasms of either ovaries or adrenals, and conditions specifically seen during pregnancy such as luteoma, hyperreactio luteinalis and placental aromatase deficiency.

At 34 weeks of pregnancy, she developed gross pedal edema, uncontrolled hypertension and proteinuria. Her liver enzymes and serum uric acid level started rising. Platelet count was reduced to 45,000 / mm³. An emergency lower segment caesarean section was performed due to impending preeclampsia and HELLP syndrome. She delivered a live healthy baby girl weighing 1.840 kg. During surgery, bilateral enlarged ovaries (6x4x3cm) with multiple haemorrhagic cysts were noted (Figure 1).

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Case report

Her immediate post partum period was uneventful. Histopathology of her placenta and umbilical cord was normal.

Her hormones were re-tested postpartum at 2 and 18 months. Her thyroid hormones were normal.

Her presentation was investigated using a 60-minute corticotropin test for 17-OHP (16.0 ng/mL, normal < 2.6) and ODST cortisol (6.0 mcg/dL, normal < 12). Her basal 17-OHP (58.5 nmol/L, normal 11-32) was normal and there was a 0.8 fold increment post ACTH (1.0 nmol/L, normal 1.6-9.1).

She had marked improvement of hirsutism. The voice became softer and the blood pressure remained normal. Ultrasound scan showed normal ovaries and adrenal glands at 4 months following delivery. At 18 months, she was totally free from all symptoms and signs of virilization except the mild persistent clitoromegaly.

Discussion

This patient’s history suggests a condition specific to pregnancy. The post partum normalization of hyperandrogenaemia supports our hypothesis that the virilization is caused by pregnancy. Following her delivery, the 60-minute corticotropin test for 17-OHP excluded Non Classic Congenital Adrenal Hyperplasia (NC-CAH) in view of the normal basal value and post stimulation value < 45.5 nmol/L (2). During pregnancy, estrogen-dependent elevation of serum cortisol binding globulin (CBG), increases plasma cortisol and ACTH lead to a 2- to 3-fold increment in plasma cortisol and the urinary free cortisol excretion (UFC). This complicates the screening process for Cushing’s syndrome during pregnancy. Therefore, dexamethasone suppression test has limited utility during pregnancy with a high false-positive rate (3). The normalized suppression test following delivery excludes Cushing’s.

Having excluded late onset congenital adrenal hyperplasia and Cushing’s syndrome, the possible causes for her presentation were aromatase deficiency, hyperreactio luteinalis and luteoma.

Placental aromatase deficiency is rare. Active human placental aromatization of androgens protects the fetus against the virilizing action of fetal androgens. In the female fetus, this is particularly important to avoid the androgen effects on the differentiation of external genitalia. In aromatase deficiency, female babies will be born with ambiguous genitalia (4). Hence, the normal external genitalia of her baby daughter made aromatase deficiency most unlikely.

Hyperreactio luteinalis and luteoma of pregnancy are two different conditions that can cause maternal virilization in pregnancy. Elevated serum testosterone levels, δ4-androstenedione, and 5α-dihydrotestosterone can be detected in patients with virilization (5,6).

Luteoma of pregnancy are commonly unilateral but can be bilateral and multinodular. They are usually composed of large cells with abundant eosinophilic cytoplasm; they often have mitotic activity leading to erroneous diagnosis of malignant tumour. Luteoma represents an unusual response of the ovarian stromal cells to the altered hormonal levels of pregnancy (5). Conversely, hyperreactio luteinalis is typically associated with an abnormally high level of human chorionic gonadotropin, and is almost always bilateral and multicystic. In contrast to a luteoma of pregnancy, which is typically seen at or near term, hyperreactio luteinalis occurs at any time during pregnancy. Both lesions regress post partum (5,6). Generally, these masses are discovered incidentally during caesarean delivery or tubal ligation. Some women develop hirsutism or virilization during late pregnancy with or without fetal masculinization due to circulating androgens. It is believed that the placental aromatization of androgens may function as a metabolic barrier that protects the fetus from effects of excessive maternal androgens, as in our patient’s baby. Another protective mechanism may be the increased fetal exposure to potent estrogens, which may buffer the influence of androgens that reach the fetus (7).

Potential complications of hyperreactio luteinalis include ovarian torsion, infarction, and haemorrhage.
bilateral ovarian cysts usually regress shortly after pregnancy, and therefore, observation is typically the only required management unless complications occur (5,6).

Other complications that have been observed are thyroid dysfunction, hyperemesis gravidarum, pre eclampsia (PE), intrauterine growth restriction, and delayed lactation. The elevation of hCG derived from placenta in a normal pregnancy could be caused by poor placentation, which could lead to the development of bilateral enlarged ovaries and a severe imbalance of angiogenic factors which can lead to development of preeclampsia (8).

In view of the above we conclude that her presentation is more in favour of hyperreactio luteinalis; which could have been confirmed by ovarian biopsy at delivery.

References
Insulinoma presenting as refractory seizure disorder

S Pathmanthan1, D U S Bulugahapitiya2, A S K Banagala3, H S K Ruwanpathirana4, G P Karunasekara5


Abstract

Diagnosis of insulinoma may be delayed when symptoms are nonspecific. Rarely neuroglycopenic symptoms are the primary feature and these patients can be misdiagnosed as having epilepsy or neuropsychiatric disease. We report a case of insulinoma presenting as an adult-onset refractory seizure disorder. The time from onset of symptoms to diagnosis was 9 years. The atypical features of the episodes of hypoglycaemia, and the poor response to treatment led to a review of diagnosis. This case highlights the importance of considering hypoglycaemia in atypical neurological or psychiatric presentations.

Introduction

Insulinoma is a rare neuroendocrine tumour arising from beta cells of islets of langerhans with an overall incidence of 4 cases per million per year. About 90% of insulinomas are solitary, benign, intrapancreatic and sporadic while up to 10% could be multiple, malignant, extrapancreatic and familial. The familial insulinomas have a special predilection for occurrence in association with MEN-1 and von Hippel-Lindau disease (1-3).

Clinical diagnosis of hypoglycaemia is confirmed with biochemical investigations. Imaging methods are useful in localisation of the insulinoma. However, localisation can be difficult as the symptoms usually precede occurrence of a tumour that can be visualised on imaging studies (4,5). Surgical excision is the treatment of choice and is curative in most cases (6,7,8).

Case report

A 32-year old female presented with frequent episodes of loss of consciousness and generalised tonic clonic fits of 9 years duration. The seizures were preceded by sweating, giddiness, and palpitations. A diagnosis of epilepsy had been made 9 years ago and despite gradual up titration and treatment with 3 anti epileptic drugs there was no resolution of the seizures. Her appetite increased over the past few years and her weight increased by 20 Kg. She also had secondary amenorrhoea since 1999 but denied any galactorrhoea or visual changes. There was no family history of hyperparathyroidism, ulcer disease, or hypoglycaemia. One sibling had diabetes mellitus. Physical examination revealed obesity (BMI 36.96), and acanthosis nigricans, but no other abnormalities.

Serum glucose level observed during an episode was 1.1 mmol/L. Administration of intravenous glucose resulted in relief of symptoms. When plasma glucose level was 1.1 mmol/L, serum insulin level was 73.80 μIU/ml (normal range: < 28.4 μIU/ml) and serum C-peptide level was 5.6 ng/ml (normal range: 0.9-7.1 ng/ml). Her pituitary adrenal axis was intact. Plasma thyroid-stimulating hormone (TSH), prolactin, follicle stimulating hormone (FSH) and leuteinizing hormone (LH) levels were within normal range. In view of the clinical features and results of laboratory investigations, diagnosis of an autonomous insulin secreting tumour was made.

Abdominal ultrasound (US) did not reveal any pancreatic lesion. A triple phase computed tomography (CT) of the abdomen demonstrated a well-defined 2.2 × 2.4 × 3.0 cm soft-tissue density mass in the head of the pancreas. The lesion was isodense on plain scan and showed early enhancement in arterial phase and appeared isodense to pancreas in venous phase of the contrast study. Scattered microcalcification within the tumour was noted too.

Whipple’s pancreatico duodendectomy was performed due primarily to the relatively large size of this tumour and the presence of microcalcification within the tumour. Intra-operative ultrasound scan was performed during surgery to confirm the location of the tumour and to exclude presence of multiple tumours. Encapsulated...
tumour was found within the pancreatic tissue, attached to the outer surface of the duodenal wall. Immediately after removal of the mass, serum glucose level increased to 10.8 mmol/L. Hyperglycaemia was observed during the first 24 hours and intravenous insulin infusion commenced. Normoglycaemic status was achieved with human insulin. Insulin was omitted on post-op day 15 and the patient experienced no further hypoglycaemic episodes.

Discussion

Diagnosis of insulinoma may be delayed if symptoms are nonspecific. The common clinical manifestation of an insulinoma is fasting hypoglycaemia, with discrete episodes of neuroglycopenic symptoms that may or may not be preceded by sympathoadrenal (autonomic) symptoms. Neuroglycopenic symptoms are predominant in some patients and these patients may be diagnosed as epilepsy or neuropsychiatric disease (3,4). In a retrospective study of 59 patients with histologically confirmed islet cell adenomas, the interval between onset of symptoms and diagnosis ranged from 1 month to 30 years, with a median of 24 months. A significant proportion (39%) was originally diagnosed with a seizure disorder (6,7).

The biochemical hallmark of diagnosis of insulinoma is the fasting hypoglycaemia in the face of inappropriately raised serum insulin and C-peptide levels and exclusion of surreptitious intake of exogenous insulin or oral hypoglycaemic agents (5).

Successful preoperative tumour localisation is achieved in about 60% of patients. The imaging modalities used for localisation of insulinoma are:

- Transabdominal ultrasound: readily available, inexpensive, and noninvasive with detection rate of 25 - 65%.
- Endoscopic ultrasound: equipment and expertise are not widely available but with detection rate of 70%.
- CT: widely available and non-invasive with a detection rate of 70% when contrast is used.
- MRI, selective angiography, percutaneous transhepatic portal venous sampling, arterial simulation venous sampling and radionuclide imaging can also be used with sensitivities ranging from 50 to 90% (4,5,9-11).

In addition to the preoperative diagnostic imaging techniques, intraoperative palpation and ultrasound are the gold standards for localising an insulinoma, with a reported success rate of 96 - 100% (9,12). Surgery is the only curative treatment of this potentially lethal condition. The nature of surgery depends upon the size, location and resectability of insulinoma. Simple enucleation is the most favoured option for solitary insulinoma, while distal pancreatectomy with or without splenectomy is preferred for multiple insulinomas occurring in the body and tail of the pancreas. Pancreatoduodenectomy (Whipple’s procedure) becomes indispensable for a non-enucleable insulinoma in the head and neck regions of the pancreas (9,10). The surgical procedure is usually chosen by the surgeon, and the incidence of post surgical complications is approximately 10% (8, 9, 13).

Medical treatment is continued when surgery is contraindicated. Streptozocin, diazoxide, verapamil,
Malignant insulinomas are rare, and therefore, little is known about their clinical presentation and long term prognosis. They are generally indolent tumours, and long survival has been reported, even in the presence of liver or lymph node metastases (12,15).

To conclude, insulinoma is a rare disease even at large centres. With its vague and varied clinical presentation, insulinoma can be a diagnostic conundrum. Diagnosis of insulinoma should be considered in any patient with unusual neurological features, including atypical convulsions refractory to pharmacotherapy.

References
Relative importance of the metabolic syndrome as a cardiovascular risk factor in Sri Lankans

Upali Illangasekera¹, N S B Dissanayake²


Abstract

The relative importance of the metabolic syndrome as a cardiovascular risk factor was determined by comparing its prevalence in a sample of 1018 subjects with cardiovascular disease with those without established cardiovascular disease. According to these data metabolic syndrome was not associated with higher risk of cardiovascular disease. However, there was positive correlation between individual cardiovascular risk factors (hypertension, smoking, dyslipidaemia and a family history of cardiovascular disease). Waist circumference on its own was only poorly correlated with cardiovascular disease compared to the other risk factors.

Introduction

Established risk factors for cardiovascular disease include hypertension, smoking, glucose intolerance, obesity and dyslipidaemia, age and family history. In an individual patient these risk factors could occur in isolation or more commonly together. In a certain category of patients they tend to cluster together more than by chance. This cluster is called the metabolic syndrome (MS) and is considered to increase future risk of cardiovascular disease (CVD) as well as diabetes (1). Rising incidence of diabetes and obesity is likely to increase the prevalence of the MS. This study was carried out with the objective of determining the prevalence of the MS in those with and without CVD and to evaluate the strength of the relationship between individual cardiovascular risk factors in those with CVD.

Methodology

The study was cross sectional in design and was carried out in Teaching Hospitals of Kandy and Peradeniya. All patients over the age of 30 years attending the Cardiology Clinic at Teaching Hospital, Kandy (n=164) and the Diabetic Clinic (n=667) at Teaching Hospital, Peradeniya over a period of one month were selected. One hundred and eighty seven (98 males, 89 females) matched for age were selected as those without CVD from hospital visitors and bystanders. Informed consent was obtained from all patients and subjects. The International Diabetes Federation (IDF) definition was used to diagnose the MS (2). Cardiovascular disease was diagnosed on clinical features such as the presence of symptoms and signs of ischaemic heart disease, being treated for such disease and investigations such as ECG, echocardiography, exercise ECG and coronary angiography. The proportion of patients with MS among those with and without CVD was determined. The relationship between individual cardiovascular risk factors and CVD was carried out by assessing partial correlation for each risk factor while controlling for others. The waist circumference which is considered to be a surrogate marker of the MS too was assessed as a cardiovascular risk factor (3).

Results

The total number of patients enrolled for the study was 831 consisting of 164 (110 males, 54 females) from the Cardiology Clinic, Teaching Hospital, Kandy, and 667 (437 males and 230 females) from the Diabetic Clinic at Teaching Hospital, Peradeniya. One hundred and eighty seven (98 males, 89 females) matched for age were selected as those without CVD from hospital visitors and bystanders. The association between the MS and the CVD is shown in Table 1. As the results indicate there was no statistically significant relationship between the MS and CVD. When the strength of the relationship between individual risk factors and CVD was assessed it was found that while diabetes was negatively correlated the least correlation was for the waist circumference compared with other cardiovascular risk factors (Table 2).
The results of this study indicate that the MS was not associated with CVD and had the least correlation with CVD compared to other risk factors such as hypertension, dyslipidaemia, smoking and the family history.

The MS is a simple entity that can be used to identify individuals who are free of CVD but who are at an increased risk of future CVD risk. Since the diagnosis of the MS is commonly based on anthropometric and clinical data it would be an ideal tool for the use in developing countries such as Sri Lanka. Early publications reported rather substantial associations between the MS and CVD (4). An atherogenic role for the MS has been proposed as there are abnormalities in insulin resistance, lipids, blood pressure, glucose tolerance, LDL particle size, HDL cholesterol, endothelial function, cell adhesion molecules, plasminogen activator inhibitor, fibrinogen and inflammatory markers including C-reactive protein. However more recent studies have shown that although the MS can predict the future development of diabetes and CVD it predicts less effectively than established predicting models such as Diabetes Risk Score and Framingham Risk Score (5). Furthermore it has been shown that clustering had no greater predictive value beyond the consideration of the individual risk factors (6). The results of the present study too supports the notion of only a limited role for the MS as a potential cardiovascular risk factor in Sri Lankans. Limitations of the study include the sampling bias and the presence of other possible confounding factors. We could not find why diabetes had a negative correlation with CVD. Possible explanation is that people who develop CVD modify their lifestyle and hence develop less diabetes. In the same way those with CVD in this retrospective study has less abdominal obesity due to better control of diet and having more exercise and have lower prevalence of metabolic syndrome. Therefore there is a need to test this hypothesis in a prospective study with a randomly selected bigger sample and especially looking at development of CVD in those with and without metabolic syndrome during the follow up.

### Table 1. Relationship between the metabolic syndrome and cardiovascular disease

<table>
<thead>
<tr>
<th></th>
<th>CVD present</th>
<th>CVD absent</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>MS present</td>
<td>157 (59)</td>
<td>432 (57)</td>
<td>582 (57)</td>
</tr>
<tr>
<td>MS absent</td>
<td>109 (41)</td>
<td>320 (43)</td>
<td>429 (43)</td>
</tr>
<tr>
<td>Total</td>
<td>266 (100)</td>
<td>752 (100)</td>
<td>1011 (100)</td>
</tr>
</tbody>
</table>

Significance: p 0.655 (t-test)

MS: metabolic syndrome, CVD: cardiovascular disease
Percentages in parentheses

### Table 2. Correlation between individual risk factors and cardiovascular disease

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Correlation coefficient</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes</td>
<td>-0.24</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>Smoking</td>
<td>0.28</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.18</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>Dyslipidaemia</td>
<td>0.29</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>Family history</td>
<td>0.77</td>
<td>p &lt; 0.05</td>
</tr>
<tr>
<td>W.C. Male</td>
<td>0.10</td>
<td>p &lt; 0.05</td>
</tr>
<tr>
<td>W.C. Female</td>
<td>0.04</td>
<td>NS</td>
</tr>
</tbody>
</table>

W.C. – waist circumference, N.S. – not significant

### Discussion

The results of this study indicate that the MS was not associated with CVD and had the least correlation with CVD compared to other risk factors such as hypertension, dyslipidaemia, smoking and the family history.

The MS is a simple entity that can be used to identify individuals who are free of CVD but who are at an increased risk of future CVD risk. Since the diagnosis of the MS is commonly based on anthropometric and clinical data it would be an ideal tool for the use in developing countries such as Sri Lanka. Early publications reported rather substantial associations between the MS and CVD (4). An atherogenic role for the MS has been proposed as there are abnormalities in insulin resistance, lipids, blood pressure, glucose tolerance, LDL particle size, HDL cholesterol, endothelial function, cell adhesion molecules, plasminogen activator inhibitor, fibrinogen and inflammatory markers including C-reactive protein. However more recent studies have shown that although the MS can predict the future development of diabetes and CVD it predicts less effectively than established predicting models such as Diabetes Risk Score and Framingham Risk Score (5). Furthermore it has been shown that clustering had no greater predictive value beyond the consideration of the individual risk factors (6). The results of the present study too supports the notion of only a limited role for the MS as a potential cardiovascular risk factor in Sri Lankans. Limitations of the study include the sampling bias and the presence of other possible confounding factors. We could not find why diabetes had a negative correlation with CVD. Possible explanation is that people who develop CVD modify their lifestyle and hence develop less diabetes. In the same way those with CVD in this retrospective study has less abdominal obesity due to better control of diet and having more exercise and have lower prevalence of metabolic syndrome. Therefore there is a need to test this hypothesis in a prospective study with a randomly selected bigger sample and especially looking at development of CVD in those with and without metabolic syndrome during the follow up.
Acknowledgements

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References

Instructions to Authors

Sri Lanka Journal of Diabetes, Endocrinology and Metabolism 2012; 2: 52-54

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.

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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 Clinical updates 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 for reviews.

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.

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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

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- 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.

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The title page should include the following:

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- Disclosure summary (see Disclosure of Potential Conflict of Interest form for instructions)
- Clinical Trial Registration Number, if applicable

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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.

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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.

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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).

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

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Authorship Criteria

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.

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To be considered, all clinical investigations described in submitted manuscripts must have been conducted in accordance with the guidelines in The Declaration of Helsinki and must have been formally approved by the appropriate institutional review committees or its equivalent. All manuscripts must indicate that IRB approval was acquired; and that when informed consent was required by the IRB, that this was obtained from subjects in experiments involving humans. Photographs of patients’ faces should be included only if scientifically relevant. Authors must obtain written consent from the patient for use of such photographs.

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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.

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