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Obesity has become one of the major public health concerns worldwide. A number of studies have reported that with each surge in weight, there is an increase in the risks for coronary heart disease, type 2 diabetes, cancers, hypertension, dyslipidaemia, stroke, sleep apnea, respiratory problems, osteoarthritis, and gynaecological problems. Although traditionally considered to be a problem associated with the developed world, with the recent economic, demographical, cultural and environmental changes, the developing world too is increasingly being burdened with the same issue. The South Asian region, with its number of diverse countries has not been spared of the problem, and has the additional issue of tackling with both under and over nutrition.

While low socioeconomic status has been associated with a higher prevalence of obesity and chronic diseases in developed countries, studies in developing nations have shown a positive socio-economic status obesity relationship with increasing income level of such countries (1). Worldwide, the prevalence of obesity among women is also the highest in upper middle-income countries (1). Recent studies have demonstrated that the prevalence of obesity and the other related cardiovascular risk factors is high in the South Asian region, and is on the rise. Studies have revealed that the prevalence of obesity in India ranges between 20.8% to 50.1% in urban areas and is as high as 32% in certain rural areas (2). In Sri Lanka, Katulanda et al have demonstrated that, according to the proposed World Health Organization cut-off body mass index values for Asians, the percentage of Sri Lankan adults in the overweight, obese and centrally obese categories were 25.2%, 9.2% and 26.2%, respectively (3). Amongst children, again going by the global trends, there is a secular trend in the prevalence of obesity. Recent studies have quoted a prevalence of obesity as high as 29% amongst school children in certain Indian cities (2). However, the same region is also burdened by under nutrition, and it is estimated that more than half of the world’s underweight children live in South Asia (4). “Nutrition transition,” termed as a combination of improved access to food and decreased physical activity level has been identified to be the prime risk factor for the increasing prevalence of overweight and chronic metabolic diseases in the developing countries, and is probably the cause of this problem in South Asia as well. Although initially such dietary changes and emergence of obesity was confined to higher socioeconomic strata of the populations among developing countries, more recent trends demonstrate a shift in the prevalence from the higher to the lower socioeconomic level (1). Nutritionists now believe that this nutrition transition is not merely due the change in the diet and physical activity, but is also the improvement in economic, social and environmental factors that is shaping the landscape of modern living as never before (4). In keeping with the global trends, South Asian nations too, have experienced a period of unprecedented economic growth, higher income level, provision of labor-saving technologies, and a significant reduction in the number of people living in extreme poverty. The global dietary transition, which is that of a shift from a diet with a higher proportion of carbohydrate based foods such as cereal grains (rice, wheat, maize), vegetables (leaves, roots, legumes) and low animal products (meat, egg, milk) to one which is lower in carbohydrate and higher in animal-based food with high sugar and caloric content and larger amount of processed food (sweets, soft drinks) has not spared the south Asian region as well. India, with around 35% of total population living on vegetarian diet has experienced a doubling in total poultry meat consumption since 2000, while in Pakistan’s total meat consumption has increased by 130% during the same period (4). Increased import of food, advancement in local food technology and in food marketing and processing industry have greatly increased the availability of processed food products, even in the remote rural areas where majority of the South Asians live. Urbanization is thought to be one major cause for the change in these dietary habits. Nepal is leading the race of urbanization in South Asia with a rate of 4.9% while that for Sri Lanka is the lowest (0.7%) (4). Furthermore, the number of people involved in

**References**

service sector employment, as opposed to agriculture based jobs is also on the rise, and this is a major factor that leads people to move into urban areas. In Sri Lanka, service oriented employment rate has increased from 27.9% to 38.4% in the period from 1985 to 2005 whereas agriculture based employment has decreased from 49.3% to 30.7% (4). With increase in urbanization, there is more access to processed food, less time to prepare food at home and to engage in physical activity. With urbanization, there’s more participation of women in the labour force, and it is likely that families may need to resort to consuming processed food rather than homemade traditional food, due to time constraints. Improvement in food technology, international trade and transport has led to the inflow of “international” food into countries, which are mostly processed food high in calories and saturated fat. This has changed the consumer market from one that consisted of mainly raw food and traditional food to one which mostly consists of processed ready-to-eat food. It is interesting to note India is the second largest (after Brazil) producer and largest consumer of sugar in the world (5).

Low physical activity which is another major contributor to obesity is also associated with low socio-economic status. Low physical activity may be due to less energy expenditure in farming and agricultural activities, increase in the number of occupations that require minimal amounts of energy expenditure and more time spent sedentarily during leisure time. Urbanization again, has created a number of office based jobs and reduced the amount of space that’s available for physical activity such as safe walkways, bicycle paths, and playgrounds. Increase in time in front of the television has not only been associated with lack of physical activity, but also with increase in the consumption of unhealthy food in front of the television, which is also influenced by adverse nutrition messages in television commercials. Studies have constantly demonstrated that low socio-economic status is associated with low physical activity level. Studies reveal that physical activity is significantly lower in Asians when compared to their western counterparts. Data from the Health Survey from England found that South Asians in England were 60% less likely to engage in physical activity than Caucasian living in the same region (6). A systematic review on physical inactivity amongst South Asians revealed that 18.5% - 88.4% of Indians, 60.1% of Pakistanis and 11% - 31.8% of Sri Lankans were physically inactive(6). However, contrary to results from other studies, which showed that lower economic status was associated with less amount of physical activity, this review revealed that skilled workers and professionals were more physically inactive and higher education was significantly associated with physical inactivity (6). Several studies have also revealed that physical inactivity is more in South Asia women than men, likely due to cultural restrictions in certain ethnic groups and the traditional role of women in household work and taking care of their families, which may leave them with very little time for recreational activities (6, 7, 8). A recent study in Sri Lanka involving both rural and urban women in 20 to 45 year age group revealed that the prevalence of overweight, obesity and abdominal obesity was 38%, 34% and 45% respectively, which was higher than what was previously observed (9). In the same study, more than half of the women were categorized as being sedentary, and none of them were involved in any sport activities. Carbohydrates were the highest contributor to energy intake (70%), and nearly 70% were consuming above the upper cut-off of recommendations for the amount of daily starch portions. There was a positive significant correlation between percentage of energy contributed from carbohydrate and waist circumference.

Over the years a number of interventions have been initiated to mitigate obesity, but with little success. The South Asian region, with its double burden of communicable and non-communicable diseases, need vigorous involvement of governments, non-governmental organizations and media to combat this problem. Promotion of school based health and nutrition programmes to control childhood obesity is also an area that has been promoted by policymakers and researchers, which may be successful in the South Asian region, as South Asians have the highest number of children in the primary schools worldwide (1). Sri Lanka, in the recent past has initiated a number of such programmes, with the involvement of both the government and non-governmental organizations. Development of public outdoor areas such as parks and jogging tracts for recreational activities, promotion of exercise programmes within Government offices (a health promotion day per week), implementation of school canteen policies, promotion of school health clubs, introducing a coding policy to indicate the sugar level in sweetened beverages and the introduction of

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*Sri Lanka Journal of Diabetes, Endocrinology and Metabolism*
Healthy Lifestyle clinics through the public health system are some of them. However, what Sri Lanka lacks is a national policy and strict regulations on the import and sale of unhealthy food, a national policy on the amount of sugar and fat that can be incorporated into locally manufactured food and regulations on advertisement of unhealthy food via social media. Furthermore, although there is a positive trend in development of safe recreational areas for exercise, we have not still managed to make them accessible to all Sri Lankans, especially for those in semi-urban and rural areas of the country. Although there are a number of school health promotional activities that have been implemented, we still haven’t addressed one of the key issues that affects school children of this country, that is inadequacy of time and resources to engage in creational activities, due to being overburdened by academic activities in today’s competitive society.

REFERENCES


THE USE OF MID UPPER ARM CIRCUMFERENCE AND SKINFOLD THICKNESS TO ASSESS UNDERWEIGHT AND OBESITY AMONG CARDIAC PATIENTS

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ABSTRACT

Introduction and Objectives: Assessment of nutritional status is a key element in the management of the cardiac patient. There are practical difficulties in using the conventional parameters such as Body Mass Index (BMI) and Waist Circumference (WC), especially in critically ill and bed bound patients. The current study evaluated the validity of Mid Upper Arm Circumference (MUAC) and Triceps Skinfold Thickness (TSFT) as alternatives for BMI and WC in assessing underweight, obese and centrally obese among cardiac patients.

Methods: A cross-sectional study was carried out among 526 patients admitted to a tertiary care hospital. Height, weight, WC, MUAC and TSFT were measured using standard techniques. Those who had a BMI ≤18.5kgm⁻² were considered as underweight and BMI>25kgm⁻² as obese. Asian cut-offs (WC>90cm for males, WC>80cm for females) were used to define central obesity. Receiver operating characteristic (ROC) curve analysis was done.

Results: Mean MUAC and TSFT were 29.1cm and 14.9mm respectively. MUAC had ROC curve area of 0.94 which was higher than that of TSFT (0.81). Based on the highest corresponding Youden's Indices, MUAC<26cm, TSFT<10.1mm were found to be suitable cut-off points for the detection of underweight patients and MUAC>30cm, TSFT>13.8mm for obese. Both parameters were valid in detecting central obesity, for which MUAC>28.8, TSFT>12.8mm for males and MUAC>26.7cm, TSFT>17.4mm for females were suitable cut-offs.

Conclusions: MUAC and TSFT were possible alternatives for the detection of underweight, obese and centrally obese cardiac patients. Among them, MUAC was found to be a better predictor. For simplicity in use, MUAC<26cm and >30cm can be used as cut-off points to detect underweight and obese patients respectively.

Key Words: Mid upper arm circumference, triceps skin fold thickness, cardiac, body mass index, waist circumference, overweight, obese, Sri Lanka.

INTRODUCTION

The impact of level of nutrition on the overall morbidity and mortality is substantial (1, 2). Both over nutrition and malnutrition are associated with adverse events, which ultimately lead to poor health outcomes (3) and therefore, evaluation of the nutritional status is a key element in the assessment of hospitalized patients. The components of the conventional methods of assessment include calculation of Body Mass Index (BMI) with the use of weight, height parameters and recognition of central obesity with Waist Circumference measurement (WC). BMI is important in identifying over nutrition (4) as well as malnutrition (5). Central obesity, which is recognized as a more accurate marker of cardio-metabolic risk (6), is practically described in terms of WC (7). Identifying the extremes of nutritional status, with the use of these anthropometric indices, aids in the nutritional management of these patients.

Although the nutritional status is an important component of patient assessment, there are practical difficulties in obtaining these measurements in hospitalized patients. Routine recording of these measurements may not be
feasible depending on the setting and the patient’s condition. A large number of patients and rapid turnover limit the usage of BMI in countries with poor resources. In critically ill or bed bound patients, ambulation is almost impossible for weight and height measurements (8). There can be conditions such as oedema with certain diseases, where the BMI may not correctly identify the nutritional status of the patient. Unavailability of correctly calibrated scales and difficulty of ambulation for measurement has led to the need for appropriate alternatives for BMI measurements in hospitalized patients. Similarly, WC measurement that needs upper body undressing and ambulation, limit the liberal usage in hospitalized patients.

Numerous indices have emerged as alternatives to BMI and WC. Sagittal Abdominal Diameter (9), Waist to hip ratio (10) and Body adiposity index (11) are among the examples. Mid Upper Arm Circumference (MUAC) and Skin Fold Thickness (SFT) are simple bed-side anthropometric measurements indicating body composition and nutritional status of patients (12). The need for patient mobilization and the amount of equipment are minimal to obtain both these parameters. Therefore, these are simple and effective tools in critically ill patients (13). MAUC has also shown a prognostic value with the ability to predict mortality and major complications (8, 13) and a close correlation with the BMI (8). Skin fold thickness, on the other hand, is an indicator of adiposity (14) and is useful screening tool in the assessment of nutritional status of the children and adolescents (15).

Adiposity is considered to be an independent risk factor for cardiovascular disease (16) and on the other hand, the malnutrition is also associated with poor disease outcomes (17). Hence there is a need for feasible and accurate indicators of nutritional status in hospitalized patients. The aim of this study is to assess the validity of MUAC and TSFT as alternatives for BMI and WC to detect underweight and obesity in cardiac patients, to arrive at appropriate cut-offs and to assess the validity of these parameters in predicting central obesity in cardiac patients.

**METHODOLOGY**

**Study design and subjects:**

The study was conducted in cardiology unit of a tertiary care hospital in Sri Lanka. Patients consecutively admitted to the unit from March 2012 to July 2012 were recruited. Socio-demographic data, details on the medical history of current disease and co-morbidities were collected. Anthropometric measurements were taken on admission using standard measurements. Data were collected by a trained medical officer. Details of the study have been reported elsewhere (18). Only the patients, giving informed written consent, were included. Ethical approval for the study was obtained from the Ethical Review Committee of National Hospital of Sri Lanka.

**Anthropometric measurements:**

The body weight was measured using an electronic scale (Seca 815, Seca GmbH. Co. kg, Germany) to the nearest 100g. The height was measured with a standard stadiometer (Seca 217, Seca GmbH. Co. kg, Germany) to the nearest 1mm. Body Mass Index (BMI) was calculated by dividing weight in kilograms by height squared in meters. According to Sri Lankan guideline cut-off values, the patients were classified into four BMI categories; underweight <18.5kgm\(^{-2}\), normal weight 18.5\(-22.9\) kgm\(^{-2}\), overweight 23-25 kgm\(^{-2}\), obese >25 kgm\(^{-2}\) (19). Waist circumference (WC) was measured midway between iliac crest and lower rib margin at the end of normal expiration using a standard measuring tape to the nearest 0.1cm. Central Obesity was defined as WC exceeding 90cm in males and 80cm in females (19).

International Society for the Advancement of Kinanthropometry (ISAK) guidelines was followed in obtaining MUAC and TSFT measurements (20). Both these measurements were taken with the patient standing upright, with arms hanging down loosely. MUAC was measured using a standard non-stretchable tape (Seca 203, seca GmbH. Co. kg, Germany) at the marked level of Mid-acromiale-radiale, positioning the tape perpendicular to the long
axis of the arm. TSFT was measured using a Harpenden Skinfold Caliper (Baty International, West Sussex, UK) over the triceps muscle. The measurement was taken parallel to the long axis of the arm at the triceps skinfold site, to the nearest 0.5mm. This point was on the posterior surface of the arm, in the midline, at the level of the marked mid-acromiale-radiale level. Three separate measurements were taken for each of these and the mean values were calculated.

**Statistical Analysis:**

Data entry and analysis was done using SPSS Version 20.0 statistical package. Receiver operating characteristic (ROC) curve analysis was done to assess the validity of MUAC and TSFT in detecting underweight, obese and centrally obese patients. Area under the ROC Curve (AUROC) and Youden’s index were generated to aid the selection of most suitable cut-off values. Coordinate points for each MUAC and TSFT values were generated. Cut-off points were decided by maximizing the sum of sensitivity and specificity. The value corresponding to the maximum of Youden’s Index was used as the optimum cut-off point. AUC values with their 95% confidence intervals were used to compare the overall diagnostic performance of the two tests. P value of less than 0.05 was considered as significant.

**RESULTS**

Characteristics of the study population are summarized in Table 1. A total of 526 patients were enrolled, among whom 61.2% were males (n=322). Mean (SD) age in the study population was 58.5 (±12.0) years. The commonest underlying medical problem for the cardiac admission was the acute coronary syndrome (n=275, 52.3%), whereas arrhythmias (n=67, 12.7%), heart failure and cardiomyopathies (n=59, 11.2%) constituted the next common diagnostic categories. Socio-demographic characteristics of the study population are summarized in Table 1. The mean Body Mass Index of the study group was 23.6 (±4.2) kgm$^{-2}$. About one-third (n=176, 33.3%) were in the obese category according to measured BMI, and underweight constituted 9.9% (n=52) of the study population. More than half of the study sample (58.17%, n=306) had central obesity.

<table>
<thead>
<tr>
<th>Patient Characteristic</th>
<th>Male n=322</th>
<th>Female n=204</th>
<th>Total n=526</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ethnicity</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sinhala</td>
<td>266 82.6</td>
<td>172 84.3</td>
<td>438 83.3</td>
</tr>
<tr>
<td>Muslim</td>
<td>24 7.5</td>
<td>19 9.3</td>
<td>43 8.2</td>
</tr>
<tr>
<td>Indian Tamil</td>
<td>4 1.2</td>
<td>0 0</td>
<td>4 0.8</td>
</tr>
<tr>
<td>Sri Lankan Tamil</td>
<td>22 6.8</td>
<td>12 5.9</td>
<td>34 6.5</td>
</tr>
<tr>
<td><strong>Education Level</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No formal education</td>
<td>25 7.8</td>
<td>30 14.7</td>
<td>55 10.5</td>
</tr>
<tr>
<td>Primary</td>
<td>96 29.8</td>
<td>79 38.7</td>
<td>175 33.3</td>
</tr>
<tr>
<td>Secondary</td>
<td>186 57.8</td>
<td>87 42.6</td>
<td>273 51.9</td>
</tr>
<tr>
<td>Tertiary</td>
<td>15 4.7</td>
<td>8 3.9</td>
<td>23 4.4</td>
</tr>
<tr>
<td><strong>Diagnosis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IHD</td>
<td>87 42.6</td>
<td>275 52.3</td>
<td>188 58.4</td>
</tr>
</tbody>
</table>
Arrhythmia 31 15.2 67 12.7 36 11.2
Cardiomyopathy/HF 9 4.4 16 3 7 2.2
Valvular heart disease 26 12.7 59 11.2 33 10.2
Infections 8 3.9 22 4.2 14 4.3
Pericardial diseases 4 2 7 1.3 3 0.9
Iry/Iry lung disease 11 5.4 15 2.9 4 1.2
Miscellaneous 28 13.8 65 12.3 37 11.5

**Weight Category**

<table>
<thead>
<tr>
<th>Weight Category</th>
<th>Underweight (&lt;18.5 kg/m²)</th>
<th>Normal weight (18.5-22.9 kg/m²)</th>
<th>Overweight (23-24.9 kg/m²)</th>
<th>Obese (&gt;25 kg/m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central Obesity Present-Male</td>
<td>139 43.2 167 80.3</td>
<td>183 56.8 37 17.8</td>
<td>175 33.3</td>
<td></td>
</tr>
<tr>
<td>Central Obesity Present-Female</td>
<td>199 52.8 37 17.8</td>
<td>183 56.8 37 17.8</td>
<td>175 33.3</td>
<td></td>
</tr>
</tbody>
</table>

**Central Obesity**

<table>
<thead>
<tr>
<th>Test</th>
<th>AUC (95% CI)</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MUAC</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI-underweight</td>
<td>0.94</td>
<td>0.90 - 0.97</td>
</tr>
<tr>
<td>BMI-obese</td>
<td>0.93</td>
<td>0.90 - 0.95</td>
</tr>
<tr>
<td>Central Obesity Present-Male</td>
<td>0.89</td>
<td>0.86 - 0.93</td>
</tr>
<tr>
<td>Central Obesity Present-Female</td>
<td>0.95</td>
<td>0.92 - 0.98</td>
</tr>
<tr>
<td><strong>TSFT</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI-underweight</td>
<td>0.81</td>
<td>0.75 - 0.87</td>
</tr>
<tr>
<td>BMI-obese</td>
<td>0.81</td>
<td>0.78 - 0.85</td>
</tr>
</tbody>
</table>

The validity of MUAC and TSFT as alternatives for BMI- Area Under ROC (AUROC) analysis is shown in Table 2. The mean MUAC of the study population was 29.1 (±5.5) cm. The mean TSFT was 15 (±6.4) mm. ROC curve analysis for MUAC and TSFT in detecting underweight patients revealed an area under the curve (AUC) of 0.94 (95% CI 0.90-0.97) and 0.81 (95% CI 0.75-0.87) respectively. In detecting obese, AUC were found to be 0.93 (95% CI 0.90-0.95) and 0.81 (95% CI 0.78-0.85) for MUAC and TSFT respectively (figure 1).
Based on the highest corresponding Youden’s Indices, MUAC value of 26.1cm (Youden’s Index 0.78) and TSFT value of 10.1mm (Youden’s Index 0.52) were found to be suitable cut-off points for detection of underweight patients. MUAC of <26.1cm showed a sensitivity of 96.2% and a specificity of 81.9% in detecting underweight. The corresponding sensitivity and specificity values for other tests are summarized in table 3. Similarly, 30cm for MUAC (Youden’s Index 0.71) and 13.8mm for TSFT (Youden’s Index 0.48) were shown to be appropriate cutoff points for identifying obese patient.

**FIGURE 1: ROC ANALYSIS FOR MUAC AND TSFT IN DETECTING UNDERWEIGHT AND OBESE**

**Fig 1a - ROC curve of MUAC in predicting underweight**

**Fig 1b - ROC curve of MUAC in predicting obese**

**Fig 1c - ROC curve of TSFT in predicting underweight**

**Fig 1d - ROC curve of TSFT in predicting underweight**

Figure 2 shows the analysis for the validity of MUAC and TSFT in predicting central obesity separately for males and females. MUAC revealed an area under the curve (AUC) of 0.89 (95% CI 0.86-0.93) and 0.95 (95% CI 0.92-0.98) for males and females respectively. Similarly, TSFT had an AUC of 0.85 (95% CI 0.80-0.89) and 0.86 (95% CI 0.80-0.92) for males and females respectively. Depending on the highest sensitivity and specificity, a MUAC of 28.8cm (Youden’s Index 0.63) for males and 26.7cm (Youden’s Index 0.80) for females were suitable cutoffs for predicting central obesity. The similar analysis identified TSFT of 12.8mm (Youden’s Index 0.54) for males and 17.4mm (Youden’s Index 0.58) for females as appropriate cut-off points for detecting obesity.
Table 3: Sensitivity and Specificity of MUAC and TSFT in detecting underweight and obese

<table>
<thead>
<tr>
<th>Test</th>
<th>Youden’s Index</th>
<th>Cut-off</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MUAC</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI-underweight</td>
<td>0.78</td>
<td>&lt;26.1 cm</td>
<td>0.96</td>
<td>0.82</td>
</tr>
<tr>
<td>BMI-obese</td>
<td>0.71</td>
<td>&gt;30 cm</td>
<td>0.89</td>
<td>0.82</td>
</tr>
<tr>
<td>Central Obesity Present- Males</td>
<td>0.63</td>
<td>&gt;28.8 cm</td>
<td>0.86</td>
<td>0.77</td>
</tr>
<tr>
<td>Central Obesity Present- Females</td>
<td>0.80</td>
<td>&gt;26.7 cm</td>
<td>0.86</td>
<td>0.95</td>
</tr>
<tr>
<td><strong>TSFT</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI-underweight</td>
<td>0.52</td>
<td>&lt;10.1 mm</td>
<td>0.71</td>
<td>0.81</td>
</tr>
<tr>
<td>BMI-obese</td>
<td>0.48</td>
<td>&gt;13.8 mm</td>
<td>0.83</td>
<td>0.65</td>
</tr>
<tr>
<td>Central Obesity Present- Males</td>
<td>0.54</td>
<td>&gt;12.8 mm</td>
<td>0.74</td>
<td>0.80</td>
</tr>
<tr>
<td>Central Obesity Present- Females</td>
<td>0.58</td>
<td>&gt;17.4 mm</td>
<td>0.66</td>
<td>0.92</td>
</tr>
</tbody>
</table>

Figure 2: ROC analysis for MUAC and TSFT in detecting central obesity in males and females

2a - ROC curve of MUAC in predicting central obesity in males

2b - ROC curve of MUAC in predicting central obesity in females

2c - ROC curve of TSFT in predicting central obesity in males

2d - ROC curve of TSFT in predicting central obesity in female
DISCUSSION

To the best of our knowledge, this is the first study done to assess the applicability of alternative measurements such as MUAC and TSFT for BMI and WC in cardiac patients. However, this concept has already been studied in hospitalized patients (8, 13). With a large subject population of different socioeconomic groups and with varying diagnoses, the sample can be considered as representative of the overall cardiac patients in Sri Lanka. Given the practical difficulties encountered in clinical practice for obtaining conventional measurements, this study provides useful alternatives.

Our findings suggest that the MUAC and the TSFT are possible alternatives to BMI, which may be used for the detection of underweight and obese cardiac patients. Considering the AUC analysis for these parameters, the overall diagnostic performance of MUAC seems to be better than the TSFT. Numerous studies have revealed the use of MUAC as a simple screening tool for nutritional status (12). It requires neither expensive equipment nor complex mathematical equations. It is increasingly being recognized as an effective and reliable assessment tool due to the simplicity in measurement and applicability to all patients including the acutely ill (8). However, it is widely described as an indicator of under-nutrition and the studies in overweight are limited to children and adolescent subgroups (21). Our study findings open room for new research to assess the potential of MUAC to be used as a screening tool for screening obesity.

TSFT is also a bedside measurement, which can be measured even in debilitated patients and according to AUROC analysis findings, it is possible for this also to be used as a valid tool to detect the underweight problem and obesity. However, its predictive ability, sensitivity and specificity seem to be lesser than that of the MUAC. TSFT measurement may have issues pertaining to the age group of patients or people being considered. A study done in Portuguese adolescents has demonstrated TSFT as a valid tool in obesity screening in younger adolescents, but with less discriminative ability in older subgroups (15). If used appropriately, it can be used as a useful tool for assessing the nutritional status of selected groups of patients.

The body fat distribution gets altered with aging and therefore, the measurements of adiposity should be adjusted according to the age. Although our study population had a significant number of older patients, (with a mean age of 58.5 (±12.0) years), the age-related variations of MUAC and TSFT were not taken into consideration and therefore it is a limitation of our study.

The cut-off values of MUAC and TSFT obtained for our cardiac patients are close to the values described for the general population. An Indian study done in a rural adult community recommend the MUAC cut-off of 24cm (22). MUAC cut-offs derived for screening chronic energy deficiency in third world adults recommend 23cm for men and 22cm for women (12). Another study done in acutely hospitalized patients recommend the cut off of 25cm for the detection of malnutrition (8). Our study finding findings are also comparable with those study results. However, separate studies may be needed to derive at different cut-offs for different groups of people.

Both MUAC and TSFT are indirect methods of assessing fat reserve. MUAC has been shown to be a useful screening tool for body fat distribution in children (23). Also, both WC and MUAC have shown a good correlation with BMI (23, 24). Cut-offs have been derived for WC and abdominal sagittal diameter to detect visceral adiposity (25). However, there are no direct studies to compare MUAC, TSFT with central obesity cut-offs in adults. Therefore, the current study aimed at arriving at possible cutoff values for our population. Our study demonstrated the satisfactory ability of these parameters to predict central obesity. It also revealed that MUAC to be a better predictor than TSFT. International cut-offs for central obesity in Asians vary according to the gender (26). We also managed to suggest separate gender-based MUAC and TSFT cut-offs to predict central obesity for males and females separately.
**LIMITATIONS:**

Fluid retention due to cardiac pathologies (e.g. heart failure) may lead to overestimation of weight measurement and the presence of ascites may lead to erroneous interpretation of waist circumference. However, we did not exclude the patients with oedema and it was a limitation of our study. To overcome this problem, a subanalysis was done after exclusion of patients with clinical evidence of fluid retention and the results obtained were not significantly different from the results of the total study population (supplementary file 1). This may be due to the fact that oedema due to cardiac pathologies is usually minimal (except for the severe congestive heart failure) in comparison to other organ impairments. Therefore, the cut-offs obtained for the total population may be considered as applicable to the overall cardiac patients, including patients with oedema.

Lack of a control group may lead to probable over-estimation of results and the applicability of our results to the general population becomes limited. The absence of gender and age stratification is also a limitation of our study.

The proper measuring technique has to be used to obtain accurate measurements of both MUAC and TSFT and recognition of the correct landmark requires knowledge and skills. We managed to minimize the measurements errors by using one trained medical officer taking 3 consecutive measurements in all the patients. However, this is a difficult task in day to day clinical practice in busy hospital clinical setups.

Skin fold calipers are expensive and require expertise in use. However, the convenience in obtaining the measurement without mobilizing the patient justifies its use. In order to apply the recommended cut-offs in routine clinical practice, it is important to have adequately trained staff and standard calipers.

**CONCLUSIONS**

Both MUAC and TSFT were possible alternatives for detection of underweight and obese cardiac patients. Among them, MUAC was found to be a better predictor. For simplicity in use, MUAC &lt;26cm and &gt;30cm can be used as cut-off points to detect underweight and obese patients respectively. These were also valid to predict centrally obese cardiac patients, for which a MUAC &gt;28.8cm for males, &gt;26.7cm for females and a TSFT &gt;12.8mm for males, &gt;17.4mm for females may be used as suitable cut-offs in local the setting.

**COMPETING INTERESTS**

The authors declare that they have no competing interests.

**AUTHORS’ CONTRIBUTIONS**

RJ, AKP and NL have made a substantial contribution to conception and design of the study. PP and RJ interpreted the data. PP and SC analyzed the data. PP, SC and RJ were involved in drafting the manuscript. All authors read and approved the final script.

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THE PREVALENCE OF ENDOCRINOPATHIES AMONG PATIENTS WITH THALASSEmia MAJOR IN THE DISTRICT OF BATTICALOA, SRI LANKA

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INTRODUCTION
Thalassaemia major is a severe autosomal recessive haemolytic anaemia caused by absence or marked deficiency of the beta globin chain of haemoglobin. The homozygous state results in severe anaemia which requires frequent blood transfusions. This, along with increased rate of iron absorption in the gut causes iron overload. Excessive iron overload due to suboptimal chelation result in deposition of iron in various tissues, primarily heart and liver and frequently involves endocrine glands. Chronic hypoxia due to anaemia, viral infections and individual susceptibility are other factors which could potentiate the toxicity of iron deposition, contributing to endocrine dysfunction (1-2).

Available data show the leading endocrine complications among patients with thalassaemia are growth retardation, hypogonadism, diabetes mellitus, hypothyroidism, hypoparathyroidism, osteoporosis and adrenal insufficiency (3).

In addition to iron overload, poor nutrition, chronic anaemia, chelating agents, liver disease, and genetic susceptibility are the other factors which have been linked to slow growth and endocrinopathies in patients with thalassaemia (4). As the prevention of thalassaemia related endocrinopathies remains a challenge, regular screening is recommended. However, it is not clear when this process should start...
or what is the best procedure for conducting it, as the age of onset of these endocrinopathies is not well defined. Hence there is a need for estimating the prevalence of common endocrinopathies in patients with Thalassaemia and risk factors for developing these complications, among Sri Lankan population. Therefore, we designed this study to estimate the prevalence of common endocrinopathies in patients with Thalassaemia major who were followed up at Teaching hospital, Batticaloa.

**METHODOLOGY**

This is a descriptive cross sectional study. The study subjects were all patients with diagnosed Thalassaemia major on regular blood transfusion for more than 2 years duration, who were attending paediatric, haematology and endocrinology clinics at Teaching Hospital Batticaloa.

All patients who have full filled the selection criteria and given consent were included. Diagnosed patients with thalassaemia intermedia, thalassaemia minor, other haemoglobinopathies and other haemolytic anaemia were excluded from the study.

The study was approved by the ethical committee of eastern university and permission from the director, Teaching Hospital Batticaloa was obtained for utilising the data and conducting the study. All participants were given assurance that their identity will not be revealed and personnel information could be kept confidential. Informed written consent was obtained from all patients, their parents or guardians if participants are younger than 16 years.

Demographic data, details of disease management (duration and age at the start of transfusion and chelation), and auxological details (height, weight, tanner staging for pubertal development) were recorded in a data collection form by the trained medical officer.

The following hormonal assessment were done: TSH, freeT4, 9am cortisol for all patients and FSH, LH, prolactin, oestradiol or testosterone for girls over 13 years of age and boys over 14 years of age.

Biochemical assessment including oral glucose tolerance test (OGTT) using 75g glucose, serum calcium, phosphate, alkaline phosphatase, haemoglobin, mean serum ferritin, renal function, liver enzymes and liver function were taken.

**Description of endocrinopathy (5)**

- Short stature was defined as height below the third percentile and below the mid-parental height centile on the CDC growth chart.
- Delayed puberty was defined as absence of breast development by the age of 13 years in girls or absence of genital development (testicular volume less than 4ml) at 14 years in boys. Incomplete puberty is defined as primary amenorrhea in females at 17 years or failure to reach Tanner genitalia stage 5 in males by the age of 18 years.
- Patients with hypogonadism (delayed or incomplete puberty) and prepubertal basal follicular stimulating hormone (FSH) and luteinizing hormone (LH) levels were considered to have hypogonadotrophic hypogonadism, and those with high basal FSH and LH levels were defined as having gonadal failure.
- Primary hypothyroidism was defined as subnormal free thyroxin (FT4) with raised thyroid stimulating hormone (TSH), subclinical hypothyroidism as normal FT4 with high TSH (5-10mu/L) and secondary hypothyroidism as subnormal FT4 with normal or subnormal TSH on more than 2 consecutive occasions.
- Hypoparathyroidism was defined as subnormal serum calcium with high phosphate with subnormal or inappropriately low parathyroid hormone (PTH) level.
- Patients were considered to have diabetes if their fasting glucose more than 126mg/dl and / or 2 hour post glucose level more than 200mg/dl. Impaired glucose tolerance was defined as 2 hour post glucose level of 140-199mg/dl and impaired fasting glucose when fasting glucose level of 100-125mg/dl.
- Adrenal insufficiency was defined as morning (9 am) serum cortisol less than 150nmol/L with or without abnormal serum sodium and potassium.

The data were analyzed using SPSS Statistical Software Package.

All numerical data were expressed as mean and standard error of mean (±SEM). Correlation among variables was assessed using Chi square test. Statistical significance is described when p-value less than 0.05.
RESULTS

A total of 95 patients including 50 females and 45 males with mean age of 11.83±4.53 years were evaluated. The characteristics of the patients are shown in table 1. The prevalence of endocrinopathies was shown in table 2 and 3. Short stature was found in 55 (57.8%). Among 42 patients who were evaluated for pubertal development, 33 (78.6%) had hypogonadism, and all were proven to be hypogonadotrophic hypogonadism. Hypocalcaemia was present in 34 (35.7%) and 24 (25.2%) had hypothyroidism. Diabetes mellitus and impaired glucose tolerance (IGT) were found in 7 (7.4%) and 13 (13.6%) respectively. Only 2 (2.1%) had cortisol deficiency.

Among this sample, the youngest age for patients with endocrinopathies were as follows (table 4): hypothyroidism; 3 years, short stature; 5 years, hypocalcaemia; 9 years, IGT; 9 years, diabetes; 10 years and cortisol deficiency; 14 years.

Sixty six patients with mean serum ferritin level above 2500ng/mL had higher incidence of hypocalcaemia than those who had less than 2500ng/mL (28 vs 5, p=0.004). Higher prevalence of hypothyroidism, hypogonadism, and short stature (18 vs 6; p=0.048, 28 vs 5; p=0.03, and 39 vs 16; p=0.054 respectively) was noted among patients with ferritin levels above 2500ng/mL.

Patients who were above 9 years of age had higher incidence of hypocalcaemia (32 vs 2; p=0.00), short stature (33 vs 22; p=0.026), and IGT (11 vs 2; p=when compared to younger patients (0.017). Although statistically not significant, prevalence of hypothyroidism (16 vs 8; p=0.085), and cortisol deficiency (2 vs 0; p=0.118) were higher among patients with longer duration of disease.

DISCUSSION

Thalassemia patients have a high prevalence of endocrinological abnormalities. Our study revealed that a significant proportion of thalassemia major patients have endocrinopathies (table 2). The international network on endocrine complications in thalassemia (I-CET) position statement and guidelines recommend annual endocrine screening from the age of 9 years and earlier if clinically suspecting short stature. In our sample the youngest age of patient with endocrinopathies were shown in table 2. Although majority of children develop endocrine disorders after 9 years, 9 (9.4%) were younger than 9 years with either short stature or hypothyroidism. Growth retardation is commonly reported in children and adolescents with thalassemia. The pathogenesis of growth failure is multifactorial including transfusion-related iron overload, chelation toxicity and other contributing endocrine disorders such as hypothyroidism, hypogonadism, growth hormone deficiency or insufficiency, zinc deficiency, chronic liver disease, under nutrition, and psychosocial stress (2, 6, 7). Our study showed 71 (75%) were having body weight less than 3rd centile, and 55 (57.5%) of children had height below the 3rd centile and below the mid-parental height centile on CDC growth chart. The limitations on using this charts for defining short stature should be considered in our population. This is due to the fact that a significant proportion of normal children are below 3rd centile. Therefore mid-parental height should be taken when defining short stature. In addition, the duration of thalassemia was significantly associated with short stature. This is probably due to iron overload and failure of gaining their pubertal growth spurt. In our study 8 (14.5%) were younger than 9 years old and the youngest was 5 years old.
One fourth of our patients had hypothyroidism. In our study, some patients were already treated with thyroxine based on elevated TSH or subnormal FT4 alone. Therefore we were unable to subcategorize the diagnosis as primary, secondary or subclinical hypothyroidism. Similar studies showed that majority of patients were diagnosed with primary hypothyroidism and secondary hypothyroidism seen only in 3.5% (8,9). The I-CET position statement and guidelines recommend annual investigation of thyroid function beginning at the age of 9 years (10). In our study 4 (16.6%) patients were below 9 years old when diagnosed with hypothyroidism and the youngest patients was 3 years of age. Hypothyroidism and short stature develop early in our population indicating the need for early screening compared to the recommended guidelines.

Hypoparathyroidism is considered as an uncommon complication and usually presents after the age of 16 years (10). In contrary to this we found a significant proportion 34 (35.7%) was complicated with hypocalcaemia and hyperphosphataemia suggestive of hypoparathyroidism and the youngest age was 9 years in our sample. The majority of the patients was asymptomatic or presented with mild symptoms. Hypoparathyroidism is thought to be the consequence of iron deposition in the parathyroid glands or due to suppression of parathyroid secretion induced by bone reabsorption resulting from increased hematopoiesis secondary to the chronic anaemia (11,12). High serum
ferritin levels and the longer duration of thalassaemia were significantly associated with hypocalcaemia in this study.

Diabetes and impaired glucose tolerance (IGT) are relatively common complications among inadequately chelated patients. As life expectancy in patients with thalassaemia rises, diabetic complications are commonly seen. The prevalence of diabetes mellitus in patients with thalassaemia major ranges from 6.4 to 14.1% in cross sectional studies (13). This current study showed presence of Diabetes mellitus and IGT in 7.4% and 13.6% respectively. Patients with thalassaemia could develop diabetes secondary to their illness and complications of therapy. Likewise, with the worldwide epidemic of diabetes, they could develop type 1 or type 2 diabetes, independently of their thalassaemia status (14,15).

Although clinical adrenal crisis is extremely rare, several studies reported a significant prevalence of biochemical adrenal insufficiency, ranging from 0% to 45%, in patients with thalassaemia. The wide variation is due to different patient characteristics and different diagnostic tests used (16,17). Only 2 patients (2.1%) had cortisol deficiency in this study. Patients are usually asymptomatic but this could be masked by symptoms commonly complained by thalassemic patients, such as myalgias, arthralgias and weight loss. In addition to cortisol deficiency, adrenal androgen levels might be decreased explaining the poor development of pubic and axillary hair observed in thalassemic adolescents (16,17).

Comparable to other studies hypogonadism was the most common endocrinopathy in our patients (18-21). Out of 42 patients (28 female and 14 males) who were evaluated for pubertal development, the overall prevalence of hypogonadism was 78.6%, including 71% of girls and 92% of boys. All our patients had secondary hypogonadism with low basal FSH and LH indicating hypothalamic-pituitary damage. This is likely to be secondary to iron deposition on gonadotrophic cells of the pituitary gland (22-24). Among patients with thalassaemia major, an impact of the genotype on gonadal function also has been documented (25).

A significant proportion of thalassaemia major patients have endocrinopathies. The longer the duration of thalassaemia, the higher the risk for developing endocrinopathies. Hypothyroidism and short stature develop early and other endocrinopathies develop after 9 years of age, indicating the need for earlier screening compared to the recommended guidelines. For early detection, regular follow-up is essential. Treatment of endocrine disorders in patients with thalassaemia is an additional burden, support from family, health care providers and psychologists are needed. Multidisciplinary team with patient centered approach will be the way forward. Joint clinic where members of both endocrinology and thalassaemia teams work together with patients will be a better option to manage these patients with complex needs. This also allows staff to learn from each other and provide a consistent approach towards every patient.

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DECLARATION OF INTEREST
There is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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REFERENCES
PREVALENCE AND ASSOCIATION OF UNDERWEIGHT, OVERWEIGHT, OBESITY, NECK CIRCUMFERENCE, HYPERTENSION AND DIABETES MELLITUS AMONG SCHOOL STAFF IN JAFFNA DISTRICT

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ABSTRACT

The aim of the study was to determine the prevalence and associations of underweight/overweight/obesity, neck circumference (NC), hypertension (HT) and diabetes mellitus (DM) among school staff in Jaffna district. It was a descriptive study on 6335 (31% were males and 69% were females) school staff. Overweight and obesity were defined according to the cut-off values for Asian population. Results showed, among males 3% were underweight, 26% were normal weight, 48% were overweight and 23% were obese. Among females 6% were underweight, 28% were normal weight, 41% were overweight and 25% were obese. Seventeen and 6% of the total population had HT and DM respectively. Average NC for males was 32.85cm for underweight, 35.48cm for normal weight, 38.27cm for overweight and 40.59cm for obese. Average NC for females was 29.13cm for underweight, 30.95cm for normal weight, 32.81cm for overweight and 34.53cm for obese. In conclusion the body mass index (BMI) distribution of the population sample shows that more people in both gender categories were predominantly overweight. About 44% of the total population is overweight. Furthermore, approximately 25% of both genders were obese. Altogether at least 2/3 of the population sample was above the healthy weight. More men were overweight/obese than women. Diabetes was less common than hypertension among the target population. However like hypertension, the prevalence of DM also increased with BMI increment. Interestingly the size of the NC increased parallels with BMI increment.

Keywords: Underweight, obesity, neck circumference, hypertension and diabetes mellitus.

INTRODUCTION

Worldwide, the prevalence of overweight, obesity, hypertension (HT) and diabetes mellitus (DM) (metabolic syndrome) are experiencing an exponential growth(1). The major reason for the increase in overweight and obesity is the consumption of too many calories and engagement of insufficient amount of physical activity. People who are at risk of developing diabetes and hypertension can delay or prevent the onset of the disease by making lifestyle changes.

Even though above mentioned diseases are increasing in number, the awareness of these diseases are still poor in developing countries. Number of cases of undiagnosed overweight or obesity, HT and DM are significantly higher among us. These diseases will contribute to development of other non-communicable diseases and increase the risk of cardiovascular mortality and morbidity (2).

According to World Health Organization(WHO), worldwide, at least 2.8 million people die each year as a result of being overweight or obese, and an estimated 35.8 million (2.3%) of global disability-adjusted life year (DALY) are caused by overweight or obesity. Overweight and obesity lead to adverse metabolic effects on blood pressure, cholesterol, triglycerides and insulin resistance (3). It is a risk factor for non-communicable diseases including coronary heart disease, stroke, as well as for diabetes, fatty liver and several cancers (2, 3). In 2012, at the WHO, World Health Assembly, governments decided to adopt a global target of a 25% reduction in premature death from non-communicable diseases by 2025(3).

According to Wijewardene et al, baseline findings of a population based survey in four provinces (Western, North Central, Southern and Uva) in Sri Lanka says the prevalence of hypertension was 18.8% for men and 19.3% for women (4). The prevalence of diabetes was 14.2% for men and 13.5% for women, while impaired fasting glycaemia was 14.2% for men and 14.1% for
The mean body mass index was 21.5 kg/m$^2$ (SD = 3.7) in men. It was lower than that in women, which was 23.3 kg/m$^2$ (SD = 4.5). The prevalence of obesity was 20.3% in men and 36.5% in women. Regional differences were seen in the mean fasting blood glucose and prevalence of diabetes, and mean BMI and prevalence of obesity. It was highest in Western province. Mean blood pressure and prevalence of hypertension were highest in the Uva province. Southern province had the lowest prevalence of hypertension and diabetes, and North Central province had lowest anthropometric measures of obesity.

Some studies have shown a correlation between overweight or obesity and neck circumference (NC) (6,7). However, we have not still defined the cut-off values of neck circumference for Sri Lankans to define overweight or obesity. There are no studies on NC and overweight or obesity in Sri Lanka to assess the correlation.

**RESEARCH DESIGN AND METHODS**

It was a descriptive study among all staff (including all the teachers and non-academic staff) of schools in Jaffna district. The approval for the study was obtained from the Ethics review committee, Faculty of medicine, University of Jaffna. A total of 6335 school staff in Jaffna district was studied and the study was conducted from October 2014 to August 2015.

Data collection was done after obtaining permission from educational department and principal of the particular school by trained interviewers, under the supervision of investigator. The medical officers of health (MOHs), public health inspectors (PHIs), public health midwives (PHMs) also participated with interviewers and investigators and assisted with data collection and health education.

Individuals were included into this study after obtaining informed written consent and data was collected through an interviewer based questionnaire.

The interviewer measured the particular individual’s height (in centimetres), weight (in kilograms) and neck circumference (in centimetres) by using standard height measuring apparatus, weighing apparatus and measuring tape respectively. Neck circumference (NC) was measured at a point just below the larynx (Adam’s apple) and perpendicular to the long axis of the neck. Then BMI calculated by interviewer using calculator. Overweight and obesity were defined as follows according to the non-communicable disease unit, ministry of health care and nutrition Sri Lanka’s cut-off values for Asian population (www.health.gov.lk/en/NCD/bmi) (8).

- BMI $\leq$ 18.4 kg/m$^2$ - Under weight
- BMI $<$ 23 kg/m$^2$ - Normal
- BMI $<$ 27.6 kg/m$^2$ - Over weight
- BMI $\geq$ 27.6 kg/m$^2$ - Obesity

Individual’s blood pressure measured by interviewer two times at least five minutes apart by using standard digital blood pressure apparatus (9,10). If the blood pressure differs by more than 10mmHg in systolic blood pressure (SBP) or more than 5mmHg in diastolic blood pressure (DBP), the third blood pressure measurement was also taken at least after five minutes later. Lowest value of the two out of three blood pressure readings finalized as the particular individual’s blood pressure. High blood pressure was defined as systolic blood pressure (SBP) $\geq$ 140 mmHg and diastolic blood pressure (DBP) $\geq$ 90 mmHg or the particular individual was a known hypertensive on treatment.

Capillary blood sugar was checked by interviewer using glucometer to identify the risk of DM. Depending on the individual’s fasting state, the blood sugar values marked as fasting or random capillary blood sugar by the interviewer. If the sugar value was under the category of impaired glucose tolerance or diabetes, it was repeated with venous sample and confirmed. DM was defined as fasting blood sugar (FBS) $\geq$ 126 mg/dl or random blood sugar (RBS) $\geq$ 200 mg/dl with symptoms.

Results were analyzed using SPSS 19. The unpaired t-test was used to determine differences between groups. Difference in distribution of categorical data was evaluated by chi-squared test. A two tailed p $<$ 0.05 was considered as significant.
RESULTS

The study population comprised of 6335 and 31% were males (1936).

The BMI distribution according to the Asian cut-off values among males showed that, 3% (57) were underweight (BMI ≤18.4 kg/m²), 26% (507) were normal weight (BMI is 18.5 – 23 kg/m²), 48% (932) were overweight (BMI is 23.1 – 27.5 kg/m²) and 23% (440) were obese (BMI ≥27.6 kg/m²). And among females 6% (263) were underweight (BMI ≤18.4 kg/m²), 28% (1207) were normal weight (BMI is 18.5 – 23 kg/m²), 41% (1815) were overweight (BMI is 23.1 – 27.5 kg/m²) and 25% (1114) were obese (BMI ≥27.6 kg/m²).

Seventeen percent of the total population (1046) had hypertension (HT), among them 20% (390) were males and 15% (656) were females. According to the BMI, 6.87% (22) of underweight, 11.44% (196) of normal weight, 16.93% (465) of overweight and 23.36% (363) of obese individuals had HT.
Six per cent of the total population (403) had diabetes mellitus (DM). Among them 8% (159) were males and 6% (244) were females. According to BMI distribution, 2.50% (08) of underweight, 5.72% (98) normal weight, 6.70% (184) overweight and 7.27% (113) obese had DM. Average neck circumference (NC) for males was 37.90cm and average NC for females was 32.51cm. Average NC for males according to the BMI was 32.85cm for underweight, 35.48cm for normal weight, 38.27cm for overweight and 40.59cm for obese. Average NC for females according to the BMI was 29.13cm for underweight, 30.95cm for normal weight, 32.81cm for overweight and 34.53cm for obese.
CONCLUSION AND DISCUSSION

The prevalence of BMI distribution shows that highest proportion of the population was in the overweight category. The BMI distribution of the population sample shows that people in both genders were predominantly overweight, 44% of the study population. This is much higher than other studies which were carried out earlier in other parts of Sri Lanka (11). Furthermore, approximately 25% of both genders were obese. Altogether at least 2/3 of the population sample was above the healthy weight. This trend of normal weight, overweight and obesity are similar to the study done by Katulanda et al previously (11). Also the trend of overweight and obese among females are similar to the study of Renuka et al (12). There were, fortunately, minimal amount of underweight people (less than 10%). Approximately ¼ of the population belongs to healthy weight. And more men were overweight or obese than women.

Our study revealed that 20% of males and 15.5% of females were hypertensive and approximately ¼ of the obese population had hypertension; it was the highest prevalence among all BMI categories. The prevalence of hypertension increased with BMI increment.

According to our study, the prevalence of diabetes mellitus is less common than hypertension among the target population and it was 6% in females and 8% in males. This prevalence is closely similar to the global prevalence of DM (8.3%) in 2013, according to sixth edition of the International Diabetes Federation Atlas of Diabetes (1). This prevalence is comparatively less in our target population than other parts of Sri Lanka (5). However like hypertension, the prevalence of DM also increased with BMI increment. However across all BMI categories only a small amount of individuals had diabetes and that was less than 10%. Further, one limitation of our study was that dysglycaemia was initially categorised according to capillary blood glucose levels and not by venous plasma glucose levels as it is recommended. However, all impaired glucose levels or levels that were compatible with diabetes were repeated with venous sample and confirmed for DM.

Interestingly, the size of the NC increased parallels with BMI increment.

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DECLARATION OF INTEREST

No conflicts of interest for any author.

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INTRODUCTION

Hyperprolactinemia is a condition with elevated prolactin levels in the blood, which may be of physiological, pathological or idiopathic origin. It essentially occurs due to pathological or pharmacological disruption of the hypothalamo-pituitary dopaminergic pathways. It is one of the commonest endocrine disorders, mostly affecting females. The prevalence of hyperprolactinemia ranges from 0.4% in an unselected adult population to as high as 9–17% in women of reproductive age (1). Galactorrhoea and hypogonadotrophic hypogonadism are the usual clinical consequence of hyperprolactinaemia and therefore, females usually present with galactorrhoea and menstrual irregularities such as oligomenorrhoea or amenorrhoea, while males experience erectile dysfunction. Both sexes may experience loss of libido and infertility.

PHYSIOLOGY

Prolactin (PRL) is a polypeptide with 199 amino acids, which is secreted from the lactotrophic cells of the anterior pituitary. Prolactin is secreted in a pulsatile manner with highest levels occurring during sleep and lowest occurring between 10 a.m to noon. The secreted prolactin gets circulated in different forms, the monomeric (little PRL) with a size of 23kd, dimeric (big PRL) where the size range from 48 – 56 kd and polymeric forms (big, big PRL) where the size is larger than 1000kd and monomeric form of prolactin is the most active form. Prolactin is mainly responsible for the milk production during pregnancy and lactation (2). Unlike other trophic hormones of the anterior pituitary, prolactin secretion is not regulated by a negative feedback from the peripheral hormones. Dopamine acts as the primary inhibitory factor for prolactin secretion. Dopamine that gets released from the hypothalamus reaches the anterior pituitary via the hypothalamic-pituitary-portal system and inhibits prolactin secretion by binding to the D2 receptors. Numerous other factors such as fibroblast growth factor, epidermal growth factor, vasoactive intestinal polypeptide (VIP), hypothalamic prolactin releasing peptide (PrRP) and oxytocin also can stimulate the synthesis and release of prolactin. Oestrogen has the ability to stimulate the prolactin gene transcription. In addition to these, serotonin opiates and histamine can also have stimulatory effects on prolactin secretion.

Hyperprolactinemia

The prolactin levels are maintained less than 25ug/l in women and less than 20ug/l in men. However, elevated prolactin levels can be seen in certain physiological conditions. Pregnancy is the commonest physiological condition with hyperprolactinaemia where the levels can go up as high as 10-fold from the...
baseline. Exercise, meals and chest wall stimulation can also lead to elevated prolactin levels. Although physical and psychological stress can increase prolactin levels, it rarely exceeds 40ug/dl (3).

Prolactinomas account for 25 – 30% of functioning pituitary tumours. Lesions affecting the hypothalamus and the tumours with compression on pituitary stalk such as non-functioning adenomas, gliomas and craniopharyngiomas can also result in prolactin elevation (4). Mild elevation of prolactin is seen in hypothyroidism due to the stimulatory effect of thyrotrophin releasing hormone on prolactin release (5). Due to the impairment renal clearance, elevated prolactin levels can also be seen in chronic renal failure (6).

Drug-induced hyperprolactinemia

There are several drug classes that can influence the prolactin release leading to hyperprolactinemia and the drugs that influence the action of central nervous system dopamine level and the activity is mainly responsible. It is important to differentiate this cause from pathological causes such as prolactinomas.

Antipsychotic Medication

Anti-psychotic drugs are one of the commonest causes of drug-induced hyperprolactinemia (7). Dopamine antagonist effects of these drugs on D2 receptors of the infundibular hypothalamic pathways and the lactrotrophs are mainly responsible for the hyperprolactinaemia. A study done on 422 patients

<table>
<thead>
<tr>
<th>Table 1. Major physiologic and pathologic causes of hyperprolactinemia</th>
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<tbody>
<tr>
<td><strong>Physiologic</strong></td>
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<tr>
<td>Pregnancy</td>
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<td>Breastfeeding</td>
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<td>Breast stimulation</td>
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<td>Sleep</td>
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<td>Stress</td>
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<td><strong>CNS disorders</strong></td>
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on antipsychotic medication has shown that the neuroleptic therapy is strongly associated with hyperprolactinemia with a significantly higher prevalence among patients on typical antipsychotics than atypical antipsychotics (8).

Table 2. Medication causing hyperprolactinemia

<table>
<thead>
<tr>
<th>Antipsychotics</th>
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<tbody>
<tr>
<td>Phenothiazines</td>
</tr>
<tr>
<td>Thioxanthenes</td>
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<tr>
<td>Butyrophenones</td>
</tr>
<tr>
<td>Atypical antipsychotics</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Antidepressants</th>
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<tbody>
<tr>
<td>Tricyclic antidepressants</td>
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<tr>
<td>Monoamine oxidase inhibitors</td>
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<tr>
<td>Selective serotonin reuptake inhibitors</td>
</tr>
</tbody>
</table>

| Opiates and Cocaine                   |

<table>
<thead>
<tr>
<th>Antihypertensive Medication</th>
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<tbody>
<tr>
<td>Verapamil</td>
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<tr>
<td>Methyldopa</td>
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<tr>
<td>Reserpine</td>
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<tr>
<th>Gastrointestinal Medication</th>
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<tbody>
<tr>
<td>Metoclopramide</td>
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<tr>
<td>Domperidone</td>
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<tr>
<td>Histamine 2 receptor blockers</td>
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</tbody>
</table>

| Estrogens                             |

Duration of treatment, age, gender and antipsychotic potency all contribute to the severity of hyperprolactinemia. This side effect is more likely to be seen in adolescents and premenopausal women (8, 9). It has been shown that hyperprolactinemic effect is a dose-related (10). Serotonin is responsible for suckling-induced prolactin release and nocturnal surges. Antipsychotics with serotonergic effects can also stimulate prolactin release via this pathway. However, the prolactin elevation due to serotonin effects are typically milder compared to the dopamine antagonist effects of these drugs. In drug induced hyperprolactinaemia, the prolactin levels are usually <100ug/l. However, some drugs such as risperidone and phenothiazines can give rise to a prolactin level exceeding >200ug/l (10).

The older generation, typical antipsychotics are frequently associated with elevated prolactin levels (11). Rapid elevation of prolactin level is seen after intramuscular injections whereas, with oral drugs, it takes about one week for the levels to rise, which becomes constant thereafter. However, the prolactin levels can get normalized within 48 – 96 hours after discontinuation of these drugs. Among typical antipsychotics, Haloperidol is considered to be the most potent drug causing hyperprolactinaemia (7). With haloperidol, rapid elevation of prolactin to a peak level of about 30-50ng/ml occurs within 6 to 9 days and then reach a plateau and remain constant below a level of <70ng/ml (12). However, a dose-dependent increase in prolactin levels has been reported in 40 – 90% of patients treated with most of the other phenothiazines (13).

Risperidone that belongs to a newer class of antipsychotics, atypical antipsychotics, can cause even higher levels of prolactin than typical antipsychotics (12, 14). Its’ dose dependent dopaminergic and serotonin antagonistic actions are mainly responsible for the hyperprolactinaemia with this drug. The prevalence of hyperprolactinemia is so common and it is seen in 70 – 100% among patients on risperidone (15). In contrast, olanzapine and quetiapine have lesser effects on prolactin release where the prevalence of hyperprolactinaemia is about 10 to 40%, and with clozapine, it is less than 5% (7). This discrepancy is mainly due to the difference in the occupancy of the D2 receptors of the pituitary, which is an organ situated outside the blood brain barrier. Risperidone has a higher affinity to D2 receptors in the pituitary, causing a significant hyperprolactinemia (16), whereas the atypical antipsychotics have a weaker affinity for the D2 receptors. It is postulated that the transient binding of these drugs to the D2 receptor and also the agonist as well as antagonist effects at the receptor level are mainly responsible for the weaker effects of these drugs on prolactin release.

Antidepressant medication

Anti-depressive drugs exert their effect on prolactin release through serotonin pathway. The effects on prolactin are variable and it is not directly related to the therapeutic effect of antidepressants. Data on the incidence of antidepressant-related hyperprolactinemia is scant. Tricyclic antidepressants cause only a mild
hyperprolactinaemia and most studies report no change in prolactin levels (17, 18). However, hyperprolactinaemia due to clomipramine is thought to be common (19). Monoamine oxidase inhibitors have shown to act as weak stimuli for prolactin elevation (18, 20). Fluoxetine, a selective serotonin reuptake inhibitor, appears to cause a modest elevation of prolactin levels (21). However, the hyperprolactinaemia associated with this class of drugs are generally mild and causes asymptomatic (22, 23).

**Prokinetics**

Metoclopramide and domperidone are notoriously known for its hyperprolactinemic effect. Both act via dopamine antagonistic mechanism. However, metoclopramide has an additional inhibitory effect on serotonin receptors of the chemoreceptor trigger zone of the central nervous system. Therefore, metoclopramide is considered to be one of the potent stimuli for prolactin release and the levels can be high as 15-fold in patients on chronic metoclopramide therapy (24). It can be associated with amenorrhoea, galactorrhoea, gynaecomastia and impotence (25).

**Anti-hypertensive Medication**

Verapamil causes short and long-term increase in basal prolactin secretion. In an outpatient clinic survey among patients taking verapamil, 8.5% patients reported having a high prolactin level (26). However, the other calcium channel blockers do not seem to have an effect on prolactin secretion (27). Methyldopa causes moderate hyperprolactinaemia by inhibiting the enzyme, aromatic-L-amino acid-decarboxylase, which converts L- dopa to dopamine. With a single dose of alpha-methyldopa (750 to 100mg), a rapid rise in prolactin occurs, reaching the peak concentration within 4 to 6 hours. Chronic methyldopa therapy is associated with a three to four-fold rise in the basal prolactin levels. Significantly high serum prolactin levels have also been reported among patients who used to be on centrally acting antihypertensive, reserpine, which is now obsolete in practice.

**Opiates**

Opiates can cause both short and long-term increase in prolactin levels and the effect is predominantly through u receptors. However, the hyperprolactinaemia that we see with group of drugs are very mild (28, 29)

**Estrogens**

The role of estrogens in hyperprolactenemia is controversial. Some studies have shown elevated prolactin in 12 to 30% of women, where as some have shown no or minimal increase while on oral contraceptive pills (30-33). However, the doses of estrogen that are used in hormone replacement therapy has not demonstrated hyperprolactinemia (22).

**Management of drug-induced hyperprolactinemia**

Patients with hyperprolactinaemia need to be evaluated properly and treated accordingly. In a patient with symptomatic hyperprolactinemia, it is imperative to identify medication as a cause at the outset itself. In addition to drug-induced hyperprolactinaemia, mild prolactin elevation can be seen with prolactin-secreting pituitary microadenomas as well as non-functioning pituitary tumours. Therefore, it is important that proper evaluation is done before reassuring the patient.

A careful history with the timing of onset of symptoms and initiation of drugs is of paramount importance.

When drug-induced hyperprolactinaemia is suspected and once the culprit agent is identified, there are several approaches that we can try to differentiate this from other causes of hyperprolactaemia (22).

1. Discontinuation of the offending drug: the prolactin levels get normalized in 3-4 days after stopping the offending drug. Measuring the prolactin levels 3-4 days of drug withdrawal is the easiest measure to differentiate from other causes of hyperprolactinaemia. However, this should be done with caution especially in patients with antipsychotic
drugs where the underlying psychosis can get aggravated.

2. Substitution of the offending drug (“switch therapy”): substitution of the offending drug with an alternative drug with a similar action that does not cause hyperprolactinemia is another way or overcoming this problem. Use of atypical antipsychotic agents such as olanzapine, clozapine or quetiapine for traditional antipsychotic medication is a good example. However, this should be attempted with careful consideration after consultation with the attending psychiatrist or the physician (34). If such substitution is not possible, imaging of the pituitary will have to be considered to exclude any mass lesions.

3. When hormone replacement such as estrogen and testosterone for hypogonadism is the reason for hyperprolactinaemia, treatment of the underlying problem and continuation of the offending drug is a challenge. If prevention of osteoporosis is the primary objective of the treatment, alternative medication such as bisphosphonate can be considered in this kind of situations.

4. Dopamine agonists therapy
There is a theoretical risk of exacerbating the psychotic symptoms with the use of dopamine antagonist therapy in patients with antipsychotic medication-induced hyperprolactinaemia. However, bromocriptine has been used without major problems (22). There is evidence to suggest that cabergoline can be used safely in patients with antipsychotic medication without exacerbating the psychotic symptoms and without having any alteration in antipsychotic effects of these medications (35). However, it is advisable to use these drugs with extreme caution with the close consultation of a psychiatrist only in patients (36, 37).

5. Aripiprazole
It is a unique atypical antipsychotic agent with partial agonist activity at the D2 receptor. Recent studies have shown aripiprazole as a potential therapeutic option for drug-induced hyperprolactinemia. Limited data have shown that it can be used as an add-on to the ongoing therapy or as switch therapy, by substituting with the original drug (38).

CONCLUSION:
Drug-induced hyperprolactinaemia is a common clinical problem and antipsychotic agents are the commonest culprits. If symptomatic, this problem needs to be properly evaluated and treated accordingly to avoid long-term complications related to associated hypogonadism.

REFERENCE:


CARDIOVASCULAR COMPLICATIONS OF CUSHING’S SYNDROME

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Cardiology unit, Teaching Hospital Kurunegala.

ABSTRACT

Cushing's syndrome (CS) is a condition caused by chronic exposure to excess glucocorticoids. Mortality rates are four times higher in CS than in the normal population and myocardial infarction, stroke, congestive heart failure and venous thromboembolic complications appear to be the main causes of mortality. In addition, hypertension, insulin resistance, obesity and dyslipidaemia are other contributing cardiovascular risk factors. Even after the disease cure, patients with CS still possess increased prevalence of cardiovascular disease. This contributes for high mortality and morbidity and they deserve to be screened, diagnosed and treated appropriately according to general acceptable practice. Management directed both against hypercortisolism and cardiovascular risk factor control seems to minimize cardiovascular events in CS.

Keywords: Cushing's syndrome, cardiovascular risk factors, metabolic syndrome, hypertension.

INTRODUCTION

Cushing's syndrome (CS) is a condition caused by chronic exposure to excess glucocorticoids. Cardiovascular disease is the major cause of morbidity and mortality in Cushing's syndrome, and excess risk remains high even in effectively treated patients (1). Cardiovascular disease in glucocorticoid excess arise from the effects on the heart, liver, skeletal muscles and fat tissues (2). Hypertension, truncal obesity, hyperglycemia, insulin resistance and dyslipidemia are important findings in CS and these give rise to an increased risk of cardiovascular disease. This clustering of cardiovascular risk factors can also occur in the general population and is known as the metabolic syndrome. Moreover altered clotting and platelet functions also contribute for high cardiac risk in CS (2,3).

CARDIOVASCULAR RISK FACTORS

1. HYPERTENSION

In patients with subclinical CS, both systolic and diastolic blood pressures are significantly elevated compared to controls (4). Hypertension was a feature reported in majority of original Cushing's cases and was found in around 80% (5,6). Diagnosed patients with Cushing's disease (CD) do not show the nocturnal blood pressure dipping and appear to have abnormal heart rate values which do not resolve after short-term remission. These features are only partially improve in the long run (7). Additionally, approximately 30% of patients tend to have persistent hypertension after the disease remission (7).

Cortisol-induced hypertension is not simply explained by mineralocorticoid induced salt and water retention or sympathetic nervous system over activity. Cortisol is the likely responsible steroid in the hypertension of Cushing’s syndrome (1). The well recognized glucocorticoid stimulated increase in angiotensinogen does not lead to increased plasma angiotensin II concentrations, and it is unlikely to be a key causal mechanism in human glucocorticoid hypertension (1). The mechanism of glucocorticoid induced blood pressure appears to be multifactorial, involving increased responsiveness to vasoconstrictors and decreased vasodilator production (7). Both cardiac output and peripheral resistance have been reported to be high in Cushing’s syndrome (8). Pressor responsiveness to catecholamines is increased by cortisol treatment (9). Inhibition of vasodilator nitric oxide is a strong candidate for the genesis of glucocorticoid hypertension (10).

Routine detection of blood pressure is useful for early verification of the persistence of CS. Currently available antihypertensive drugs are indicated in CS, with no special preference due to the disease itself (7).

2. HEART

There is evidence for cardiac structural changes associated with CS. Reduction of mid-wall systolic performance and diastolic dysfunction related to CS
may contribute to the high risk of cardiovascular events observed in this patient population (11). Hypertension related organ remodeling, especially cardiac hypertrophy, is a frequent finding in CS. Long term exposure to excess circulating cortisol also may contribute directly to left ventricular concentric remodeling (12). Some studies showed about 40% of patients with cortisol excess tend to have myocardial hypertrophy and impaired contractility (11). Moreover CS can manifest as cardiomyopathy (13, 14).

In CS there is a sympatho-vagal imbalance with relative increase of parasympathetic activity. Although the pathophysiological significance of this autonomic dysfunction is still unknown, this cardiac autonomic disturbance is linked with increased mortality (15). In addition, coronary flow reserve which is an index of coronary microvascular function has been demonstrated to be pathologically low in a small study done on CS patients without clinical evidence of ischaemic heart disease. This Impaired microvascular functions may contribute for high cardiac mortality (16).

3. Atherosclerosis and Endothelial Dysfunction

When compared with a population with similar cardiovascular risk factors, more severe form of atherosclerosis is demonstrated in CS and this may be due to long term exposure to cortisol (17). Endothelial dysfunction is the initiating event for atherosclerosis and this can be multifactorial in CS. Recent assessments of endothelial functions through flow mediated dilatation of brachial artery have showed impairment of endothelial functions in patients with CS compared to controls. This method may be useful to identify high risk individuals earlier than conventional methods (18).

Though cortisol typically behaves as an anti-inflammatory hormone, in excess it can provoke inflammation and accelerated atherosclerosis via insulin resistance, pro-inflammatory cytokine regulation and alteration in cortisol binding protein (19). Androgen excess in adrenal-cortical stimulation may accelerate the atherosclerosis in both males and females (20). Hyperhomocysteinemia and reduced serum folate concentrations are associated with cortisol excess while homocysteine levels are normalised during remission. Elevated homocysteine levels may cause the prothrombotic state which leads to high cardiovascular risk (21). Elevated blood endothelin-1 levels and osteoprotegerin levels are also found in CS and this may play a role in early and accelerated atherosclerosis (22).

As a consequence of growth-promoting properties of circulating cortisol and/or increased vascular oxidative stress there is a hypertrophic remodeling in subcutaneous small resistance arteries (23). Persistently elevated cardiovascular risk in CS despite remission of hypercortisolism has been shown in a study using multi-detector CT coronary angiogram. This study demonstrated that patients at remission for mean duration of 11 years, especially women and younger patients are still at high cardiovascular risk (24 – 26). Therefore more longitudinal studies are required to determine the implications of specific coronary abnormalities, and effect of medical treatment and lifestyle modifications.

4. Dyslipidemia

Dyslipidaemia in CS is likely to be multifactorial, including direct effect of cortisol on very low-density lipoprotein (VLDL) synthesis, free fatty acid production, and hepatic endothelial lipase activity (27). Insulin resistant state is also likely to be responsible for abnormal lipid metabolism in CS (28). These include elevated VLDL, low-density lipoprotein (LDL-cholesterol), triglycerides, and total cholesterol levels with decreased high-density lipoprotein (HDL-cholesterol). Persistence of dyslipidemia and central obesity after long-term remission of CS have been demonstrated in one study recently (25).

5. Impaired Glucose Tolerance, Insulin Resistance, and Diabetes Mellitus

Glucose levels are higher in patients with CS irrespective of aetiology (29-31). Elevated fasting blood glucose level is a feature of active CS than in remission and this may even be found in subclinical CS (32,33). However this is more common in exogenous glucocorticoid administration. Insulin resistance is another feature and elevated insulin levels persist five years after cure of CD (26,34). Age, genetic predisposition and lifestyle, in combination with duration and degree of hypercortisolism, may contribute to the impairment of glucose tolerance in the natural history of CS (7).

6. Metabolic Syndrome

According to National Cholesterol Education Program Adult Treatment Panel III (ATP III) criteria to diagnose metabolic syndrome, there should be at least 3 out of the following; central obesity (waist circumference ≥ 102 cm or 40 inches in males; ≥88 cm or 36 inches in females); fasting hypertriglyceridemia (TG ≥ 1.7 mmol/L or 150 mg/dL), fasting low HDL-
cholersterol (HDL-C < 40 mg/dL in males, <50 mg/dL in females); blood pressure ≥ 130/85 mmHg or current use of antihypertensive medications; fasting plasma glucose ≥ 5.6 mmol/L (100 mg/dL), a diagnosis of diabetes or current use of glucose lowering medication (35).

Metabolic syndrome is more frequent in CS and it tend to persist for at least five years after the cure (36). Both hypertension and central obesity are more prevalent in active CS patients than in remission, and they tend to persist for long term, for a mean of eleven years (37). Elevated total trunk fat mass and low lean body mass are characteristics of active CS. Persistence of these abnormalities of body composition with an unfavorable adipokine profile and persistent low grade inflammation are confirmed in cured subjects (38-40). Therefor CS should be considered as a state of low grade inflammation, even after long term remission and this leads to increased cardiovascular risk (41).

7. CEREBROVASCULAR

Even though little is known about the prevalence of cerebrovascular disease in CS, it is known to be increased (38). High prevalence of conventional cardiovascular risk factors, and hypercoagulability probably contribute for this (42). Data from the HypoCCS database supports for an irreversible effects of prior hypercortisolism on the cerebrovascular system (38).

8. PROTHROMBOTIC STATE

Venous thromboembolism was described as the cause of death in up to 1.9% of CS. Non provoked venous thromboembolism risk is doubled in CS. Risk of postoperative venous thromboembolism is varied between 0 and 5.6% (43). High levels of fibrinogen, factor VIII, factor IX, von Willebrand factor and the evidence of enhanced thrombin generation are the suggested reasons for glucocorticoid induced hypercoagulopathy. Additionally, surgery, and obesity almost certainly contribute for this thrombotic tendency (44).

Up regulation of the synthesis of plasminogen activator inhibitor type 1, which is the main inhibitor of the fibrinolytic system and enhanced metabolic function of endothelial cells with secondary hyperfibrinolysis are also suggested contributory factors for pro-thrombotic state in CS (44-47). These patients are predisposed to thrombotic events during inferior petrosal sinus (IPS) sampling as well as during post-surgery. Therefore patients with active CS must be considered as hypercoagulable state and antithrombotic prophylaxis should be offered.

CONCLUSIONS

Majority of CS patients get some manifestations of metabolic syndrome and they tend to persist even after disease remission. This contributes for high mortality and morbidity and they deserve to be screened, diagnosed and treated appropriately according to general acceptable practice. Even after the disease cure, they still possess increased prevalence of clinical and biochemical abnormalities like atherosclerosis, obesity, hypertension, impairment of glucose tolerance, hyperlipidemia, and hypercoagulability. Cardiovascular risk typical of active CD was reported high even 5 years after remission. Their carotid artery walls are stiff with markedly reduced caliber. At the same time the prevalence of carotid atherosclerotic plaques is high compare to sex- and age-matched control populations. Persistent unfavourable adipokine profiles, vascular damage, accumulation of central body fat and low grade inflammation despite biochemical disease control lead to persistently high mortality. Because of the underlying microvessel remodeling and associated essential hypertension, hypertension in CS may persist despite the remission.

Oral glucose tolerance test, 24-hour ambulatory blood pressure monitoring, electrocardiography, electrocardiogram, and carotid ultrasound have been proposed in patients with CS as well as during follow-up of patients with biochemical cure to establish the cardiovascular risk. Management directed both against hypercortisolism and cardiovascular risk factor control seems to minimize cardiovascular events in CS. The assumption of resolution of cardiovascular risk after normalization of hypercortisolism is currently questioned and the awareness of this persistently increased cardiovascular risk in patients after cure must steer to strict control of improvable cardiac risk factors.

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SUCCESSFUL TREATMENT OF SEVERE THYROTOXICOSIS WITH RADIOIODINE THERAPY IN A PATIENT WITH THYROTOXIC CARDIOMYOPATHY

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ABSTRACT

Thyrotoxic cardiomyopathy (TCM) is a potential life threatening complication of thyrotoxicosis which is potentially reversible with early achievement of euthyroid state. Management of severe thyrotoxicosis in the presence of TCM is a challenging task, especially when thioamides are contraindicated.

A 58 yr old male with poorly controlled Grave’s disease of 10 years presented with worsening symptoms of thyrotoxicosis and leg swelling. On examination he was thyrotoxic with a smooth diffuse goiter and also had inactive Grave’s orbitopathy. He had irregularly irregular pulse rate, grossly elevated jugular venous pulses, enlarged heart with tricuspid regurgitation and pulmonary hypertension. FT4 was >8.34 ng/dl (0.8-1.6 ng/dl), free T3 was 20.39 pg/ml (2.3-4.3 pg/ml) and TSH was 0.01 mU (0.5-5.0 mU/L). Serial ECGs showed slow atrial fibrillation with transient complete heart block and echocardiogram showed dilated TCM. He had pancytopenia, most likely resulting from concurrent carbimazole therapy. Medical management of cardiomyopathy was initiated along with lithium, prednisolone and judicious use of beta blockers to control his thyroid status. Within one week he was subjected to radioactive iodine (RAI) therapy following which he was rendered euthyroid.

RAI is a safe mode of definitive therapy in patients with TCM provided careful stabilization of underlying cardiac status. Early definitive therapy is required to achieve euthyroid status to minimize irreversible TCM.

Keywords: Thyrotoxicosis, cardiomyopathy, radioactive iodine therapy.

INTRODUCTION

Thyrotoxic cardiomyopathy (TCM) is a potential life threatening complication of thyrotoxicosis. It is a cause for reversible cardiomyopathies and in approximately one third of patients with TCM may be reversed with the permanent resolution of hyperthyroidism(1). Prolonged duration of poorly controlled thyroid status, male gender and advanced age are predictors of irreversible TCM. Managing severe thyrotoxicosis in the presence of TCM can be challenging especially when thioamides are contraindicated. We report a case on the successful control of severe thyrotoxicosis with radioactive iodine therapy (RAI) in a patient with TCM and carbimazole induced pancytopenia.

CASE

A 58-year-old Sri Lankan male, diagnosed with Grave’s disease (GD) for 10 years duration, presented with episodic palpitations, presyncope, sweating, loose stools and ankle swelling. He has had poor disease control and had defaulted clinic follow up and was self-medicating with carbimazole 45 mg daily. There was no history of fever or central nervous system instability.

On examination he was emanciated, sweating and tremulous with smooth diffuse goiter and bilateral pitting ankle edema. He was anicteric, afebrile and oriented. He had orbitopathy with clinically inactive eye disease. Pulse rate was 70 beats per minute and irregularly irregular. Blood pressure was 130/70. Jugular venous pulse was elevated to the level of his ear lobes. He had a shifted cardiac apex, tricuspid regurgitant murmur, loud P2 and a pulsatile liver.

Serial electrocardiograms showed slow atrial fibrillation (AF) with transient complete heart block, and chest X-ray demonstrated a grossly dilated heart with relatively clear lung fields. Echocardiogram showed severely dilated right atrium and ventricle with severe tricuspid regurgitation and moderate pulmonary hypertension. Left ventricle was slightly dilated with an ejection fraction of 60%. His Free T4 (FT4) levels were >8.34 ng/dl (0.8-1.6 ng/dl), free T3 levels were 17.39 pg/ml (2.3-4.3 pg/ml) and TSH was 0.01 mU (0.5-5.0 mU/L). His full blood count (FBC)
revealed pancytopenia with haemoglobin of 10 g/dl, white blood cell count of 3,140 ×10^9/L with absolute neutrophil count of 942×10^9/L and platelets of 60,000. ESR was 30 mm in 1st hour and C Reactive Protein was 4 mg/l (<6 mg/L). He had mildly high aspartate aminotransferase (AST) 55 U/L with normal levels of alanin transferase (ALT), albumin and globulin levels. Renal functions were normal. He was diagnosed with severe thyrotoxicosis complicated with thyrotoxic cardiomyopathy and carbimazole induced pancytopenia.

His cardiomyopathy was managed with diuretics, warfarin, sildenafil and judicious use of beta blocker. Due to pancytopenia, carbimazole was omitted and he was started on lithium 500 mg thrice daily and prednisolone 30 mg daily. Following omission of carbimazole his haematological indices improved within 4 days. As he was at high risk of developing lithium toxicity, he was well hydrated and monitored for lithium toxicity both clinically and biochemically. Within a week he was subjected to radioactive iodine therapy (RAI) at a dose of 20 mCi as definitive control of thyrotoxicosis was required urgently. Beta blockers were judiciously used up to two weeks following RAI therapy to block the effect of thyroxin on the heart in the rare event of thyroid crisis. He developed symptomatic resolution within one week and his FT4 dropped to 0.98 ng/dl following one month of treatment with RAI.

**DISCUSSION**

Thyrotoxicosis is a common disorder with a prevalence of 3% in females and 0.3% in males in iodine replete areas. Thyrotoxic cardiomyopathy (TCM) is a life threatening condition associated with morbidity and mortality. The prevalence of dilated TCM in thyrotoxicosis is 1% and one third of these cases are irreversible (1).

TCM is defined by myocardial damage caused by the toxic effects of excessive thyroid hormones resulting in alterations in energy production by myocytes, intracellular metabolism and myofibril contractile function. Main manifestations of TCM are left ventricular hypertrophy, heart rhythm disturbances (commonly AF), dilation of heart chambers with heart failure (HF), pulmonary hypertension, and diastolic dysfunction.

Atrial fibrillation which is the commonest arrhythmia in thyrotoxicosis is attributed to the high β-adrenoreceptor density at the surface of atrial cardiomyocytes making it sensitive to the arrhythmogenic effects of thyroid hormone(1). Second or third degree heart blocks complicating thyrotoxicosis is rare and likely due to the interstitial inflammation of the AV node, His-bundle and it's branches(2). Pulmonary hypertension develops due to spasm of pulmonary arterioles causing increase in pulmonary resistance. Heart failure (HF) in thyrotoxicosis occurs due to the isotonic contraction (volume overload) of left ventricle and mixed overload (both volume and resistance overload) of right ventricle. Thus right ventricular HF is more common in hyperthyroid state. Concomitant tricuspid valve insufficiency and regurgitation can worsen the situation. A possible mechanism for valve involvement in GD is the synthesis of glycosaminoglycan in endocardium (which is similar to its presence in the pathogenesis of ophthalmopathy) leading to the thickening of valve cusps(1).
Duration of hyperthyroidism, male sex and advanced age are the main predictors of development of TCM (1). Most studies agree that once the effect of thyroid hormones is eliminated, myocardial damage may be reversible in patients with less than 6 months disease duration (3-5). Persistent euthyroid state is of great importance in improving cardiovascular prognosis. Long term medical management most often results in poor disease control or unacceptable side effects, as was the case in our patient who developed carbimazole induced pancytopenia. The choice of definitive therapy (radioactive iodine/surgery) is not always easy in these patients. Due to unfavourable cardiac status these patients are poor surgical candidates and therefore RAI becomes the more favorable option. In the past, there had been some safety concerns on RAI induced thyroiditis and thyroid storm following therapy with RAI. However these complications are extremely rare and controversial(6,7). Studies done on the safety of RAI have demonstrated that it was well tolerated even in patients with severe thyrotoxicosis with very high levels of thyroid hormones(8). In another study of patients with thyrocardiac disease treated with RAI, no worsening of thyrotoxicosis was observed(9).

However, RAI can induce a short term increase of thyroid hormone levels(10). The American thyroid association 2016 guidelines recommends the use of carbimazole, before and after RAI treatment in patients with severe hyperthyroidism, the elderly, and those with comorbidities (cardiac, pulmonary, renal dysfunction, infection and poorly controlled diabetes etc) that puts them at risk of developing complications due to worsening of thyrotoxicosis. The patient should be medically stable and beta blockers should be used judiciously in preparation for RAI therapy.

Our patient with dilated TCM and carbimazole induced pancytopenia successfully underwent RAI therapy within one week of presentation to our unit, and was rendered euthyroid within a month. However due to long standing thyrotoxicosis which had not been under control, reversibility of dilated cardiomyopathy cannot be expected.

**CONCLUSION**

RAI therapy is a safe definitive mode of therapy for patients with severe thyrotoxicosis and TCM. However careful stabilization of the underlying cardiac condition with the judicious use of beta blockers is required in preventing the complications which can arise in the extreme rare event of thyroid storm in such patients. Early and permanent achievement of euthyroid status is vital in reversing TCM.

*Figure 2 - Effects of Thyroid Hormone on Cardiovascular Hemodynamics (1)*
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CASE REPORT

MISLEADING FREE T4 DUE TO AUTO-T4 ANTIBODIES RESULTING IN ABNORMAL THYROID FUNCTION TESTS: A CASE REPORT

D Karuppiah, S I Majitha, S Dilakkumar, M Pravinson

Teaching Hospital Batticaloa, Sri Lanka.

ABSTRACT

Introduction: The presence of elevated TSH with high free T4 is considered as an abnormal thyroid function test. This may be due to false elevation of serum T4 associated with autoantibodies to T4. We report a case that presented with high serum free T4 and TSH associated with autoantibodies to T4.

Case presentation: A 40 year old female patient presented with tiredness and sweating. She was diagnosed with primary hypothyroidism two years ago based on elevated TSH. She was treated with thyroxine 50mcg per day for 6 months and then she was defaulted. Examination revealed a thin lady with BMI of 18.5 Kg/m² with a mild goiter. She was otherwise clinically euthyroid. Investigations revealed abnormal thyroid function test (TFT) with TSH of 43.6mIU/l and freeT4 of 3.06ng/dl. Her TFT was repeated on three laboratories which showed elevated TSH and upper normal to elevated freeT4. She had high titres of anti thyroid peroxidase (TPO antibodies) > 1300mIU. Her thyroid scan revealed small multinodular goiter and fine needle aspiration cytology confirmed Hashimoto’s thyroiditis. In view of the clinical findings the following possibilities were considered; assay interference, TSHoma and thyroid hormone resistance. TSHoma seemed less likely due to normal pituitary gland on MRI and normal SHBG. Further analysis of the sample was done with comparison between one step and two step methods using Canta ur and Delfia assays respectively. There was no evidence of assay interference in respect of TSH (38.73 vs 44.1mIU/l) and free T3 (3.9 vs 5.3pmol/l), however the freeT4 measurements were not consistent across the two platforms (25.6 vs 11.8 pmol/l). In addition, the total T4 measurement was elevated (219nmol/l; normal range 69-141) with 32% recovery after PEG treatment. Taken together, the results were suggestive of autoimmune hypothyroidism with evidence of freeT4 (and total T4) assay interference due to anti-T4 autoantibodies. The patient was treated with thyroxine and thereafter monitored using a TSH assay alone to guide treatment adequacy.

Conclusions: Clinicians must be aware of possible assay interference including the measurement of freeT4 in the differential diagnosis of abnormal TFT that do not fit the patient’s clinical presentation.

Key words: abnormal thyroid function, autoantibodies, FreeT4 assay interference.

CASE PRESENTATION

A 40 year old single female patient presented with tiredness and sweating. She was diagnosed with primary hypothyroidism two years ago based on elevated TSH. She was treated with thyroxine 50mcg per day for 6 months and then she was defaulted. She did not report any headache, visual problems, excessive sweating or dizzy episodes. Her bowel habits were normal. She had regular menstrual periods and did not complain menorrhagia. Apart from mild bronchial asthma she did not have any significant personal or family history. She was a non-smoker and did not consume alcohol. Examination revealed thin lady with BMI of 18.5 Kg/m² with a mild goiter. She was otherwise clinically euthyroid (Figure 1).

Investigations revealed abnormal thyroid function test (TFT) with TSH of 43.6mIU/l and FT4 of 3.06ng/dl. Other hormonal profile and biochemical tests were shown in table 1. Her TFT was repeated to confirm the findings on three separate laboratories.
with different platforms which was shown in table 2. She had high titres of anti thyroid peroxidase (TPO antibodies) > 1300mIU. Her thyroid scan confirmed small multinodular goiter with largest nodule of 3.9x2.3cm. Fine needle aspiration cytology (FNAC) of the nodule showed clusters of Hurtheloid cells with scattered multi nuclear giant cells, lymphocytes and plasma cells suggestive of Hushimoto’s thyroiditis (Thy 2, Bethesda 2).

She had elevated TSH in all tests with variable FT4 between upper normal to high levels for the reference range. In view of the clinical findings the following possibilities were considered; assay interference, TSH producing tumour and thyroid hormone resistance. Although she complained of excessive sweating and had a low BMI, her MRI (magnetic resonance image) of pituitary showed normal size pituitary gland (Figure 2). In addition, she had normal SHBG. In this context, TSH secreting pituitary adenoma deemed less likely and other two entities need exclusion.

Due to lack of availability of further specific investigations in our institute, patient’s blood sample was send to the metabolic research laboratories, Addenbrooke’s hospital, Cambridge. Further analysis of the sample was done with comparison between one step and two step methods using Cantaur and Delfia

### Table 1

<table>
<thead>
<tr>
<th>Tests</th>
<th>Results</th>
<th>Normal Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haemoglobin</td>
<td>12.4</td>
<td>12 -15g/dl</td>
</tr>
<tr>
<td>Serum Creatinine</td>
<td>0.7</td>
<td>0.8 – 1.3 mg/dl</td>
</tr>
<tr>
<td>Fasting blood glucose</td>
<td>88</td>
<td>65 -100 mg/dl</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>241</td>
<td>&lt;225 mg/dl</td>
</tr>
<tr>
<td>LDL cholesterol</td>
<td>120</td>
<td>80 -125mg/dl</td>
</tr>
<tr>
<td>Triglyceride</td>
<td>179</td>
<td>50 -150mg/dl</td>
</tr>
<tr>
<td>9 AM Cortisol</td>
<td>297</td>
<td>100-500nmol/l</td>
</tr>
<tr>
<td>FSH</td>
<td>3.48</td>
<td>1 - 10mIU/l</td>
</tr>
<tr>
<td>LH</td>
<td>10.6</td>
<td>1 - 10mIU/l</td>
</tr>
<tr>
<td>Prolactin</td>
<td>376.7</td>
<td>50 - 500mIU/l</td>
</tr>
<tr>
<td>SHBG</td>
<td>78</td>
<td>40 – 120 nmol/l</td>
</tr>
</tbody>
</table>

### Table 2

<table>
<thead>
<tr>
<th>Platform / Method</th>
<th>Lab1</th>
<th>Lab2</th>
<th>Lab3</th>
<th>Lab4</th>
</tr>
</thead>
<tbody>
<tr>
<td>VIDAS</td>
<td>43.6 mIU/l (0.5-5)</td>
<td>40.5 mIU/l (0.5-5)</td>
<td>33.1 mIU/l (0.5-5)</td>
<td>38.34 mIU/l (0.5-5)</td>
</tr>
<tr>
<td>Enzyme linked fluorescent assay</td>
<td>One step</td>
<td>One step</td>
<td>One step</td>
<td>ELFA</td>
</tr>
<tr>
<td>Seimens Immulite</td>
<td>Solid phase,</td>
<td>VITROS</td>
<td>Direct labelled</td>
<td>Enzyme linked</td>
</tr>
<tr>
<td></td>
<td>enzyme labelled</td>
<td></td>
<td>antibody</td>
<td>fluorescent assay</td>
</tr>
<tr>
<td></td>
<td>chemiluminescent</td>
<td></td>
<td>competitive</td>
<td></td>
</tr>
<tr>
<td></td>
<td>competitive immune</td>
<td></td>
<td>immune assay</td>
<td></td>
</tr>
<tr>
<td></td>
<td>assay</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FT4</td>
<td>3.06 ng/dl (0.9-2)</td>
<td>19.9 pmol/l (9-20)</td>
<td>12.8 pmol/l (10-19)</td>
<td>16.01 pmol/l (9-20)</td>
</tr>
<tr>
<td>FT3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
assays respectively (table 3). There was no evidence of assay interference in respect of TSH (38.73 vs 44.1mIU/l) and free T3 (3.9 vs 5.3pmol/l), however the freeT4 measurements were not consistent across the two platforms (25.6 vs 11.8 pmol/l). In addition, the total T4 measurement was elevated (219nmol/l; normal range 69-141) with 32% recovery after PEG treatment.

Taken together, the results were suggestive of autoimmune hypothyroidism with evidence of freeT4 (and total T4) assay interference due to anti-T4

### Table 3

<table>
<thead>
<tr>
<th></th>
<th>ADVIA Centaur assay 1 step test</th>
<th>Delfia assay 2 step test</th>
</tr>
</thead>
<tbody>
<tr>
<td>TSH (mU/L)</td>
<td>38.73</td>
<td>44.10 (0.4-4.0)</td>
</tr>
<tr>
<td>Reference Range</td>
<td>(0.35-5.5)</td>
<td>Linear to Dilution and normal PEG recovery</td>
</tr>
<tr>
<td>FT4 (pmol/L)</td>
<td>25.6</td>
<td>11.8</td>
</tr>
<tr>
<td>Reference Range</td>
<td>(10-19.8)</td>
<td>(9-20)</td>
</tr>
<tr>
<td>Reference Range</td>
<td>(10-19.8)</td>
<td>Linear to Dilution and normal PEG recovery</td>
</tr>
<tr>
<td>FT3 (pmol/L)</td>
<td>3.9</td>
<td>5.3</td>
</tr>
<tr>
<td>Reference Range</td>
<td>(3.5-6.5)</td>
<td>(3.0-7.5)</td>
</tr>
<tr>
<td>Total T4 (nmol/L)</td>
<td></td>
<td>219</td>
</tr>
<tr>
<td>Reference Range</td>
<td></td>
<td>(69-141)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>32% Recovery with PEG precipitation; suggesting possible assay interference</td>
</tr>
<tr>
<td>TBG (ug/ml)</td>
<td></td>
<td>17.9</td>
</tr>
<tr>
<td>Reference Range</td>
<td></td>
<td>(14-31)</td>
</tr>
<tr>
<td>Anti TPO Antibody</td>
<td></td>
<td>&gt;1300</td>
</tr>
<tr>
<td>Reference Range</td>
<td></td>
<td>(0-60mIU)</td>
</tr>
</tbody>
</table>
autoantibodies. The patient was treated with thyroxine and thereafter monitored using a TSH assay alone to guide treatment adequacy. Two months after treatment her TSH went down to 2.3 mIU/l confirming the diagnosis.

DISCUSSION

Thyroid function evaluation usually includes measurement of TSH and free or total thyroxine (T4 and T3). Majority of patients' clinical picture is consistent with thyroid function evaluation. However in some circumstances there may be discordant results which is inconsistent with the patients' signs and symptoms. When a patient presented with unusual thyroid test and the clinical presentation and the test results do not fit well, it is important to consider other rare possibilities. Our patient presented with elevated TSH and variable levels of free T4. Elevated TSH with elevated or non supressed free T4 will be a result of TSH secreting pituitary adenoma, resistance to thyroid hormone (RTH) or laboratory artefact.

TSH secreting pituitary adenomas (TSHomas) are characterized by high levels of circulating free thyroid hormones (FT4 and FT3) in the presence of non-supressed serum TSH concentrations (1). Most of the patients have a long history of hyperthyroidism and uni or multinodular goiter is described in the majority (2,3). Although our patient had increased sweating, a mild multinodular goiter and low BMI, TSHoma was excluded by a normal pituitary gland on MRI, normal SHBG and thyroid function test showing false elevation of FT4 with two step assay.

RTH is characterised by a reduced responsiveness of target tissues to thyroid hormone due to mutations on the thyroid hormone receptor beta gene (4). Patients with RTH are generally euthyroid. However, in a minority of patients who have predominant central or pituitary resistance, thyrotoxic features have been described (5). Common features of RTH includes goitre, but they may infrequently have tachycardia, hyperkinetic behaviour, cardiac abnormalities, auditory disorders, low body weight, language disabilities and subnormal intelligence (6). In our patient, the presence of goitre and low body weight are consistent with this diagnosis, as is the elevated TSH and FT4. However, TSH is only mildly elevated or in the upper half of the reference range in RTH. Our patient had TSH of more than 30μu/L. The other fact should be considered is the level of FT3. Patients with RTH should have elevated FT3 in proportion to FT4 whereas this patient had normal FT3.

The combination of elevated TSH and elevated FT4 in our patient raised the possibility of laboratory artefact. Although it is generally considered that FT4 assays are more reliable than the old fashioned total T4 assay, it is questionable in some occasions (7). The analog methods are generally used in FT4 assays where a labelled T4 analog competes with the serum FT4 for binding to an antibody. The commonly available methods in Sri Lanka employ one step immuno assay. While one step assay is affected by thyroid hormone autoantibodies, which directly compete with endogenous FT4, a two-step assay using an additional washing step induces a non-competitive reaction that removes the unbound FT4 and interfering factors (8). Non-specific binding of heterophile antibodies, thyroid autoantibodies or rheumatoid factor may interfere with thyroid hormone measurement. The prevalence of anti T4 and T3 antibodies in the general population is estimated to be 10% and in autoimmune thyroid disease about 40% (9). This patient had very high titres of anti-TPO antibodies. Autoantibodies to thyroid hormones may lead to abnormal FT4 by interference with the one step tests (9,10). This also causes artefacts in total T4 measurement.

The patient’s sample was checked on various laboratories in our country (VIDAS, IMMULITE, VITROS, ELFA) but all methods used one step tests. These showed upper normal to elevated FT4. When thyroid function test was repeated in two step test using Delfia assay, the FT4 level was not increased. This suggested that FT4 in one step assay was falsely elevated, point towards the possibility of the presence of anti T4 antibody. The direct tests to detect heterophil antibodies were not available in our department. Therefore the exact nature of interfering substance is not known in our patient. But the overall clinical picture is suggestive of auto immune hypothyroidism with evidence of freeT4 (and total T4) assay interference due to anti-T4 autoantibodies.
CONCLUSION

This case emphasize the importance of cautious interpretation of thyroid function test when there is discrepancy between clinical picture and laboratory results. Clinicians must be vigilant to the possibility of antibodies to FT4 in the presence of autoimmune thyroid disease. Support of chemical pathologist will help to avoid unnecessary time consuming investigations and guide proper management of patients.

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INTRODUCTION

Prader Willi Syndrome (PWS) is a common genetic cause of childhood obesity with a prevalence rate of 1:10,000-1:25,000\(^1\). It is the first human disorder to...
be recognized as related to genomic imprinting due to the failure of expression of paternal genes presented in the region of chromosome 15q11.2-q13. The disease is characterized by hypotonia at birth, feeding difficulties during infancy, developmental delay, intellectual disability, childhood onset of obesity with hyperphagia, endocrine dysfunction and neuropsychiatric issues. The diagnosis is suspected based on clinical features and confirmed by genetic studies(3). The endocrinological, cognitive and behavioural alterations occurring in PWS is secondary to hypothalamic dysfunction.

As the underlying pathophysiological basis for PWS phenotype is unclear, current therapies have shown limited efficacy and are directed at symptomatic control only. Growth hormone (GH) replacement is a standard of care for children as well as some adults as deficiency of this hormone is present in almost all children and most adults with PWS(4). Replacement therapy results in improvement of height, body composition, bone mineral density, exercise endurance and causes a favorable impact on development and behavior(5). However it does not tackle hyperphagia and morbid obesity which is one of the most challenging issues in managing these patients. Typical overweight or obesity results from a small error in average daily energy balance. In contrast children with PWS have been known to ingest 6 times their daily energy requirement(7). Caretakers of adults with PWS have documented 30 pounds of weight gain over a matter of days when patients had free access to food(4).

The exact molecular mechanisms as to the occurrence of obesity and hyperphagia in PWS remain incompletely understood. The satiety hormone, “Leptin” is found in normal levels in these patients but their hypothalamus seems to be unresponsive to its effect. Studies have found out that “Ghrelin”, the hunger hormone is high in these patients even after a meal. However the hypothalamus seems to be insensitive to this hormone as well(8). Other studies have shown defects in hypothalamic neuropeptides such as oxytocin, hypocretin/orexin as possible causes for hyperphagia in these patients(9).

At present there is an urgent need for pharmacological options as constant supervision is demanding and distressing for both the patient and the caregiver and surgical options such as bariatric surgery are contraindicated in this population.

Glucagon like peptide agonist -1(GLP-1 agonist) (liraglutide and exenatide) were originally developed for the treatment of patients with type 2 diabetes mellitus. Secreted by the L cells in the small intestine, in response to nutrient ingestion, GLP-1 agonists, increase Insulin secretion, and suppress glucagon in a glucose dependent manner. It decreases food intake by delaying gastric emptying and increasing satiety. GLP-1 agonists stimulate satiety by binding to its receptor in the hypothalamus and reduce calorie ingestion by delayed gastric emptying(10). This drug has shown to reduce appetite and induce weight loss in both diabetic and non-diabetic populations(11).

We present a case highlighting our experience with Glucagon-like peptide-1(GLP 1) receptor agonists in an adolescent with PWS and the challenges encountered in managing these patients in a developing nation.

**CASE PRESENTATION**

A 16 year old Sri Lankan female presented with short stature, obesity and primary amenorrhea. She had been diagnosed as Prader Willi Syndrome (PWS) during early child hood but had defaulted medical follow up. She has had feeding problems due to poor sucking during infancy and has had to be breastfed. All her developmental milestones had been delayed and although attending a normal school, her performance was far below average. She had suffered from hyperphagia and behavioral issues regarding controlling of feeding since early child hood.

She was morbidly obese with a height of 130 cm (<3rd centile), weight of 102 kg (>97th centile) and Basal Metabolic Index (BMI) of 60. She had the characteristic facial appearance of PWS, consisting of almond eyes with strabismus, thin upper lip with down turned mouth and small hands and feet. Acanthosis nigricans was evident. She had inadequate development of secondary sexual characteristics with Tanner 2 staging for both breast and pubic hair.

Investigations revealed pre diabetes with HbA1c of 6.2% and fasting blood glucose of 120 mg/dl.
Hormonal evaluation revealed hypogonadotrophic hypogonadism with low serum estradiol of 18 pg/ml (21-312) and low levels of Luteinizing hormone 0.1 U/L (1.9-12.5) and Follicular Stimulating Hormone 0.69 U/L (2.5-10.2). Serum Insulin like Growth Factor (IGF-1) levels were low at 130 ng/ml (age matched reference range 226-903) and subsequent Insulin tolerance Test confirmed growth hormone deficiency with sufficient levels of cortisol. She was clinically and biochemically euthyroid with serum free Thyroxin levels of 1.29 ng/dl (0.8-1.6) and Thyroid Stimulating Hormone levels of 1.09 mU/l (0.35-5.5). Prolactin levels were normal at 196mU/L (60-620). Imaging of the pituitary was normal.

**Figure 1 – Patient with PWS**

As the primary concern of her caregiver was obesity and overeating which was difficult to control, it was decided to give her a trial of liraglutide. She was commenced on sub cutaneous liraglutide 0.6 mg daily for two weeks which was subsequently increased to 1.2 mg daily. She was referred for counseling and behavioural therapy for overeating was but had defaulted their follow up. During the three months following commencement of liraglutide, the patient experienced a marked change in behavior. Her appetite diminished and she lost 3 kilograms. Her HbA1c improved from 6% to 5%. However her caregiver was finding it increasingly difficult to afford liraglutide which is not supplied free from the state-sector hospitals. Thus unfortunately the drug was discontinued. She was commenced on replacement of growth hormone, and estradiol as well as metformin. However hyperphagia recurred and she regained her lost weight over the next 4 months. Counseling and behavioral therapy was emphasized again but declined by the patient and her caregiver.

**DISCUSSION**

Our patient had a good response to GLP-1 agonists by demonstrating a 3 kg weight loss over a three month period and showed a favorable reduction in HbA1c. However the most remarkable effect was the reduction in appetite leading to better control of her eating habits.

Lately GLP-1 agonists have been considered as a new therapeutic option in tackling hyperphagia and obesity among PWS patients. This is due to its potential effects on ghrelin suppression, central appetite suppression and increase in the energy expenditure and stimulation of insulin secretion[12].

Several studies have looked at its therapeutic utility in patients with PWS. A small placebo controlled cross over study done on the effects of a single dose of exenatide on appetite, gut hormones and glucose homeostasis in adult patients with PWS and obese controls, demonstrated increase in satiety independent of measured appetite hormones, lower glucose levels and insulinotropick effect in both groups[12]. Ghrelin levels and energy expenditure were not affected and gastrointestinal side effects were common among the obese patients but absent among patients with PWS. Similarly the drug was well tolerated in our patient as well. A Case reported from Japan of a patient with PWS on liraglutide therapy for one year duration, demonstrated suppression of appetite throughout the treatment duration and favorable reductions in body weight, visceral fat, HbA1c and Ghrelin levels[13]. Fintinin et al reported
improvement or stabilization of altered glucose metabolism and clinical parameters more evident during the first year of treatment in 6 patients with PWS who were treated with GLP-1 agonists for 2 years(14). All these studies demonstrated that liraglutide was well tolerated. This is postulated to be due to the high threshold for pain and nausea among these patients. However more studies on the dosing and duration of treatment are warranted.

Concerns of liraglutide include its potential to delay gastric emptying, with a theoretical risk of gastric rupture in a patient population vulnerable to the risk of hyperphagia induced injuries and even death(15). Unpublished pilot studies have shown that GLP-1 agonists further exacerbates the slow gut movements in patients with PWS. This warrants careful supervision of patients on GLP-1 agonists. At present, GLP-1 agonists are undergoing phase 2 clinical trials and are not yet routinely prescribed(4). Miller et al looked into various types of medication inclusive of GLP-1 agonists, oxytocin analogues and ghrelin analogues which are currently undergoing clinical trials. However as of today there is no drug which has been proven to be effective for regulation of hyperphagia in these patients.

Our patient was able to take the drug for 3 months, during which time she developed marked reduction of appetite enabling her to reduce 3 kg of the body weight and favourable reduction in HbA1c. However liraglutide is currently not provided by the state sector, thus necessitating patients to purchase it. Unfortunately, due to its high cost liraglutide had to be discontinued, following which recurrence of hyperphagia and weight gain occurred. Attempts to refer her again for behavioral therapy were also not successful.

PWS is a challenging disease which needs a multidisciplinary approach to successful management. Inaccessibility to modern and expensive drugs, social stigma against seeking psychiatric and behavioral therapies, lack of support groups and organized institutional care for such patients are some of the obstacles faced by developing countries where the ever rising communicable and non-communicable diseases drain the bulk of the health budget. Thus rare and complex diseases such as PWS tend to be overlooked. However as PWS is increasingly being diagnosed in infancy, early, efficient and cost effective intervention for tackling issues such as hyperphagia and obesity would invariably improve the quality of life of these patients.

CONCLUSION

PWS is a complex disease with hyperphagia and obesity causing much morbidity and indirect mortality. At present there are no efficient cost effective medical options which are routinely used to tackle this problem. Our patient with PWS who was treated with liraglutide for 3 months demonstrated remarkable improvement in hyperphagia, weight loss and glycemic control. However due to the high cost of liraglutide, therapy had to be discontinued resulting in recurrence of hyperphagia and weight gain. This case highlights the potential benefits of GLP-1 agonists in these patients and obstacles faced by developing nations in tackling such diseases.

ABBREVIATIONS

PWS – Prader Willi Syndrome
GH- Growth hormone
(GLP 1 agonist ) - Glucagon-like peptide-1 agonist
BMI - Basal Metabolic Index

REFERENCES


CASE REPORT

A CASE OF A FEMALE PRESENTING WITH RECURRENt EPISODES OF DIABETIC KETOACIDOSIS, DENOVO POST KIDNEY TRANSPLANT

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Department of Nephrology and Transplantation, Teaching Hospital Karapitiya, Galle.

ABSTRACT

New onset diabetes after transplant (NODAT) occurs in a quarter of patients following renal transplants. NODAT is known to shorten the graft and patient survival. It is under diagnosed as a result of using fasting blood sugar or HbA1c as the investigation of choice, as hyperglycemia tends to occur mainly post prandially.

Immunosuppressants are thought to play a major role in the causation of NODAT. Among those calcineurin inhibitors are thought to cause pancreatic beta cell exhaustion and corticosteroids to induce peripheral insulin resistance. By the time impaired glucose tolerance manifests, nearly 50% of pancreatic beta cells have become dysfunctional. Therefore if we chose to treat NODAT the traditional way using lifestyle modifications, oral hypoglycemics and then insulin, we may lose the opportunity to reverse the damage to pancreatic beta cells. Beta cell sparing using intensive Insulin therapy is the recommended treatment coupled with metformin in the prevention and treatment of NODAT.

Keywords: NODAT, calcineurin inhibitors, beta cell exhaustion, post prandial hyperglycemia

CASE

A 50 year old female with end stage renal disease due to chronic obstructive uropathy underwent a renal transplant in October 2016. Her immediate post transplant period was complicated by acute pancreatitis and bactereamia, requiring a prolonged hospital stay. She was commenced on triple immunosuppressants including prednisolone, tacrolimus and mycophenolate mofetil and continued. She was discharged on above medications with a satisfactory graft function. (serum creatinine 1.02mg/l) One and a half months post kidney transplant, she was admitted with polydipsia, polyuria and loss of appetite for 4 days duration. Sepsis was excluded and preliminary investigations revealed a random blood sugar of high index when tested with the glucometer, ketone bodies in urine and acidosis on arterial blood gas analysis. She was managed as diabetic ketoacidosis which has occurred denovo following kidney transplant. Throughout the period of admission, her graft function remained stable but she experienced severe muscle cramps and pain restricting movements of her lower limbs, following treatment with intravenous Insulin. Investigations revealed severe and prolonged hypokalemia which was managed with intravenous potassium chloride and later on with oral supplements. She was discharged on Insulin and later titrated and managed on oral hypoglycemic agents (OHA) with satisfactorily controlled blood sugar.

While she was on oral tolbutamide 500 mg three times a day, she was readmitted at 6 months post kidney transplant with nonspecific symptoms and fever suggestive of sepsis. Her investigations revealed keto acidosis for the second time triggered by sepsis. Focus of sepsis could not be identified but urine; blood cultures and chest XR were negative. She received treatment with Insulin and empirical antibiotics and discharged when inflammatory markers were satisfactory and blood sugar was under control. Following this episode she was discharged on Insulin and her graft function continued to remain satisfactory.

DISCUSSION
NODAT occurs in nearly quarter of renal transplant recipients (RTR)(1). It is associated with shortened graft and patient survival and increased risk of infection and cardiovascular events. Even though post-transplant hyperglycemia is common, there’s still no consensus for the time frame to diagnose NODAT. Many cases of NODAT are missed due to the usage of fasting blood sugar as the diagnostic investigation as hyperglycemia tends to occur postprandially. HbA1c is also an erratic marker as hemoglobin level tends to be unstable during the early post-transplant period. Oral glucose tolerance test captures abnormalities of hyperglycemia more accurately.

There are modifiable and non-modifiable risk factors for NODAT such as age, ethnicity and family history. Among the modifiable risk factors immunosuppressant medications play a major role in the causation of NODAT. Calcineurine inhibitors (CNI) cause pancreatic beta cell exhaustion and reduced uptake of glucose by muscles and adipocytes. Tacrolimus when compared with cyclosporine is a better immunosuppressant as well as a drug with potent diabetogenic properties (2). mTOR inhibitors are also recognized as diabetogenic in studies involving RTR. Corticosteroids contribute to causation of NODAT by inducing peripheral insulin resistance. As a result there had been attempts at rapid withdrawal of steroids, the process of which was hindered by the increase in acute rejection episodes(3).

The traditional approach to management of NODAT has been to modify lifestyle factors, add OHA and then escalate to Insulin in a stepwise fashion. But nearly 50% of the pancreatic beta cells are dysfunctional by the time impaired glucose tolerance manifests (4). Thus by approaching above stepwise manner in the treatment, we may lose the opportunity to reverse the damage to pancreatic beta cells. It is well established that severe hyperglycemia in itself is toxic to pancreatic beta cells (5,6). Therefore by normalizing plasma glucose early in the post-transplant period, beta cells can be spared from the vicious cycle of glycotoxic injury and ultimately development of NODAT. Beta cell sparing with the usage of intensive insulin therapy was employed in post-transplant hyperglycemia. It is proven in studies that treatment with insulin on patients who develop NODAT has made them become independent of insulin therapy while those who have been on OHA required ongoing anti diabetic treatment (7). Beta cell function can be preserved for at least 3.5 years with early and intensive therapy for 3 months with insulin and metformin. After 3 months of intensive therapy the subjects on continued insulin or OHA showed excellent glycemic control and retained beta cell function as measured by c peptide levels(8). Exogenous insulin has shown pathophysiological basis of resting the pancreatic beta cells in the prevention of NODAT. There is no evidence to suggest satisfactory and efficacious use of OHA alone in the treatment or prevention of NODAT (9). Lifestyle modifications should be started pre transplant in overweight patients in parallel with increased physical activity. Early and intense life style intervention in patients listed for transplant, rapid steroid withdrawal in low risk patients, dividing the daily dose of prednisolone, and changing from tacrolimus to cyclosporine when appropriate, could minimize the risk and impact of NODAT. Perhaps a very important step will be the early institution of insulin to rest the pancreatic beta cells. The transplant community and treating physicians have to brace themselves to the changing paradigms in the prevention and management of NODAT.

CONCLUSION:

NODAT is a common occurrence among renal transplant recipients. As the development of this dampens the benefits of transplant it is of utmost importance for the treating physicians to be aware of the pathogenesis and the basis for treatment of this entity. The development of NODAT is mainly caused by the transplant medications in susceptible patients with risk factors. It should be understood that conventional stepwise approach to therapy in NODAT would be detrimental as beta cell exhaustion and apoptosis will make the patient dependent on anti-diabetic treatment for the life time unless intensive therapy with exogenous insulin is used in the outset. It is proven in studies involving patients with renal transplants that early institution of Insulin rests the beta cells and prevents further damage by eliminating the glycotoxic effect. Such patients have been found to be independent of Insulin therapy after considerable periods of time and some can be completely taken off anti diabetic medication for the rest of their lives.
Therefore exogenous Insulin should be the choice in treatment of post-transplant hyperglycaemia in order to prevent development and continuity of NODAT.

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DWARFS IN HISTORY

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I recently encountered this very interesting gentleman (figure 1) during my travel to Europe. I thought it worthwhile to introduce him to the endocrinology arena so that due appreciation is given to him from that point of view.

Figure 1

He initially caught my eye as a painting of an adult man stuck in a child-like body. This painting is unique for its front and back portraying making it a three-dimensional art form. He was not a beautiful creature. But he stood proud in his-self, displaying his fascinating body. He was cherubic with a protruding abdomen which was in part due to the exaggerated lumbar lordosis. The most striking feature about him was his stature. He was short with a standing height markedly below the 3rd percentile for his age and sex. But in contrast his sitting height was within normal limits reflecting a normal trunk length. He also had disproportionately short limbs and short stubby digits. His chest was flattened antero-posteriorly and there were redundant skin folds in the limbs.

I was told that he was a distinguished member of the court of the grand duke of Tuscany. Although he was known for his superior intellect, he was in the business of entertainment and he did have a ‘comical’ appearance. This was due to a combination of an oversized head with frontal bossing, mid facial hypoplasia, flattened nasal bridge and a prominent mandible. In fact his main role in the court had been as a jester, but later he had even been the advisor of the duke given his wisdom in court matters and ability to charm the duke.

I will now introduce the individual of interest, who is the dwarf Braccio di Bartolo - better known as Morgante, named ironically in reference to the theatre work by Luigi Pulci, whose protagonist Morgante was a giant. Morgante was the favourite court dwarf and prized entertainer of Cosimo I de Medici who was the grand duke of Tuscany, well remembered for creating political stability in the 16th century Florence. This dwarf was ‘clever, learned and kind’ according to Giorgio Vasari, the art historian and had a distinguished presence in the Medici court.

Morgante is portrayed in 3 places in the city of Florence where I met him as a tourist. He was depicted in a small fountain by Giambologna in the Bargello, another small fountain (called Bacchino) by Cioli in the Boboli Gardens, and the double painting by Bronzino in the Uffizi. In all three he is naked and this might be a reflection of the artistic beauty the duke saw in his dwarf’s disproportionate body, although the animals and birds with the dwarf points to a derogatory nature.
In Giambologna’s fountain (figure 2) Morgante sits on a dragon with his hand raised to still the waters imitating Neptune, the Roman god of the ocean.

In this marble fountain (figure 3) by Valerio Cioli, Morgante is seen riding the tortoise with his right hand in a similar position to that of Marcus Aurelius’ equestrian statue in Rome. The tortoise itself is a symbol of Cosimo, chosen to illustrate one of his mottos: Festina lente (more haste, less speed). Here again the features of achondroplasia is made prominent and the normal genitals are also in keeping with the condition.

Bronzino’s painting (figure 1) reveals him completely naked and shows both anterior and posterior views of the plump moustachioed dwarf who is ‘bird hunting’. Here he holds an owl tied with a string. For nearly 5 centuries the dwarf’s nakedness had been obscured by vines and grapes, but in 2010 the painting has been restored back to its true form at Florence’s Uffizi museum.

**DISCUSSION**

Dwarfs in the Renaissance period did not have an easy life. From an early age they were subjected to ridicule and abuse, and were often sold to circuses where they had to perform degrading acts. Some were sold off to the courts of royalty for entertainment, where a few even succeeded to become advisors of their lords, as in the case of dwarf Morgante.

Although the artistic and historical aspects of these Renaissance pieces were fascinating, I being a clinician and an endocrinologist was drawn to dwarf Morgante mainly due to short stature, rhizomelic shortening of the long bones and craniofacial abnormalities, which made me make a diagnosis of Achondroplasia. Achondroplasia, which is the commonest form of dwarfism is characterised by short limbs, with the patients’ sitting height in the normal range. In the affected individuals the arms and thighs more are severely involved than the forearms, legs, hands, and feet (3).

Achondroplasia has been described in art form as far back as the Egyptian civilization. Egyptian art depicts dwarfs as personal attendants, animal tenders, jewellers and entertainers as well as high-ranking individuals in the society closely related to the king. The well-known ones were Seneb, Pereniankh, Khnumhotpe, and Djeder. There are also depictions of two dwarf gods, Ptah and Bes in Egyptian art (1). Although short and unattractive, due to their normal intellect and comical appearance dwarfs have become important figures in all era of history.

Achondroplasia is transmitted as an autosomal dominant trait due to a single gene mapped to the short arm of the fourth chromosome (band 4p16.3) (2). But 80% of the cases are sporadic. The heterozygous state is affected and the homozygous is ordinarily fatal in the first few months of life. The molecular defect is in the fibroblast growth factors (FGF), which are structurally related proteins associated with cell growth, migration, wound
healing, and angiogenesis. At the cellular level, their function is mediated by transmembrane tyrosine kinase receptors, known as fibroblast growth factor receptors (FGFR) (4). The gain of function mutation in FGFR3 of which the primary function is to limit osteogenesis causes increased signal transduction leading to the primary defect in achondroplasia, which is abnormal endochondral ossification. Periosteal and intramembranous ossification is normal. The end results are short and broad tubular bones.

Current therapeutic strategies focus on reducing the signal transductions from the mutant FGFR3. Therapies directly targeting FGFR3, such as kinase inhibitors and neutralizing antibodies are still in the experimental stage. C- natriuretic peptide (CNP) which antagonizes the downstream effects of the aberrant FGFR3 signal, is another medication which is currently undergoing early Phase II clinical trials, that has been shown to normalize bone growth in mouse models of achondroplasia (5).

REFERENCES

A 49-year-old woman was evaluated after an adrenal nodule is discovered on a CT scan (Abdomen) obtained because of uncontrolled hypertension. She also complained of irregular periods and hirsutism. There was no weight gain over the past year. She was a known hypothyroid patient on thyroxine 75ug daily. She had no history of diabetes mellitus, palpitations, headaches, or sweating and no pertinent family history. She was on prazocin 1mg tds, amlodipine 10 mg mane, carvedilol 6.25 mg bd, thyroxine 75ug mane, clopidogrel 75mg nocte and atorvastatin 20 mg nocte. On physical examination, blood pressure was 148/96 mmHg, pulse rate is 88/min, and BMI is 34 KgM². General physical examination findings were normal.

Laboratory studies: Electrolytes Na-144 meq/L, K-3.9 meq/L, Aldosterone to renin activity ratio 1.1 (normal <30), 9 am Cortisol 359 nmol/L (138-690 nmol/L), Low dose dexamethasone suppression test - <22nmol/L, 24 hour urinary VMA: 7.3mg/24 hr(1-11 mg/24 hr). Her testosterone level was normal.

She underwent a comprehensive Contrast Enhanced CT Adrenal which revealed hypoplastic, fused supernumerary left kidney cranial to normal left kidney.

Supernumerary kidneys are a rare congenital anomaly of the urogenital system, where there are one or two accessory kidneys. Less than 100 cases are documented. Patients may be asymptomatic. If present, symptoms range from fever, pain to abdominal mass. Most of the kidneys are on the left and is smaller in size with reduced excretion as in our patient.

Her hypertension was diagnosed as essential hypertension and currently under control on 3 antihypertensives.
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GENERATION GAP

Generation gap is a gap of communication that leads to misunderstanding and disharmony. It refers to the gap between young and old. It is about mindsets and methods and it is not one-sided. Youth is full of passion and drive and is risk-friendly. The old have wisdom and experience and they are risk-averse. So, work together.

Just passion and risk-taking are not enough; neither are experience and wisdom because we live in a dynamic world. Strategies have to change and for this we need understanding and flexibility. The older and younger generations need to communicate, synergise and draw the best from each other. A healthy conversation and dialogue is essential to bridge the gap.

Sometimes adults behave like children and even need to be taken care of. Sometimes they want to pamper their children; at other times they expect children to behave like adults. Isn't this confusing?

Use the power of love and then you will know how to deal with old people. Yes, as they get old they behave like children. Give them love and understanding. Learn to enjoy dealing with them. They are also going through transition. Be committed and compassionate then you will get the right mode to help them. "He gives not the best, who gives the most but he gives the most who gives the best". Learn to give your best. Be the giver and then that giving itself enhances the quality of life. What is wrong if you pamper your parents? After all it is their second childhood. Don't you pamper your children? Don't use too much of logic but just shower love.

(The Speaking Tree)

May all beings be Well and Happy!