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Obesity has already taken its stride as a global epidemic. Gaining of recognition as a chronic disease has changed its viewpoint optimistically in a positive direction. With the advent of this new outlook, the identification, assessment and management of obesity have acquired a new perspective worldwide. Obesity is a silent killer. The trend is undoubtedly to embrace the population across the globe as a whole, involving all age groups.

The concern of increasing adiposity is currently on the spotlight, thus the present moment is the ideal time to explore further and act upon. The pertinent international organizations are actively geared towards formulating actionable recommendations to combat this menace. The foremost areas identified include the need of a more meaningful definition of obesity; further study to refine the utility of a complications-centric clinical approach to obesity; upgraded and more structured nutrition and obesity education; and heightened public awareness. Subsequent steps encompass founding applicable recommendations and developing logistics for effective implementation (1).

According to the 1998 “Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults – The Evidence Report”, overweight is defined as a body mass index (BMI) of 25 kg/m$^2$ to 29.9 kg/m$^2$ and obesity as a BMI of $\geq 30$ kg/m$^2$ (2, 3). Current estimated figures based on the National Health and Nutrition Examination Surveys show that 69% of adults are either overweight or obese, with approximately 35% obese. It is noted that obesity estimates for 2009 and 2010 did not differ considerably from estimates for 2003 to 2008; hence the prevalence rates of obesity appear to be levelling off in certain parts of the world (2, 4). Never the less, overweight and obesity continue to be a prevailing health concern and on the upswing, especially in some racial and ethnic minority groups, as well as in those with lower income and less education (2).

South Asian population is highly vulnerable to metabolic syndrome. Gone are the days that malnutrition and infectious diseases are considered as concerns in South Asia and minimal attention was given to obesity. Ingrained poor attitudes towards obesity among South Asians are a major obstacle towards our goal. The less informed should do away with the misconceptions regarding overweight and obesity. Sri Lanka is a low-middle-income South Asian country with a population exceeding 20 million. Obesity and linked metabolic problems are sprouting as major health problems in the country with an estimated 20% of all adults suffering from dysglycemia and 11% from type 2 diabetes (5). The Sri Lanka Diabetes and Cardiovascular Disease Study (SLDCS) conducted between 2005 and 2006, reported an obesity prevalence (BMI $\geq 25$ kg/m$^2$) of 14.3% and 19.4% in males and females respectively (6). Minimizing the discrepancy between body weight parameters and prevailing fallacies has to be eradicated to create an attitudinal change in a favourable direction.

Fulfilment of anthropometric criteria per se does not constitute the diagnosis of overweight and obesity as a health problem (1, 7). Obesity has become a vital health-related issue. It needs a more holistic and comprehensive classification system inclusive of the presence of allied complications. Type 2 diabetes, prediabetes, dyslipidaemia, hypertension, polycystic ovarian syndrome, obstructive sleep apnoea, non-alcoholic fatty liver disease and osteoarthritis are a handful of well understood obesity related complications which need to be contemplated in the diagnostic process (2). Data regarding the role of combating obesity as a method of preventing cancers are also emerging. Therefore weight reduction unquestionably decreases overall morbidity and premature death.

New guidelines are on the horizon and numerous international bodies are active participants in this undertaking. In 2013 the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and The Obesity Society (AHA/ACC/TOS) jointly published a guideline for the management of overweight and obesity in adults (2). Various international and regional organizations are currently taking part in instituting more practical and user friendly frameworks for handling this problem.

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Multidisciplinary team approach is the essence to success. Lifestyle interventions should not be underestimated as the cornerstone to the sustained positive outcome. The scarcity of modes of medical intervention is a major obstacle in managing obesity. A multitude of medications have emerged as new therapies since withdrawal of sibutramine. The new agents are lorcaserin, phentermine and phentermine/topiramate which in its combined form is supposed to be more efficacious than either agent alone (9). Multinational, randomized, placebo-controlled, double-blind phase 3 trials are ongoing regarding the place of higher dose liraglutide in achieving a clinically meaningful weightloss in overweight or obese patients with type 2 diabetes. The advent of these agents is very exciting to the pharmaceutical industry and sounds promising to the clinicians. Despite the influx of modern pharmacotherapies, the easy access to these agents in developing and underdeveloped countries is a serious issue. This is a major hindrance for clinical practitioners which tend to discourage the momentum of this endeavour.

The magnitude of the problem of overweight and obesity in our country should not be underrated. This has already gained attention and enthusiasm of the whole spectrum of health care providers; nevertheless, it’s not properly streamlined. We need to identify our needs and requirements and take actionable steps with a local flavour. A dedicated special task force is one way of integrating the diverse array of stakeholders in this respect with the broader objectives of awareness building, disseminating knowledge and formulating tangible recommendations. The steering of such plan has to be taken at the policy level. Physicians, endocrinologists, family physicians, nutritionists, dieticians, bariatric surgeons and representatives from the education sector should take collective effort to reach every corner of the country in order to combat this health threat. The concept of having a network of dieticians and nutritionists who are well trained and able to cater the current demands is a necessity. Dietary intervention should be implemented in conjunction with the knowledge of cross cultural differences. Food policies need to be revised. The relative scarcity and the high cost of healthy food should be identified as a key drawback in disseminating good food practice. Easy accessibility and the low cost of less healthy food items have to be fought against. Influence of mass media on food marketing need to be handled in a more tactful manner especially to safeguard the younger generation.

The prescribers of anti-obesity medications need regular on going awareness programmes to assist them in updating on the newly emerging approaches. Therapeutic agents need to be more easily available at a reasonable cost at a national level. Surgeons who actively engage in bariatric surgery need to be encouraged further and provided with the necessary facilities. More public awareness is required to enhance the acceptance of these procedures. The well conducted coordination between bariatric surgeons and the rest of the team is critical as this is not a speedy solution to obesity and further follow-up is needed to prevent regaining of weight. A properly streamlined referral system to tertiary care centres is vital.

Behavioural interventions need to be more strategic and acceptable to the individual. The rate of long-lasting success is trivial if the mind-set of readiness to change is not created in the individual. The aims and targets need to be more realistic, modest and achievable. The barriers precluding access to relevant facilities need to be identified and rectified. A setback of such activity is the non-acceptance at all levels which is a major obstacle in implementing on a broader platform. The entire spectrum of health care providers should be represented throughout the process to overcome this practical issue. The undergraduate and postgraduate education should emphasize more on nutrition including medical nutrition therapy. This can strengthen the network necessary to build-up a long-lasting success. The entire spectrum including prevention, recognition, assessment, identification of complications and management needs to be looked into. Policy makers should be actively integrated into the strategic planning and application. The local data published from various regions need to be given more recognition and this evidence based evaluation could be utilized to guide policy making decisions.

The Endocrine Society of Sri Lanka (ESSL) has taken the initiative in intervening by developing a national guideline on management of obesity. This emphasises the importance of providing standardized obesity care to reduce the burden of obesity at a national level. It is noteworthy to mention the different cut-offs adopted for the classification of obesity, highlighting the impact from a local viewpoint. It is timely and highly appropriate that the ESSL has published the guideline on Management of Obesity in this issue of Sri Lanka Journal of Diabetes, Endocrinology and Metabolism (SJDEM). This will undeniably cater the wide range of professionals actively involved in obesity care in the country.

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The second diabetes attitudes wishes and needs (DAWN2) study: relevance for Sri Lanka

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Key words: DAWN, psychosocial, diabetes mellitus

Health in Sri Lanka

The health system of Sri Lanka is the pride of South Asia. In domains such as life expectancy, maternal mortality, and child mortality, and indicators linked with provision of health care, Sri Lanka leads the South Asian region (1). This success has come about because of multiple factors. One of these is the large cadre of qualified, trained, and committed health care professionals, at all levels of education, who work towards providing better health care to the citizens of the country. At the same time, Sri Lanka has faced major psychosocial trauma, such as the war and the tsunami in the year 2004. Coping with these traumatic episodes has been a major challenge for the country, which responded by developing a large psychological support programme. This provides ‘psychological first aid’, community and personal mental health, services as well as stress management support to people suffering from post-traumatic stress disorder. This programme is executed through a large cadre 8000, trained peer educators, who are supported by qualified mental health professionals (2).

Diabetes in Sri Lanka

Though Sri Lanka can justifiably boast of major achievements in health care, it faces newer challenges in public health. Apart from the post traumatic stress disorder which followed the tsunami, there are other health conditions which need addressal. One of these is diabetes. Sri Lanka’s insular geography has not been able to protect it from the Genghis Khan-like spread of the diabetes pandemic. Current statistics from the International Diabetes Federation (IDF) reveal that 7.5% adult Sri Lankans currently have diabetes mellitus, while another have?? impaired glucose tolerance. These numbers are projected to rise to 9.1% and 5.9% by 2030 (3). Recent studies have expressed more alarming age-adjusted prevalence of diabetes mellitus in urban population at 20.3% in men and 19.8% in women (4). These figures are much higher than predictions based on studies done earlier proving that the trajectory of diabetes is much more alarming than the IDF predictions for 2030 (3,4,5). While diabetology and endocrinology services are often able to manage the biological aspects of diabetes mellitus, the psychological issues get neglected at times.

DAWN 2 methodology

The recently conducted Second Diabetes Attitudes Wishes and Needs (DAWN 2) study, has explored the barriers to addressal of the psychological aspects of diabetes. Through its data, it also tries to identify solutions to optimize the situation. In the DAWN 2 study, approximately 16000 respondents, including 9000 patients with diabetes (PWD), over 2000 family members of people with diabetes (FM), and nearly 5000 health care professionals (HCPs) were interviewed with a wide range of questions (6). The questions were designed to elicit their views and perceptions on matters related to diabetes care (7, 8, 9). Respondents completed group-specific questionnaires, in which items were designed to allow cross-group comparisons on common topics. Validated psychometric tools and instruments were developed to assess self-management, attitudes/beliefs, disease impact/burden, psychosocial distress, health-related quality of life, healthcare provision/receipt, social support and priorities for improvement in the future. The questionnaires were completed online, by telephonic interview, and during face-to-face interviews in countries with low internet access. In each country, the diabetes population was well represented across geography, age, gender, education and disease status (6).

Through Sri Lanka was not a part of the 17 participating countries, spread over 4 continents, the global data seems relevant from the Sri Lankan perspective. Inclusion of neighboring countries (India), and nations with similar religious philosophy (China, Japan), as well as nations will and an equally strong sociocultural fabric, based on family ties and kinship (Algeria, Turkey, Mexico) in the DAWN 2, list add weight to its relevance for Sri Lanka.

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DAWN 2: psycho-morbidity in people with diabetes

DAWN 2 (6) has revealed that 14.8% of all PWD are likely to have depression (WHO-5 score ≤28) (country range 8.3 -20.3 %). This figure is concordant with the 13.4% of participants (country range 8.8 - 24.0 %) who rated quality of the life as being ‘poor’ or ‘very poor’. However, when questioned, 41.1% PWD (country range 20.8- 65.0%) reported significant diabetes-related distress. PAID (Problem Areas in Diabetes score ≥4 this sentence doesn’t make sense brackets opened are not closed). They also reported a negative impact of diabetes on their relationship with family/friends/peers in 19.7% cases (country range 11.6-30.4%), and on emotional well-being in 44.8% cases (32.7-75.6%).

These figures highlight the heavy burden of diabetes on emotional health. In spite of this, only 32.8% of people with diabetes report having been asked if they felt anxious or depressed, by a member of their health care team, during the preceding 12 months (country range 15.9-56.0%).

The best quality of life is seen in China, France and India, while the worst reports originate from UK, Algeria and Japan. In the WHO -5 psychological well-being scale, Mexico, Denmark and India take the top 3 spots. Diabetes distress seems highest in the Netherland, USA and Denmark while the condition impacts relationships maximally in Turkey, India and the Russian Federation. The most negative impact on emotional well being is reported from Japan, the Russian Federation, and Poland. At the same time, Mexican, Russian and British health care providers fared best in asking people with diabetes if they felt anxious or depressed.

These heterogeneous answers provide no clue as to how Sri Lankan HCPs would fare in a national version of DAWN 2.

Familiar solution

The DAWN 2 study did uncover a latent, yet potent, source of support for people with diabetes. This source of support is, simply put, more people. 82.2% (54.3-97.3%) of people with diabetes ranked their family as being somewhat or very supportive. Similar responses were given for friend ‘people close to you’, people at work or school, and other people in community by 59.9% (18.8-85.8%) 24.8 (7.3-46.9%) and 28.9% (5.1-72.6%), PWD respectively.

The Indian cohort of people with diabetes responded that 72.6% of other people in the community, 42.3% of people at work or school, 84.5% of friends or people close to them and 97.3% of family were supportive. These proportions are the highest or near-highest amongst all DAWN 2 nations (7). Responses from Sri Lanka would be quite similar, keeping in new the shared socio-cultural ethos of both neighbors.

Sri Lanka has a large cadre of volunteers, trained to provide psychological support to those in need. Perhaps their services could be used to provide support to people with diabetes, who face multiple emotional challenges. This would provide professional satisfaction to the volunteers, make full utilization of their training, and create employment opportunities as well. The public health system would benefit, as understaffed clinics would find it easier to cope with the burden of management of diabetes. Most of all, the person with diabetes would benefit from the extra support received.

Summary

The DAWN 2 results have highlighted the high prevalence of diabetes related distress (≈40%), likely depression (≈15%) and negative impact on emotional well being (≈45%) in people with diabetes.

At the same time, the study has unveiled the existence of a strong support system: family (80%), friends/ ‘people close to you’ (60%), people at work or school (25%) and community members (30%). The last two statistics hide the best possible scenario: in countries similar to Sri Lanka, approximately 40% of colleagues at work or school, and 75% of community members are supportive. Sri Lanka can easily utilize its vast pool of citizen volunteers, trained in providing ‘psychological first aid’, to help in providing support to people with diabetes.

This will certainly improve diabetes care for people with diabetes, while helping the cause of their family members and health care professionals as well. The DAWN 2 study should spur efforts to collect nationwide data on relevant psychosocial aspects of diabetes, as well as harness the existing human resource pool to meet the challenge of diabetes epidemic. The concept of mass, community based, ‘psychological first aid’ in diabetes may turn out to be Sri Lanka's contribution to global diabetes care praxis.

References


Association between anthropometric parameters and testosterone deficiency in men

C M Wickramatilake¹, M R Mohideen², C Pathirana¹


Abstract

Objectives: Obesity and anthropometric measures are related to the testosterone concentration in men, although debate remains as to which anthropometric parameters are most important. Fat mass or adiposity is an important negative determinant of total serum testosterone level. We aimed to investigate the relationship of anthropometric measurements with serum total testosterone level and to find out the most reliable predictive anthropometric measurements of testosterone deficiency.

Methods: Three hundred and nine male subjects were recruited. Anthropometric measurements: weight, height, waist and hip circumferences were obtained. Body mass index (BMI) and waist-to-hip ratio (W/H) were calculated. Baseline total testosterone (TT) level was estimated.

Results: There was a significant negative correlation between TT level and waist circumference (r = -0.146, p = 0.010), W/H ratio (r = -0.173, p = 0.002) and age (r = -0.559, p = 0.001). The relationship between the response (Testosterone deficiency/ No testosterone deficiency) and the model variables of age (OR = 1.35, p = 0.042) and waist circumference (OR = 1.99, p = 0.035) showed significant odds ratio (OR), while BMI and hip circumference exhibited non-significant OR.

Conclusion: There is evidence for supporting the association between anthropometric measurements and serum total testosterone level. Waist circumference was the most reliable predictor of testosterone deficiency.

Key words: anthropometric measurements, testosterone, men

Introduction

Obesity is a worldwide epidemic which is on the rise in the Asian nations¹. Obesity is associated with a multitude of health adverse outcomes such as coronary artery disease, osteoarthritis, diabetes mellitus and lowered testosterone (2).

Observational studies have shown a strong association of obesity with low circulating testosterone levels in men. Age-associated decline in testosterone is correlated with the loss of lean body mass and increased fat mass (3). Conversely, there is evidence that healthy ageing by itself is uncommonly associated with marked reductions in testosterone levels (4), because age-related testicular dysfunction is partly compensated by the age-associated increase in pituitary LH secretion (2). However, obesity may blunt this LH rise, leading to hypothalamic-pituitary suppression irrespective of age which cannot be compensated by physiological mechanisms and may result in testosterone deficiency (2). Other than obesity, testosterone deficiency has been shown to be associated with the risk of developing coronary artery disease (5, 6) and its risk factors like diabetes mellitus, hypertension and metabolic syndrome (7, 8).

Therefore obesity may contribute to low testosterone levels in blood in adult men. Hence anthropometric measures are related to the testosterone concentration in men, although debate remains as to which anthropometric parameters are most important in the prediction of testosterone deficiency. Therefore we aimed to investigate the relationship of anthropometric measurements with serum total testosterone level and to find out the most reliable predictive anthropometric measurements of testosterone deficiency.

Materials and methods

This was a hospital based study which included male

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subjects in the age range of 30-70 years. Three hundred
and nine study subjects were recruited using convenient
sampling. Subjects with a history of recent surgery or
major trauma within three months or a history of acute
coronary syndrome in the past three months, malignancy,
chronic inflammatory disorders, current acute severe
infections, dementia or any structural damage to the
central nervous system, renal dysfunction, chronic liver
disease, alcohol dependency based on the CAGE
questions were excluded from the study (10). Those on
disease, alcohol dependency based on the CAGE
central nervous system, renal dysfunction, chronic liver
diseases, thyroidectomy, and testicular problems (undescended
tests, testicular injury, tumor or infection) were not
recruited to the study. Sample size was calculated using
the equation for a descriptive cross-sectional study
described by Lwanga SK and Lemeshow S (9).

An interviewer-administered questionnaire was used to
collect relevant information from the study subjects.
All baseline anthropometric measurements were made by
the same investigator, using the same instruments. Height
was measured following the standard technique by a
portable stadiometer (IUCHI, Yamato Scientific, Japan) with
the precision of +/-0.1 cm and readability up to 200 cm.
Weight was measured using a portable beam balance
(Bauman, Germany) with the precision of +/-0.1 kg and
readability up to 100 kg. Waist circumference was measured
to the nearest 0.1 cm according to the standard technique
using a non-stretchable measuring tape. Hip circumference
was measured at the maximum protuberance of the
buttocks to the nearest 0.1 cm. Mean of the two readings
(three times, if difference between two readings was ≥0.5
cm) was taken as the final value of each circumference
measurement. Body mass index (BMI) and waist-to-hip
ratio (W/H ratio) were calculated. Body mass index
categories were defined according to the guidelines for
Asian adults (11). Serum total testosterone was estimated
by an enzyme immune assay kit.

The research project was approved by the Ethical
Review Committee of Faculty of Medicine, University of
Ruhuna, Galle, Sri Lanka and conducted according to the
ethical guidelines outlined in the Declaration of Helsinki.
Permission was obtained from all necessary local
authorities to conduct the study. Informed written consent
was obtained from all the participants.

Data were analyzed using appropriate statistical tests.
Continuous variables were examined for normality and
presented as mean and SD. Pearson correlation coefficient
was used to find out the relationship between continuous
variable. Significance was defined when the p value was
less than 0.05. Multivariate logistic regression analysis
was used to find out the predictors of testosterone
deficiency which was defined, using the total testosterone
cutoff of ≤10.4 nmol/L according to American Association
of Clinical Endocrinologists (AACE) (12).

Results

Baseline characteristics are shown in table 1.

Table 1. Baseline characteristics

<table>
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<tr>
<th>Variable</th>
<th>Mean ± SD (n = 309)</th>
<th>Range</th>
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<tbody>
<tr>
<td>Age (yrs)</td>
<td>54 ± 9.7</td>
<td>30-70</td>
</tr>
<tr>
<td>Total testosterone (nmol/L)</td>
<td>13.7 ± 5.8</td>
<td>4.5-34.0</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>22.5 ± 4.2</td>
<td>13.0-46.4</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>79.9 ± 10.5</td>
<td>52.5-115.5</td>
</tr>
<tr>
<td>Hip circumference (cm)</td>
<td>86.6 ± 8.4</td>
<td>45.0-121.2</td>
</tr>
<tr>
<td>Waist-to-hip ratio</td>
<td>0.92 ± 0.06</td>
<td>0.75-1.17</td>
</tr>
</tbody>
</table>

Data presented as mean ± SD, BMI = Body mass index

The scatter plots show the correlation between
testosterone and the anthropometric measurements.
There was a significant negative correlation between total
testosterone (TT) and age (r = -0.559, p = 0.001) (Figure
1.a), waist circumference (r = -0.146, p = 0.010)

(Figure 1.b) and waist-to-hip-ratio (r = -0.173, p
= 0.002) (Figure 1.c). However, there was no significant
correlation between total testosterone and body mass
index (r = -0.028, p = 0.627), hip circumference (r = -0.085,
p = 0.138). The prevalence of obesity (BMI > 25 kg/m²) in
the study group was 62 (20%) according to the Asian
guidelines.

There were 73 (23.6 %) with testosterone level less
≤10.4 nmol/L indicating testosterone deficiency according
to the American Association of Clinical Endocrinologists (12).
There were 19 (6.2 %) patients with hypogonadism having TT
less than 6.9 nmol/L (12). Based on the odds ratios and the p
values in logistic regression analysis, waist circumference showed highest predictive
ability of testosterone deficiency (Table 2) out the
anthropometric indices.

TT level ≤ 10.4 nmol/L indicates the testosterone
deficiency. Response variable was presence or absence
of testosterone deficiency. Predictor variables used in the
model were age, BMI, waist and hip circumferences. Results
of multivariate logistic regression analysis were presented
as odds ratio (OR) and confidence intervals (CI). BMI = Body mass index.
Figure 1. Scatter plots with regression showing the correlation between total testosterone (TT) and (a) age, (b) waist circumference and (c) waist-to-hip-ratio (W/H).

Table 2. Anthropometric measurements as predictors of testosterone deficiency

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR</th>
<th>95 % CI</th>
<th>p</th>
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<tr>
<td>BMI</td>
<td>0.99</td>
<td>0.89 - 1.10</td>
<td>0.861</td>
</tr>
<tr>
<td>Waist circumference</td>
<td>1.99</td>
<td>1.24 - 2.92</td>
<td>0.035</td>
</tr>
<tr>
<td>Hip circumference</td>
<td>1.02</td>
<td>0.96 - 1.09</td>
<td>0.523</td>
</tr>
<tr>
<td>Age</td>
<td>1.35</td>
<td>1.12 - 2.78</td>
<td>0.042</td>
</tr>
</tbody>
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Discussion

Waist circumference, waist-to-hip-ratio and age showed a significant negative correlation with serum total testosterone level, although BMI and hip circumference showed non-significant correlation according to the present study. Age was a significant independent predictor of TT deficiency (<10.4 nmol/L). Waist circumference had the highest odds ratio for testosterone deficiency being the most significant anthropometric predictor, while BMI and hip circumference were not found as significant predictors of testosterone deficiency. It is established that body mass index indicates the general obesity; while waist circumference reflects central obesity and hip circumference demonstrates peripheral obesity. These anthropometric measurements are known to indicate the body fat distribution.

Fat mass or adiposity is an important negative determinant of total testosterone level (13). Most studies confirm that serum free testosterone (FT) and total testosterone (TT) inversely correlates not only with anthropometric parameters such as waist circumference and BMI, but also with total body fat mass measurements in men. De Pergola et al. (2003) showed that FT is inversely correlated with BMI and waist circumference and the fat mass was measured by bioimpedance analysis (14). Dunajksa et al. (2004) revealed an inverse correlation between testosterone level and body mass index, waist and total body fat mass obtained by dual-energy X-ray absorptiometry (15). Another study found a negative association between testosterone and BMI and fat mass (16). Furthermore, Abate et al. (2002) showed a negative correlation between FT and waist circumference, waist-to-hip ratio, skin fold thicknesses, total fat mass and fat distribution in abdominal compartments, except...
retroperitoneal (17). The findings of our study suggests that central adiposity which is reflected by waist circumference is more associated with the testosterone deficiency. However, we were unable to perform other related biochemical test such as FT and bioavailable testosterone (BT) and to determine the body fat mass due to the financial constraints and the limited facilities available.

There are suggested mechanisms to explain the implication of obesity as a cause of hypotestosteronaemia in men. Low levels of testosterone are expected in men with increased fat mass, because peripheral conversion (by aromatase enzyme) of testosterone to oestrogens is increased (18). In addition, elevated leptin and similar agents in obesity may also act as suppressors of testosterone synthesis at the level of hypothalamic-pituitary-gonadal axis (19) and at testicular level suppressing the testosterone synthesis (20).

Total testosterone showed significant negative correlation with age. It is known that there is an age-related gradual decline of testosterone in men (21). There are different mechanisms that can be used to explain the age-related changes in serum testosterone levels in men. There are primary testicular changes with a diminished testicular secretory capacity and an altered neuroendocrine regulation of the Leydig cells with apparent failure of the feedback mechanisms to fully compensate with aging. Moreover, there is an independent increase of SHBG binding capacity (22). The age-associated increase of SHBG levels is by about 1.2% per year (21), so that the decrease of FT and BT serum levels is larger than that of total serum testosterone (21). Age-related loss of muscle mass is accompanied by fat gain in older adults (23) which may increase peripheral conversion of testosterone to oestrogens (18).

Conclusion
There is evidence to support the inverse association between anthropometric measurements and serum TT level. Waist circumference was the most reliable predictor of testosterone deficiency among the anthropometric measurements.

Conflict of interest
The authors declare that they have no conflicts of interest concerning this article.

Acknowledgement
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References
Association between anthropometric parameters and testosterone deficiency in men


Effects of consumption of traditional Sri Lankan meals on glycaemic response in healthy individuals

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Abstract

This is a part of Sri Lanka diabetes diet study, conducted with the objective of finding out the glycaemic responses to real life, day to day meals in the Sri Lankan diet, of in patients with diabetes.

**Objective:** To study the glycaemic response of string hoppers made of white and red rice consumed with typical Sri Lankan curries in healthy volunteers. Thirty healthy volunteers (20-60yrs, M: F 13:17) were given meals with white and red rice string hoppers with different curries, making 8 types of meals. All 30 were given all 8 menus on different days, containing 50 grams of available carbohydrates. String hoppers (white and red rice flour) were given with one of the following curries on one occasion: coconut gravy + coconut sambol (*Cocos nucifera*), lentil curry [Mysore dhal] (*Lense culinaris*), legume curry [bean curry] (*Phaseolus vulgaris*) and fish curry [Indian scad] (*Decapterus russelli*). Subjects were subjected to fasting for 12 hours. A fasting glucose was done and after consuming the food, blood glucose was tested every half hour till 2 hours. Glycaemic index (GI) was calculated by standard method. The GI of string hoppers made of white rice flour had significantly higher GI values compared to red rice flour string hoppers, except when consumed with beans (legume) curry. Highest GI (69.2±9.47) was seen with string hoppers and coconut gravy/coconut sambol. However there was significant difference between white and red rice (69.20 ± 9.47 Vs 50.46 ± 9.74). Lowest GI was seen, when string hoppers were eaten with legume curry, irrespective of whether the rice flour was red or white (39.93 ± 8.14 vs 41.96 ± 9.86).

**Conclusion:** String hoppers when eaten with various curries, have different GI values for the same quantity of available carbohydrate. Coconut gravy with string hoppers gave the highest GI. Legume curry combined with red or white rice string hoppers gave the lowest GI value. Adding high fibre vegetables seem to reduce the glycaemic response of a carbohydrate meal in normal subjects. This phenomena has to be tested in diabetes patients.

**What’s already known about this topic?**

Glycaemic indices of most carbohydrates are known. However in Sri Lanka, most patients think that brown rice flour has a better glycaemic response compared to white rice flour.

**What does this article add?**

We have shown that, irrespective of whether it is brown or white rice flour that is used to make string hoppers, the hypoglycaemic response is similar. Adding vegetables reduces the glycaemic indices significantly, irrespective of the type of rice.

**Key words:** diabetes nutrition, diabetes diet, medical nutrition therapy, glycaemic index, glycaemic load, glycaemic response

Introduction

Diabetes mellitus is a complex metabolic disorder characterized by persistent hyperglycaemia resulting from defects in insulin secretion or action or both (1). The prevalence of diabetes mellitus (DM) has rapidly increased in Asian countries including Sri Lanka during the past decade. Katulanda et al (2) concluded that in Sri Lanka 1 in 5 adults have either diabetes or pre diabetes and yet many more in the population may be undiagnosed.

According to American Diabetes Association (ADA), medical nutritional therapy (MNT) is an integral component of diabetes management and of diabetes self-
management education. Yet, many misconceptions exist concerning nutrition and diabetes. Moreover, in clinical practice, nutrition recommendations that have little or no supporting evidence have been and are still being given to people with diabetes (3). Lack of trained dieticians specialized in diabetic meal-planning and limited resources in Sri Lanka results in poor structured education and dietary advice given to patients. Sato et al (4) recommended a successful diabetic diet exchange will help to control patient’s weight and plasma glucose concentrations. Most of the studies done on Sri Lankan food have been done on non-diabetic healthy volunteers with single carbohydrate meals. Very few studies have been done with mixed meals, but with non-diabetic healthy volunteers (5-7). According to Hettiaratchi et al (5) scientific data on postprandial glycaemic response of common meals is essential when formulating diets.

Wolever et al (8) recommended that glycaemic response is a measure of how quickly a food is absorbed into the blood stream as glucose. The glycaemic response depends on multiple factors like glycaemic index (GI), glycaemic load (GL), portion size, and apparent volume of the food after cooking and the quantity consumed. There is currently much scientific and popular interest in the role of low glycaemic index (GI) food in the management of weight and metabolic disease risk. However, both observational and interventional studies are hampered by lack of knowledge of GI values for many foods (9). Glycaemic index is useful as it ranks food items depending on the blood glucose response following a meal. GI is defined as the incremental area under the blood glucose response curve elicited over a two-hour period by a 50 gram carbohydrate portion of a food, expressed as a percentage of the response to the same amount of carbohydrate from a standard food taken by the same person. According to Chlup et al (10), GI values food are categorised as low, medium and high. Food with a GI value of 70 or more are considered to be a high GI diet, with an index value between 55 to 69 as medium GI diet and less than 55 as low GI diet. Low GI diet is beneficial in both types of diabetes mellitus.

WHO/FAO expert committee endorses the use of GI in planning diets for individuals with diabetes (11). Patients with diabetes need to undergo dietary modifications and are advised to avoid food which give rapid and high blood glucose responses. Therefore, knowledge of the blood glucose raising potentials of commonly eaten meals is important to avoid excessive blood glucose response. Although there are data on GI of some basic Sri Lankan foods, sufficient information is not available on mixed Sri Lankan meals.

According to Martin et al (12) GI is estimated with a standard amount of carbohydrate load which may or may not be the normal serving size. Glycaemic load was introduced to apply the GI concept to the normal serving sizes of foods (edible portions).

Glycaemic load is calculated as

\[ GL = \frac{[GI \times \text{amount of carbohydrate (grams) in the edible portion}]}{100} \]

Thus, high GI/low carbohydrate diets or low GI/high carbohydrate diets can have the same GL.

Objective of the study

To study glycaemic index of string hoppers made of white and brown rice flour in combination with different types of traditional Sri Lankan curries.

Research Methodology

Setting

The study was carried out in the Royal Care Hospital, Akurana, Kandy and Teaching Hospital, Peradeniya, Sri Lanka.

Subjects

The participants in this study were 30 healthy volunteers recruited from the nursing staff, laboratory assistants and other workers. Seventeen females and thirteen males between age group of 20-60 years were recruited after obtaining their written consent.

Ethical clearance

Ethical clearance for this study was obtained from the ‘Ethical Review Committee’, Post Graduate Institute of Science, University of Peradeniya, Sri Lanka.

Subjects were excluded if they reported a history of gastrointestinal disorders, suffered from diabetes, were taking medication for any chronic disease conditions, were pregnant, breastfeeding, or intolerant or allergic to any of the foods. Diabetes was excluded by history and fasting plasma glucose concentration [normal range of clinical diagnosis of diabetes level \(\geq 7.0 \text{ mmol/l} (13)\)].

Data on name, age, sex, ethnicity, location, marital status, education, occupation, family size, socio economic status, weight, height, blood pressure, pulse rate, dyslipidaemic conditions, alcohol consumption, smoking habits, fast foods consumptions and any other metabolic disorder were obtained through an interviewer administered questionnaire.

Anthropometry measurements

Height

Height was measured using a stadiometer and recorded to the nearest 10th of a centimetre with the
subject looking straight ahead and with the back against the vertical support of the instrument.

**Weight**

Weight was measured without shoes, on an eagle electronic platform weighing scale, standardised against a known weight every day.

**Blood pressure**

Blood pressure was measured in the seated position after the participants have rested for at least 5 minutes. The measurement was taken using the supported left arm at the heart level, using OMRON HEM 907 device (14).

**Design**

All thirty volunteers were served with eight menus consisting of white and brown rice flour string hoppers on eight different days. They were served with 4 different dishes either alone or in combination, which provided 7.5 g carbohydrate from curries. The portions of the string hoppers were calculated to provide 42.5 g carbohydrate. The dishes were typical Sri Lankan curries used with string hoppers for a morning meal or dinner. The four types of dishes were, ‘polsambol’ (Cocos nucifera) (grated coconut mixed with chillie powder, green chilli, onion and added salt for taste) with coconut gravy (coconut milk with turmeric, chilli powder, onion and salt for taste), legume curry (Phaseolus vulgaris) (beans cooked with plenty of gravy, which includes coconut milk, chilli powder, onion, turmeric powder and salt for taste), lentil curry (Lens culinaris) (made with Mysore dhal cooked with coconut milk and salt for taste) and fish curry [Indian scad] (Decapterus russelli) (fish cooked with coconut milk with added curry flavours and salt for taste). The food was professionally prepared in the expected quality and quantity according to the Sri Lankan menu. The portions were packed and marked with a set sign. Each serving contained 50 g of carbohydrates. Portion sizes were calculated to provide 50 g available carbohydrate (15).

**Determination of the GI**

The Glycaemic response and GI values of 8 food items were measured according to the WHO/FAO recommended methodology. Subjects attended each testing session after a 12 hour overnight fast, having been instructed not to consume unusually large meals, drink alcohol, exercise vigorously or smoking on the previous day, and to avoid cycling or walking to the laboratory (9). On the first three visits, subjects were given 50g glucose (State Pharmaceutical Corporation of Sri Lanka). Blood glucose was measured in capillary whole blood obtained by finger prick. The first blood sample was taken in the fasting state, and second sample was taken exactly 15 min after the first sip of the drink (13). Finger prick blood samples were done at 15 minute intervals in the first hour and at 30 minute intervals in the next hour after glucose intake. The average of three trials of reference food was calculated.

Meal 1, meal 2, meal 3, meal 4, meal 5, meal 6, meal 7 and meal 8 were given to the same individuals at, four days interval and blood samples obtained and estimated for blood glucose as mentioned above.

Data was analysed according to the method recommended by (FAO/WHO, 1998). The incremental area under the blood glucose response curves (IAUC,) for the test meals were calculated geometrically using the trapezoid rule, ignoring the area below the fasting baseline. For each test food, the IAUC, was expressed as a percentage of the mean IAUC, for the three repeats of the reference food consumed by the same subject.

GI of a test food is calculated with reference to 50g glucose (16).

\[
GI = \frac{\text{IAUC of test food}}{\text{IAUC of glucose}} \times 100
\]

The results were analysed using SPSS version 17.

**Results and Discussion**

This study is a part of an ongoing Sri Lanka diabetes diet study in which we are planning to study the glycaemic response of real life menus in normal subjects and patients with diabetes. In this study we have studied 30 healthy volunteers. Mean age and body mass index of the volunteers were 36 (±8.89) years, and 22.7 (±1.46) kgm² respectively. Characteristics of healthy volunteers in the study are shown in table 1.

**Table 1. Characteristics of healthy volunteers in the study**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean ± SE</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>Men/Women</td>
<td>13 / 17</td>
<td></td>
</tr>
<tr>
<td>Age [years]</td>
<td>36 ± 8.89</td>
<td>18.5-23.413</td>
</tr>
<tr>
<td>BMI [kg/m²]</td>
<td>22.7 ± 1.46</td>
<td>18.5-23.413</td>
</tr>
<tr>
<td>Pulse rate [min-1]</td>
<td>74.8 ± 3.92</td>
<td>60-90</td>
</tr>
<tr>
<td>Blood pressure systolic</td>
<td>112.2 ± 7.54</td>
<td>90-140</td>
</tr>
<tr>
<td>Blood pressure diastolic</td>
<td>75.6 ± 7.24</td>
<td>60-90</td>
</tr>
<tr>
<td>Fasting blood glucose</td>
<td>85.2 ± 8.26</td>
<td>&lt;126mg/dl</td>
</tr>
</tbody>
</table>

Sri Lanka Journal of Diabetes, Endocrinology and Metabolism
In this study, we have used white and brown rice flour string hoppers with 4 types of curries, making 8 menus. The curries used were coconut gravy milk with polsambol, lentil curry, fish curry and legume curry and 240 GI measurements were carried out in 30 volunteers. Each volunteer was given all menus, i.e.; 8 types of meals (white rice flour string hoppers with 4 types of curries and brown rice flour string hoppers with 4 types of curries as shown in Table 2). GI values of the meals ranged from 39 to 69. The white rice flour string hoppers with coconut gravy and polsambol and white rice flour string hoppers with fish curry elicited medium GI values of 69.20 ± 9.47, 56.13 ± 9.94 respectively (Table 2). Majority of the string hopper meals showed GI values<55. Brown rice flour string hoppers meals tested were found to have lower value of GI compared to white rice flour string hoppers. All white rice flour string hoppers tested had relatively high GI values except white string hoppers with beans curry (Table 2).

Paired T test was used (28 comparisons each consisting of 30 pairs) to see whether the differences of glycaemic index between two meals is statistically significant.

When we compared the brown rice flour string hoppers with addition of various curries, GI values varied. Though there are variations in GI values of various curries, only addition of legume curry has shown a significant reduction in GI. White rice flour string hoppers with various curries also show the same result with addition of legume curry showing a significant reduction in GI.

Moreover, of all the 8 meals, meal 1 (brown rice flour string hoppers with legume curry) and meal 8 (white rice flour string hoppers coconut gravy + polsambol) showed the lowest and highest GI respectively. The meal 3 (brown rice flour string hoppers with lentil curry) and meal 5 (brown rice flour string hoppers with fish curry) have similar GI. The addition of legume curry irrespective of whether it is white or brown rice flour significantly reduced the GI value compared to all other curries. Except the menu with bean curry, with all other curries there was no significant difference between the GI values whether it is white or brown rice flour. These results show that different types of rice flour have a similar GI, and adding various curries altered their GI, though statistically not significant, except with legume curry.

In Sri Lanka, many health professionals strongly recommend diabetes patients to use red rice and red rice flour for their meals, which is not palatable. This study shows that by adding high fibre containing vegetables to either red or white rice flour string hoppers, glycaemic index of that food could be significantly lowered and there is no difference between red and white rice string hoppers. This finding will be of value for patients who would like a diet that is palatable.

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There were two important studies in the recent past from Sri Lanka on glycaemic response of mixed meal (typical Sri Lankan food) in non-diabetes patients. Both studies showed that adding vegetables to meals significantly decreased the glycaemic response of the particular carbohydrate meal (5-7).

Pirasath et al (6) estimated the GI values of parboiled rice with green leaf curry (Amaranthus sp), parboiled rice with gravy and parboiled rice with green leaf curry and gravy and similar combinations of ‘kurakkan pittu’ and ‘atta pittu’ in healthy volunteers. They concluded that ‘kurakkan pittu’ is inferior to ‘atta pittu’ and parboiled rice, and adding curries to basic foods decrease the GI. They further indicated that the GI of the diet does not depend only on the type of the basic food but also on the side dishes consumed (7). From the results it can be concluded that glycaemic index of a mixed diet is influenced by the

<table>
<thead>
<tr>
<th>No</th>
<th>Type of meals</th>
<th>GI for meals Mean±SD (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meal 1</td>
<td>Brown rice flour string hoppers + beans curry (BSHB)</td>
<td>39.93 ± 8.14</td>
</tr>
<tr>
<td>Meal 2</td>
<td>White rice flour string hoppers + beans curry (WSHB)</td>
<td>4196 ± 9.86</td>
</tr>
<tr>
<td>Meal 3</td>
<td>Brown rice flour string hoppers + lentil curry (BSHL)</td>
<td>44.30± 9.25</td>
</tr>
<tr>
<td>Meal 4</td>
<td>White rice flour string hoppers + lentil curry (WSHL)</td>
<td>53.46 ± 9.57</td>
</tr>
<tr>
<td>Meal 5</td>
<td>Brown rice flour string hoppers + fish curry (BSHF)</td>
<td>45.26 ± 9.25</td>
</tr>
<tr>
<td>Meal 6</td>
<td>White rice flour string hoppers + fish curry (WSHF)</td>
<td>56.13 ± 9.94</td>
</tr>
<tr>
<td>Meal 7</td>
<td>Brown rice flour string hoppers + coconut gravy + polsambol (BSSHCSKH)</td>
<td>50.46 ± 9.74</td>
</tr>
<tr>
<td>Meal 8</td>
<td>White rice flour string hoppers + coconut gravy + polsambol (WSHCSKH)</td>
<td>69.20 ± 9.47</td>
</tr>
</tbody>
</table>
ingredients included in the curries. Therefore, when dietary advice is given to patients with diabetes and those at risk of coronary heart disease, the side dishes to the basic food must be considered. The lower GI value foods are better choices for these patients and they concluded that consumption of food containing fibre, significantly reduce the rise in blood glucose concentration and recommendation of the food should be made after analyzing the glycaemic index, glycaemic load and energy contents of the food.

Hettiaratchi et al (5) estimated the GI values of 5 common meals in Sri Lankan healthy individuals. This study was done with menus like red rice and coconut gravy; string hoppers made of wheat flour or rice flour with coconut ‘sambol’, egg, coconut gravy; manioc (Manihot esculenta) with coconut ‘sambol’; and red rice with lentil curry, Centella asiatica salad, egg, coconut gravy. This study showed that irrespective of the type of carbohydrate used, glycaemic index was high when eaten with only coconut gravy. When curries were added the glycaemic response significantly changed, giving lower glycaemic index.

Similar results were obtained in our study. Adding curries to basic foods altered the GI. Adding different curries to string hoppers made of white rice flour changed the GI values of the meals. Similar phenomenon was noted with string hoppers made of brown rice flour. Irrespective of the type of flour, adding bean curry significantly reduced the GI value of the food. Hettiaratchi et al (5) also concluded that, legume in the rice mixed meal decreases the GI value of the food. Hettiaratchi UPK, Ekanayake S, Welihinda J. Do Sri Lankan meals help decrease blood glucose response? Ceylon Medical Journal 2009; 54 (2): 39-42.


Martin CL, Murphy SP, Au DLM. Compiling glycaemic index and glycaemic load values for addition to a food composition database. Journal of Food Composition and Analysis 2008; 21(6): 469-73.


A study on prolactin abnormalities and male factor infertility using experimentally induced hyperprolactinaemia and hypoprolactinaemia in male rats

R Hasan


Abstract

Introduction: Male factor infertility due to endocrine disturbances has a prevalence of 1% amongst couples investigated for childlessness. Abnormalities in prolactin levels are encountered in a significant proportion.

Objective: To determine the effects of prolactin on the male reproductive tract in otherwise normal rats.

Methods: This case control study was carried out in the Faculty of Medicine, Karapitiya using 200 male white rats of Wistar strain. Six groups of rats with 30 in each group were maintained. The first group was the control group (G1). In the second group (G2) hypoprolactinaemia was induced using oral bromocriptine. The third group (G3) was made hyperprolactinaemic using oral chlorpromazine. The fourth (G4) and fifth (G5) groups were given subcutaneous injections of fluphenazine in a low dose and high dose respectively to induce hyperprolactinaemia. After 100 days 20 rats from each group were subjected to serum prolactin (PRL) level measurements using the Immulite® random access chemiluminescent immunoassay method and subsequent microscopic studies of their reproductive tract were carried out.

Results: The difference between serum PRL concentrations of rats in G2, G3, G4 and G5 as compared to the control group were highly significant by student’s t-test (p<0.001).

The microscopic studies of the male reproductive tract of rats in G2, G3, G4 and G5 show changes in spermatogenesis, concentration of spermatozoa, cellular arrangement within the seminiferous tubule, loss of microvilli and reduction in the luminal diameter.

Conclusion: Serum prolactin abnormalities result in significant changes in the male reproductive tract and spermatogenesis.

Key words: male factor infertility, prolactin, seminal fluid analysis

Introduction

Infertility is defined as the failure of a couple to conceive after at least 12 months of unprotected intercourse (1). Infertility could be due to male factors, female factors or a combination of both in infertile couples. Male factor infertility is prevalent in more than 50% of infertile couples (1). Male factor infertility could be either primary or secondary (1).

Infertility affects 10-15% of the world’s population with two million new couples with infertility being reported per year leading to immense psychosocial and personality problems in most cases (2, 3, 4, 5). The burden of the problem implies the need to broaden our understanding of the pathophysiology of infertility in order to develop efficient intervention and treatment.

The variety of causes of male factor infertility can be classified arbitrarily into pre testicular, testicular and post testicular causes (6). Other important causes are idiopathic spermatozoan abnormalities, infection of the male accessory reproductive glands namely the prostate, seminal vesicles, iatrogenic insults to the testicles such as testicular irradiation, antimitic medication, androgen therapy, use of anabolic steroids and antihypertensive medication, antibiotics and antipsychotic medication and
autoimmune causes (7). A link between male factor infertility and low sperm count has been described of which the exact mechanism of which is unknown (7).

The pre testicular causes accounts for up to 10% of male factor infertility and mainly includes hormonal factors. This signifies the roles of follicular stimulating hormone (FSH), leutinizing hormone (LH) and prolactin (PRL) produced by the anterior pituitary. Elevated levels of PRL have been shown to result in drastic inhibition of sperm production and its quality (7). Hypothalamo-pituitary hypo-function contributes to infertility in about 1% of cases (2).

Prolactin abnormalities can result from trauma, tumours in the pituitary gland, malfunction of the pituitary gland, chronic liver disease, thyroid dysfunction as well as genetic and chromosomal defects such as the Klinefelter syndrome (8).

Hyperprolactinaemia has been known to cause male factor infertility resulting in decreased libido and impotence. Treatment with bromocriptine to suppress the elevated PRL level has been very successful in reversing the condition and achieving a pregnancy. The role of PRL on the male reproductive tract has been shown in only a few studies and the exact role in male factor infertility remains unclear. Hence this study was carried out.

Morphological studies need to be carried out in order to clarify firstly, the exact role of PRL on the male reproductive tract and secondly, to establish how abnormal PRL levels in the male results in male factor infertility.

Methodology

This case control study was carried out in the animal house of the Faculty of Medicine, Karapitiya. The objective of this study was to determine the effects of prolactin on the male reproductive tract in otherwise normal rats and thereby to determine whether abnormality of PRL levels playa contributory role in male factor infertility. Ethical consent for this study was obtained from Ethical Review Committee, Faculty of Medicine, University of Ruhuna, Sri Lanka.

Male white rats belonging to the Wistar strain were obtained from the Medical Research Institute, Borella, Colombo and also from breeding carried out at the animal house, Faculty of Medicine, Karapitiya. 10 ± 2 week old rats weighing 200 ± 10 g in weight were maintained at a room temperature of 28 ± 4 degrees Celsius and fed with animal feed made of pellets obtained from Messers Moosajees Ltd, Colombo, for a period of 2 weeks. The quantity of feed and volume of water consumed by the rats was measured on a daily basis and data recorded. 200 male white rats belonging to the Wistar strain of 10 ± 2 weeks age were selected. Six groups of rats of 30 each were introduced and maintained in separately labeled cages. These groups were subjected to following procedures.

Group 1 (G1) – The 30 rats in this group were maintained under normal conditions at room temperature, in order to obtain a control value for the normal serum PRL level of rats.

Group 2 (G2) – The 30 rats in this group were fed with oral bromocriptine 4.65 mg per kg body weight per day in a divided dose given twice a day dissolved in 2 ml of distilled water. Another lot of 30 male white rats, age and weight matched, were fed with an equal volume of distilled water and served as a control. A daily chart of food intake, drugs intake, and fluid intake and body weights was maintained.

Group 3 (G3) – The 30 rats in this group were fed with oral chlorpromazine 10mg per kg body weight per day in a divided dose given twice a day, dissolved in 2 ml of distilled water. Another 30 male white rats, age and weight matched, were treated exactly as described in the control of the previous group.

Group 4 (G4) – The 30 rats in this group were treated with daily subcutaneous injections of fluphenazine in sesame oil in a dose of 0.42 mg per Kg body weight per day in a single daily dose given in the morning. The injections were administered using sterile plastic insulin syringes. A daily chart of food intake, drugs intake, and fluid intake and body weights was maintained.

Group 5 (G5) – The 30 rats in this group were treated identically as with group 4 except that the dose of fluphenazine was increased to 0.84 mg per Kg body weight per day.

Group 6 (G6) – The 30 rats in this group served as control for the rats treated with subcutaneous injections of fluphenazine in groups 4 and 5. They were given an equal volume of sesame oil as injections.

Hyperprolactinaemia was induced in the rats using oral chlorpromazine and subcutaneous injections of fluphenazine. Hypoprolactinaemia was induced in the rats using bromocriptine. The dosages of drugs used in the induction of experimental variations in serum PRL concentrations were obtained from the British National Formulary. The oral drugs were dissolved in measured volumes of distilled water and administered to the rats using a feeding tube.

After 100 days of treatment, of the 30 rats in each group, 20 were subjected to measurement of serum PRL concentrations and subsequent morphological studies were done by microscopic studies to assess the effects of PRL variations on the male reproductive tract.
Assessment of prolactin levels in rat serum

20 rats from each group were subjected to serum PRL assays by drawing 2ml of blood using sterile plastic disposable syringes under aseptic conditions. The PRL concentrations were measured using the chemiluminescent immunoassay method machine. The machine used in the study has sensitivity of 0.5ng/ml for PRL measurements. Many samples of rat serum would have PRL concentrations below this amount and would therefore not be read by the machine. In order to overcome this difficulty the procedure adapted was modified as follows.

100μl of rat serum was mixed with an equal volume of serum obtained from a male human volunteer with previously estimated PRL concentration. The mean value for serum PRL concentration of the donor sample obtained from 4 assays done on different days was 7.3ng/ml. Following the assays the concentration of PRL in the rat serum was determined by calculating the difference between the mean value and the value for the human serum alone.

A strict parallelism test involving recovery of added known quantities of rat serum PRL was not possible in this study due to the unavailability of the necessary rat hormone in pure form. To compensate for this, studies were carried out utilizing different volumes of rat serum (spiking recovery test).

Morphological studies of male reproductive tract of experimental rats

3 rats from each of the above 6 groups were subjected to light microscopic studies. Each rat was anaesthetized using ether. Their male reproductive tract was dissected and preserved in 10% formalin for 5 days. Sections of the testis, epididymis, vas deferens, seminal vesicles and prostate were obtained using a new razor blade from each of the rats sacrificed.

Another 3 rats from the above groups were subjected to light microscopic studies of the testes and epididymis by using Bouin’s fixative. These sections were then subjected to the preparation of tissues and stained with haematoxylin and eosin for light microscopic studies.

Results

As shown in table 1, the difference between the obtained values and corrected values for the serum PRL concentrations in the control group of rats was found to be highly significant by student’s t-test (p<0.001).

The differences between the experimentally obtained values as well as the corrected values for the serum PRL concentrations of the rats treated with bromocriptine as compared to the control group were highly significant by student’s t-test (p<0.001) (Table1).

| Table 1. Comparison of G1 with G2, G3, G4 and G5 |
|----------------|----------------|----------------|----------------|----------------|----------------|
| Group         | Body weight (g) | Average food intake per day (g) | Average fluid intake per day (ml) | Total serum PRL conc. (Obtained value (ng/ml)) | Serum PRL conc. (Corrected value (ng/ml)) |
|               | mean SD         | mean SD         | mean SD         | mean SD         | mean SD         |
| G1            | 287 7.8472      | 39.7 3.3419     | 30.9 2.0749     | 10.34 1.0013    | 3.04 1.0013     |
| G2            | 282.7 8.2914    | 39.1 2.6537     | 28.15 2.2775    | 8.1 0.5047      | 0.8 0.5047      | <0.001       |
| G3            | 287.6 9.6212    | 38.85 3.0483    | 28.5 2.5236     | 13.4 1.3518     | 6.1 1.3518      | <0.001       |
| G4            | 285.95 8.3444   | 39.45 2.5021    | 25.7 1.8945     | 19.31 2.5764    | 12.005 2.5804   | <0.001       |
| G5            | 286.75 8.9788   | 40 2.6754       | 26.65 2.2775    | 22.248 2.9539   | 14.948 2.9539   | <0.001       |

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Results of morphological studies are as follows.

**Figure 1a. Testicular tissue of control rat**
Section prepared from the upper pole of the testis. 
(H&E/LM × 132)
The normal cellular distribution around the periphery of the seminiferous tubules, which has been cut in section, is seen with numerous spermatogonia and spermatocytes. The lumen is filled with spermatozoa (a).
Elongated and round spermatids are seen in the tubule on the extreme right.

**Figure 1b. Testicular tissue of rat treated with oral bromocriptine**
Section prepared from the upper pole of the testis. 
(H & E/LM × 330)
Spermatogonia and numerous secondary spermatocytes are seen. Cellular debris and both round and elongated spermatids are seen within the lumen. Spermatozoa are hardly seen in this section.

**Figure 1c. Testicular tissue of rat treated with oral largactil**
Section prepared from the upper pole of the testis. 
(H & E/LM × 132)
Numerous elongated spermatids (a) and some cellular debris are seen within the lumen.
A few sperm heads (b) are also seen towards the periphery of the tubular lumen.

**Figure 1d. Testicular tissue of rat treated with a low dose of fluphenazine**
Section prepared from the upper pole of the testis. 
(H & E/LM × 132)
Section shows a Sertoli cell (a) with a few elongated spermatids attached to it. The rest of the Sertoli cells tend to be free of spermatids.

**Figure 1e. Testicular tissue of rat treated with a high dose of fluphenazine**
Section prepared from the upper pole of the testis. 
(H & E/LM × 330)
A high population of secondary spermatocytes (a) and a few elongated spermatids (b) are seen.
The differences between the experimentally obtained values as well as the corrected values for the serum PRL concentrations of the rats treated with chlorpromazine as compared to the control group were highly significant by student’s t-test (p<0.001) (Table1).

The differences between the experimentally obtained values as well as the corrected values for the serum PRL concentrations of the rats treated with a low dose of fluphenazine as compared to the control group were highly significant by student’s t-test (p<0.001) (Table1).

The differences between the experimentally obtained values as well as the corrected values for the serum PRL concentrations of the rats treated with a high dose of fluphenazine as compared to the control group were highly significant by student’s t-test (p<0.001) (Table1).

Discussion

This data demonstrates that experimentally generated altered serum prolactin levels are caused by the drugs bromocriptine, chlorpromazine and fluphenazine (Table 1). It is noteworthy that the rats subjected to experimental variations in their serum PRL do not differ in average daily food intake or fluid intake and average body weight gain, when compared controls, showing that the drugs used for bringing about artificial variations in the serum PRL did not have any effect on the metabolism of the rats maintained in the experiment (p>0.05).

Oral bromocriptine given in the dose administered induced a state of hypoprolactinaemia in the rats whereas oral chlorpromazine and subcutaneous injections of fluphenazine in the doses administered induced a state of hyperprolactinaemia. The degree of hyperprolactinaemia is affected by the dose of fluphenazine administered, with the increase in serum PRL levels being parallel with the dose of fluphenazine.

Morphological studies carried out under light microscopy demonstrate that abnormalities in PRL concentrations have a strong bearing on the process of spermatogenesis. Depending on the level of PRL variation, different stages of the spermatogenic cycle appear to be affected. These findings are corroborated by Negro-Vilar et al (9) who reported the existence of a relationship between alterations in endogenous PRL levels and testicular function in developing rats. However the latter have not reported conclusive findings with regard to the effect of abnormal PRL levels on the male reproductive tract in rats.

The results of the testicular studies show that spermatogenesis is affected at the spermatid stage formation, possibly due to damage to Sertoli cells. Under normal circumstances spermatids complete their maturation into elongated spermatids while being attached to the Sertoli cells.

However damage to Sertoli cells as in the case of this research experiment impairs this maturation process whereby incompletely mature spermatids are released into the lumen of the seminiferous tubule. It is possible that the spermatid binding to the Sertoli cell is impaired due to a membrane damage brought about by PRL abnormality. This needs further clarification by way of morphological studies on Sertoli cells including electron microscopic studies.

Experimentally induced hyperprolactinaemia appears to arrest spermatogenesis at a stage involving spermatid maturation. The extent of arrest appears to be dependent on the level of serum PRL level. For example in the hypoprolactinaemic rats there are more spermatids (mainly the elongated forms) than in the hyperprolactinaemic rats. Furthermore, cellularity is reduced in the testicular studies of hyperprolactinaemic rats when compared with the hypoprolactinaemic rats. The number of spermatozoa seen in the seminiferous tubules also appears to be reduced when compared to those in the control studies. This reduction is more marked in the hyperprolactinaemic rats when compared with the hypoprolactinaemic group.

Another interesting finding is that amongst the hyperprolactinaemic group of rats the results of the morphological studies show variations in the extent of damage to the male reproductive tract. Rats with very high PRL levels treated with higher doses of fluphenazine show morphological changes with far less spermatids (both the elongated and round forms) than in those rats with moderately high PRL levels (induced by oral chlorpromazine or subcutaneous injections of fluphenazine in a dose of 0.42 mg/kg body weight). Morphological findings in the latter group show more spermatids (both the round and elongated forms). The rats with very high PRL levels also have markedly lowered sperms within the lumen of the seminiferous tubules, the latter group also exhibiting a reduction in cellularity and the presence of more cellular debris within the lumen.

Morphological studies of the epididymis of the rats in each experimental group, showed a marked reduction in the microvilli of the epithelial lining, again showing a direct variation depending on the level of serum PRL of the rats. Additionally, the epididymal studies showed a reduction in the caliber of the tubule in the hyperprolactinaemic rats. Measurement of the tubular diameter showed a 30% reduction when compared with the normal tissue.

Light microscopy of the vas deferens, seminal vesicles and the prostate of rats with abnormal PRL levels and the control group demonstrates that PRL had no notable effect on any of these sites of the male reproductive
tract. These sites as have been noted earlier are merely a passage where secretions are added and serve as a conduit for the passage of sperms during ejaculation (10).

In summary, we demonstrate that a very high PRL level impairs spermatogenesis at or before spermatid formation resulting in a marked reduction of,

- Spermatid formation.
- Sperm counts.
- Cellularity of the seminiferous tubules.
- The number of microvilli in the epididymal epithelial lining.
- Caliber of the epididymis.

The above findings in the hyperprolactinaemic rats together with the appearance of cellular debris seen in testicular tissue suggest that hyperprolactinaemia impairs spermatogenesis in a dose dependent manner in the male. The possible site of damage is likely to be the Sertoli cells.

In addition to the findings of Charreau et al. (11) and Negro-Vilar et al. (9), our study demonstrates that prolactin exerts a direct effect both on the Sertoli cells and on the epididymal epithelium.

Study of the experimental rat model with drug induced abnormal PRL levels demonstrated an effect on the fertility potential by changes at different stages of the spermatogenic cycle. Morphological studies confirm that abnormal PRL levels cause a disruption of the spermatogenic cycle at a stage between the formation of secondary spermatocytes and the elongated spermatids. The exact locus of damage appears to be dependent on the level of the serum PRL concentration.

It is very likely that PRL abnormalities result in damage to the structural and functional integrity of the Sertoli cells of the seminiferous tubules thereby leading to disarrangement of the spermatogenic series of cells. It is probable that this leads to a variation in the size of the Sertoli cells which could result in damage to the intercellular junctional complexes of these cells. If this is so, it would have serious repercussions on the formation of the basal and luminal compartments of the epithelial lining of the seminiferous tubules resulting in damage to the blood testis barrier and thereby to the spermatogenic series of cells.

The site of damage in the spermatogenic cycle appears to be mainly at the secondary spermatocyte stage as the majority of tissue sections studied have shown that the cellular disarrangement is most marked at a stage after the formation of the secondary spermatocytes.

The resulting damage to the cellular integrity of the spermatogenic cycle results in the impairment of the output of spermatozoa. This became evident from the morphological studies carried out in the experiment. In most occasions only a few spermatozoa were observed in the lumen of the seminiferous tubules and thus in the lumen of the epididymis and vas deferens.

**Conclusion**

In conclusion it could be said that there appears to be a definite effect of the variations in the concentrations of the serum PRL both on the Sertoli cells of the testis and also on the epithelial lining of the epididymis in a dose dependent manner. These findings need further studies in order to ascertain the molecular level at which PRL affects these sites.

**Acknowledgement**

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**References**

Eating behaviours of adolescents with type 1 diabetes mellitus attending clinics in two Nigerian hospitals

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Abstract

Background/Aim: Eating behaviours are key determinants of glycaemic control in adolescents with type 1 diabetes mellitus but its pattern is poorly documented in Nigeria. This study was done to assess the eating behaviours of adolescents with type 1 diabetes mellitus attending clinics in two Nigerian hospitals and compare the results with those of their non-diabetic peers.

Methods: The study compared the eating behaviours of 20 adolescents with type 1 diabetes mellitus with those 20 age- and sex-matched non-diabetics peers. Using a semi-structured interviewer-administered questionnaire, information was obtained on the number of meals eaten every day, habit of skipping meals, the skipped meals, reasons for skipping meals and the frequency of consumption of local Nigerian foods and fruits.

Results: Boiled cocoyam, boiled unripe plantain and beans were the three leading food items consumed by adolescents with diabetes mellitus. Consumption of fruits such as carrot, cucumber and egg plant was more popular among adolescents with diabetes than among their peers without diabetes. The frequency of consumption of fruit juice and sugar-sweetened soft drinks was higher in the controls compared with adolescents with diabetes. Over half (55.0%; 95% CI=50.1-59.9) of the adolescents with diabetes mellitus admitted skipping breakfast and consequently, skipping insulin administration. The reasons for skipping meals included lack of appetite and time in the morning, dislike for available food items at home and being angry with parents.

Conclusion: Skipping of meals associated with skipping of insulin administration was the unhealthiest eating behaviour exhibited by adolescents with diabetes mellitus. Factors that influenced skipping of meals included family food insecurity and psychosocial issues.

Key words: adolescents, eating behaviour, Nigerians, type 1 diabetes mellitus.

Introduction

Adolescence is the transitional phase of development between childhood and adulthood. It is associated with deterioration of metabolic control in individuals with diabetes mellitus (2, 3). Erratic meal and exercise patterns, poor adherence to treatment regimens, hazardous and risk-taking behaviours, eating disorders and endocrine changes associated with puberty adversely affect metabolic control among adolescents with diabetes. Nutritional management is one of the cornerstones of diabetes care and education (2). Cultural factors and socioeconomic status influence the dietary habits of individuals (4). The presence of diabetes mellitus influence eating behaviours and cause psychological disturbances (4). Knowledge of the pattern of eating behaviours in the given population is essential to effective advice on dietary and lifestyle changes in individuals with diabetes mellitus. It is widely accepted that diabetes cannot be successfully managed without behavioural modification (5). Diabetic patients need to focus on diet and limit weight gain as part of their medical regimen. They are often asked to limit or avoid particular foods, especially simple carbohydrates and/or fats and must consistently stick to regular mealtimes so as to coordinate insulin with blood glucose changes. This pronounced emphasis on weight, diet, and food may render adolescents with type 1 diabetes mellitus (T1DM) vulnerable to the development of disordered eating behaviour. Habitual dietary restraint has been consistently

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associated with binge eating severity in school populations (6). Wooley and Wooley in their study concluded that once any degree of overconcern with food and weight develops, disordered eating patterns almost inevitably follow (7).

The issue of abnormal eating pattern is particularly relevant in individuals with T1DM, where even occasional (presumably normal) binge episodes may worsen glycaemic control (5). Eating disorders in patients with diabetes mellitus is of particular concern in adolescents because of their association with poor glycaemic control, noncompliance with medical nutrition therapy (MNT) and increased risk of diabetes-related complications (8-10). Some studies suggest that the essential elements of successful MNT might lie in the food choices that are made, such as limitation of carbohydrate rather than limitation of energy intake (11). Adolescents with diabetes need special help in learning to eat and drink in social situations with a view to minimizing feelings of being different. Studies have reported that the prevalence of disturbed eating behaviour in individuals with T1DM range from 10% to 49% (12, 13). Some eating problems seen as relatively mild or insignificant in non-diabetic patients can give rise to a clinically important disturbances of self-care and glycaemic control in T1DM (14).

The purpose of the present study was to describe the eating behaviours of adolescents with diabetes mellitus attending clinics in two Nigerian hospitals in Benin City and compare the results with non-diabetic peers.

**Subjects and methods**

The study involved adolescents (aged 10-19 years old) with type 1 diabetes mellitus who were attending the Paediatric Endocrine-Metabolic Clinic of the University of Benin Teaching Hospital (UBTH) and the General Paediatric Clinic of St Philomena Catholic Hospital (SPCH), Benin City between July, 2013 and March, 2014. The controls were non-diabetic adolescents matched for sex and age, attending clinics in the two hospitals. The controls had no medical nutritional issues and were not on any prescribed diet. Ethical approval was obtained from the Research and Ethics Committee of UBTH and permission to conduct the study was obtained from the hospital authority of SPCH. The data were obtained using a semi-structured interviewer-administered questionnaire. To allow for uniformity, the interview was conducted by one of the authors (ANO). The questionnaire was divided into two parts: the first part sought information on socio-demographic data, such as age of participants, the number of people in the household, educational status and occupation of parents, religion and state of origin. The socio-economic status (SES)of the parents was determined, using the classification suggested by Olusanya et al (15). Thus, they were classified into five classes (classes I and II into high, class III into middle and classes IV and V into low social class). The family size was categorized into small (no sibling or one or 2 siblings); medium (3 or 4 siblings); large (5 or more siblings). The second part of the questionnaire consisted of questions relating to eating behaviours, such as number of meals eaten every day, habit of skipping meals, the skipped meals and reasons for skipping meals. Meal skipping was assessed by asking the participants how often over the past two weeks they had skipped breakfast, lunch and dinner. The habit of skipping meals was assessed by questions on frequency of skipping meals: those who answered “yes” or “sometimes” were regarded as skippers while those who answered “no” were regarded as non-skippers. The number of days meals were skipped per week was noted. The questionnaire included food frequency questions on diet-related behavior on consumption of local Nigerian foods such as rice, beans, yam, cocoyam, unripe plantain, bread, fruits, vegetables, ice cream and the use of canned fruit juice and sugar-sweetened soft drinks. The subjects were categorized into three age groups: early adolescence, 10-13 years; middle adolescence, 14-16 years; and late adolescence, 17-19 years.

**Statistical analysis**

Where applicable and appropriate, descriptive statistics such as frequencies, means, ratios, standard deviations, confidence intervals, percentages were used to describe all the variables.

**Results**

We interviewed 40 (20 diabetic and 20 non-diabetic) adolescents attending clinics in the two hospitals. The 20 diabetic participants consisted of 9 boys and 11 girls. Of 40 participants, 80.7%, 16.8% and 2.5% were from Christian, Muslim and Traditional religion families respectively. Based on state of origin and religion, the eating pattern did not differ. The mean age of all the participants was 14.8±1.9 years (95% Confidence Interval, CI=14.7-14.9). The socio-demographic characteristics of the participants are depicted in Table 1. Half of the participants (50.0%) were aged between 14-16 years. Majority of the participants (83.2%) lived with family members and over two-thirds (69.7%) in households with five to seven members. Nearly half (48.9%) of the participants were from families of middle socio-economic status. All the diabetics had type 1 diabetes and were on pre-mixed twice daily insulin regimen. The types of dietary practices by the participants are displayed in Table 2, with cocoyam, boiled unripe plantain and beans being the most frequently consumed food items among the diabetic
A study on Prolactin

subjects compared to rice, yam and eba (a cassava dough) among the non-diabetics. The frequency of consumption of fruit juice and sugar-sweetened soft drinks was lower in diabetics compared with the controls. No single food item was consumed daily. Some of the food items are consumed in the school without the knowledge of parents. Both diabetic (50.0%) and non-diabetic (75.0%) participants eat bread or consume garri (dry grounded cassava product) soaked in cold water when hungry before the next meal was due, 2-3 times a week. As shown in Table 3, over half (55.0%) of adolescents with diabetes skipped breakfast. The leading reasons cited for skipping breakfast were as follows: lack of appetite in the morning, diabetic 6 (30.0%) versus non-diabetic 9 (45.0%); lack of time, diabetic 5 (25.0%) versus non-diabetic 7 (35.0%). The reasons for skipping lunch/dinner were because they did not like available food, diabetics 8 (40.0%) versus non-diabetic 6 (30.0%); or were angry with mother/father, diabetics 10 (50.0%) versus non-diabetic 6 (30.0%). All the diabetic participants skipped administration of their insulin any time they skipped their meals. As depicted in Table 4, adolescents with diabetes in the age group of 14-16 years tended to skip meals more frequently than the other adolescent age groups. In addition, the frequency of skipping meals increased with age among adolescents without diabetes. Fifteen (75.0%) of the 20 adolescents with diabetes and 12 (60.0%) of their non-diabetic peers reported that the food item they would have liked to eat was not available most of the time. The family gathered together for meals in 25.0% and 20.0% of cases in diabetic and non-diabetic participants respectively, with father being the most frequently missing member.

Table 1. Distribution of age groups, socioeconomic status (SES), family size, and occupation in diabetic and non-diabetic participants

<table>
<thead>
<tr>
<th>Age groups</th>
<th>Diabetic participants (n=20)</th>
<th>Non-diabetic participants (n=20)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No (%)</td>
<td>No (%)</td>
</tr>
<tr>
<td>Early adolescents (10-13 years)</td>
<td>6 (30.0)</td>
<td>6 (30.0)</td>
</tr>
<tr>
<td>Middle adolescents (14-16 years)</td>
<td>10 (50.0)</td>
<td>10 (50.0)</td>
</tr>
<tr>
<td>Late adolescents (17-19 years)</td>
<td>4 (20.0)</td>
<td>4 (20.0)</td>
</tr>
<tr>
<td><strong>Socioeconomic status (SES)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High SES</td>
<td>4 (20.0)</td>
<td>5 (25.0)</td>
</tr>
<tr>
<td>Middle SES</td>
<td>9 (45.0)</td>
<td>11 (55.0)</td>
</tr>
<tr>
<td>Low SES</td>
<td>7 (35.0)</td>
<td>4 (20.0)</td>
</tr>
<tr>
<td><strong>Family size</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Small</td>
<td>2 (10.0)</td>
<td>4 (20.0)</td>
</tr>
<tr>
<td>Medium</td>
<td>14 (70.0)</td>
<td>12 (60.0)</td>
</tr>
<tr>
<td>Large</td>
<td>4 (20.0)</td>
<td>4 (20.0)</td>
</tr>
<tr>
<td><strong>Current occupation</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Student (attending school)</td>
<td>12 (60.0)</td>
<td>13 (65.0)</td>
</tr>
<tr>
<td>Non student (not attending school)</td>
<td>3 (15.0)</td>
<td>3 (15.0)</td>
</tr>
<tr>
<td>Apprentice artisan</td>
<td>5 (25.0)</td>
<td>4 (20.0)</td>
</tr>
</tbody>
</table>
**Table 2. Frequency of consumption of some food items among diabetic and non-diabetic participants**

<table>
<thead>
<tr>
<th>Food items</th>
<th>Frequency of consuming different food groups per week</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Diabetic participants (n=20)</td>
</tr>
<tr>
<td></td>
<td>4-6 times/wk</td>
</tr>
<tr>
<td></td>
<td>No (%)</td>
</tr>
<tr>
<td>Cassava-based food items</td>
<td>5 (25.0)</td>
</tr>
<tr>
<td>Rice</td>
<td>7 (35.0)</td>
</tr>
<tr>
<td>Yam</td>
<td>5 (25.0)</td>
</tr>
<tr>
<td>Boiled unripe plantain</td>
<td>14 (70.0)</td>
</tr>
<tr>
<td>Boiled cocoyam</td>
<td>17 (85.0)</td>
</tr>
<tr>
<td>Bread</td>
<td>9 (45.0)</td>
</tr>
<tr>
<td>Beans</td>
<td>15 (75.0)</td>
</tr>
<tr>
<td>Fried foods</td>
<td>7 (35.0)</td>
</tr>
<tr>
<td>Sugar-sweetened soft drinks</td>
<td>2 (10.0)</td>
</tr>
<tr>
<td>Canned fruit juice</td>
<td>2 (10.0)</td>
</tr>
<tr>
<td>Fruits (carrot, cucumber, egg, plant, apple)</td>
<td>16 (80.0)</td>
</tr>
<tr>
<td>Other fruits (oranges, pine apple, banana)</td>
<td>5 (25.0)</td>
</tr>
<tr>
<td>Vegetables</td>
<td>14 (70.0)</td>
</tr>
<tr>
<td>Ice cream</td>
<td>3 (15.0)</td>
</tr>
</tbody>
</table>

**Table 3. Frequency of skipping main meals among diabetic and non-diabetic participants**

<table>
<thead>
<tr>
<th>Main meals</th>
<th>Diabetic participants</th>
<th>Non-diabetic participants</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No (%)</td>
<td>No (%)</td>
</tr>
<tr>
<td>Breakfast</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skippers</td>
<td>11 (55.0)</td>
<td>15 (75.0)*</td>
</tr>
<tr>
<td>Non skippers</td>
<td>9 (45.0)</td>
<td>5 (25.0)</td>
</tr>
<tr>
<td>Total</td>
<td>20 (100.0)</td>
<td>20 (100.0)</td>
</tr>
<tr>
<td>Lunch/Dinner</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skippers</td>
<td>8 (40.0)</td>
<td>14 (70.0)</td>
</tr>
<tr>
<td>Non skippers</td>
<td>12 (60.0)</td>
<td>6 (30.0)</td>
</tr>
<tr>
<td>Total</td>
<td>20 (100.0)</td>
<td>20 (100)</td>
</tr>
</tbody>
</table>

*Some respondents skipped more than one main meal.
Discussion

Findings of our study are similar to a previous study (16) in that adolescents with diabetes mellitus have modified some of their eating behaviours according to recommendations – fewer frequency of consumption of fruit juice and sugar-sweetened soft drinks and consumption of low calorie-containing fruits such as carrot, cucumber and egg plant compared with their peers without diabetes. In individuals with diabetes, healthy eating practices are advised to attain optimal glycaemic control and minimize its variability (17), reduce weight gain and cardiovascular complications (18).

We found that meal skipping is the unhealthiest dietary practice in the majority of diabetic adolescents. A previous study has reported that skipping breakfast significantly decreased daily energy and nutrient intake (20). Studies have also linked skipping of meals with occurrence of overweight and obesity (21, 22), augmenting several diabetes-related complications. The additional presence of obesity in an adolescent with diabetes mellitus fuels the occurrence of complications. Families gathered together for meals, only in a quarter of cases in adolescents with diabetes. This observation is disappointing because it has been shown that eating together in a family gathering, help in establishing better eating practices and monitoring of food intake including portion size and this has been associated with a better glycaemic control (23).

Consistent with the result of a study in Turkey (24), the leading reason cited by the participants in our study for skipping breakfast was lack of appetite and time. This finding is worrisome because breakfast has been tagged the most important of all the three main meals (20). The reasons cited by participants in this study for skipping lunch/dinner were because of lack of desired food item at home or being angry with parents. Non-availability of food at home that is appealing to the appetite of the adolescent bothers on family food insecurity. Effective access to a variety of local food is essential for a successful medical nutrition therapy (MNT). The issue of being angry with parents is a reflection of psychosocial interactions that could influence adherence to the recommendations of MNT.

Over four-fifth and two-thirds of adolescents with diabetes consumed cocoyam and unripe plantain daily compared with one-tenth and one-fifth of their peers without diabetes. Nutritional analysis indicate that cocoyam has a high fibre content and a low glycaemic load (25), implying that it is a healthy food item for adolescents with diabetes. Similarly, boiled unripe plantain is rich in low glycaemic index carbohydrates, dietary fibre, iron, vitamins and minerals, making it a suitable food item for adolescents with diabetes (26). These two food items are cheap and readily available in Nigeria. However, metabolic studies have shown that the glycaemic responses to different carbohydrates consumed by individuals with diabetes were identical (27, 28). This might mean that the high fibre, mineral and vitamin content of these two food items is what is more important. Studies have shown that supplementation of diets with fibre resulted in improvement in glycaemic control and lipaemic profiles in individuals with diabetes (29). In a study that tested the glycaemic index of Nigerian foods, beans had the most desirable glycaemic index. However, the investigators cautioned that the total caloric intake was the most important issue and whatever food that is consumed by the diabetic (including beans) must be accommodated within the prescribed daily caloric allowance (31). Caution need to be exercised in extrapolating the findings of our study to the whole country because of the cultural differences within our country. Cultural practices influence dietary choices in

Table 4. Frequency of skipping meals according to age among diabetic and non-diabetic participants

<table>
<thead>
<tr>
<th>Age group</th>
<th>Diabetic participants (n=20)</th>
<th>Non-diabetic participants (n=20)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No skipping meal (%)</td>
<td>No skipping meal (%)</td>
</tr>
<tr>
<td>10-13 years (n=6)</td>
<td>2 (33.3)</td>
<td>10-13 years (n=6)</td>
</tr>
<tr>
<td>14-16 years (n=10)</td>
<td>6 (60.0)</td>
<td>14-16 years (n=10)</td>
</tr>
<tr>
<td>17-19 years (n=4)</td>
<td>2 (50.0)</td>
<td>17-19 years (n=4)</td>
</tr>
</tbody>
</table>
any given population (32). Some of the differences may be due to dietary advice given to the diabetic group.

In conclusion, our study found that skipping of meals and subsequent insulin administration was the unhealthiest eating behaviour exhibited by adolescents with T1DM in Nigeria.

References


Abstract

Thalassaemia is the commonest genetically transmitted disease in the world and it is due to mutations in the genes encoding the alpha or beta globins causing defective haemoglobin synthesis. Beta thalassaemia Major, the commonest variety of the disease is associated with a significant morbidity and mortality. Endocrine complications associated with thalassaemia play a significant role in the quality of life of these patients. Iron overload, due to multiple blood transfusions and increased iron absorption from the intestine causes excess iron deposition in many organs including endocrine organs and are responsible for most of these complications. Although, chelation therapy is always combined with blood transfusions, suboptimal chelation leads to deposition of iron in these organs causing endocrine disorders. Hypogonadotrophic hypogonadism is considered to be the commonest endocrinopathy in patients with thalassaemia. Other complications such as growth hormone deficiency, delayed puberty, hypothyroidism, hypoparathyroidism, diabetes mellitus, osteoporosis and adrenal insufficiency are also not uncommon. Therefore, it is important that these patients are screened for these complications regularly at appropriate ages and treat accordingly and it is important to have a multidisciplinary approach in following up these patients.

Introduction

Thalassaemia is the commonest monogenic, genetically transmitted disease in the world. It is a hereditary anaemia due to defective haemoglobin synthesis resulting around 240,000 infants born annually with major haemoglobinopathies and at least 190 million carriers worldwide (1). It was first reported among children around the Mediterranean Sea. However, with the population migrations, the condition has spread to parts of Africa and the Mediterranean region, the Middle East, the Indian subcontinent, and Southeast Asia. Although this condition is prevalent in Sri Lanka, the exact figure is not known. It is estimated from gene frequencies that there are more than 2000 patients requiring treatment at any one time, in Sri Lanka (2).

Management of thalassaemic patient is a challenging task and the management of endocrine complications needs specialized care. A study which looked at the prevalence of endocrine complications among 3817 thalassaemia patients around the world has shown endocrine complications such as short stature (in 31.1% of males and 30.5% of females), growth hormone deficiency (in 7.9% in males and 8.8% in females), delayed puberty (in 40.5%), hypoparathyroidism (in 6.9%), impaired glucose tolerance (in 6.5%), insulin-dependent diabetes mellitus (in 3.2%) and primary hypothyroidism (in 3.2% of patients) (3).

Pathophysiology

Normal adult haemoglobin (HbA) consists of a tetramer, made up of two alpha-globin and two beta-globin subunits. The two major types of thalassaemia, alpha and beta are named accordingly due to the defects in these protein chains. Beta Thalassaemia being the commonest variety is due to complete or near-complete lack of beta-globin, leading to transfusion-dependent severe anemia. Compared to $\beta$ Thalassaemia Major, $\beta$ Thalassaemia Intermedia, $\beta$ Thalassaemia Minor, E/$\beta$ Thalassaemia, S/$\beta$ Thalassaemia and D/$\beta$ Thalassaemia are milder forms of $\beta$ Thalassaemia varieties.

When there is absence or defective synthesis of either alpha or beta globin chains, there will be an excess of either of these globin chains, leading to precipitation of the excess globin in erythroid precursors. This in turn will lead to, red cell membrane damage causing red cell destruction leading to anaemia and compensatory erythroid hyperplasia. Both ineffective erythropoiesis and anaemia will result in down-regulation of expression of hepcidin. It is a small peptide that inhibits iron absorption in the small intestine. In spite of having elevated iron stores in thalassaemia, the reduced expression of hepcidin leads to increased iron absorption from the intestine causing iron overload. This is thought to be the reason as to why iron overloading is seen even in the minimally transfused patients with thalassaemia. Initially, the excess
iron is sequestered in the cells of the monocyte-macrophage system. However, with the continued accumulation, monocyte-macrophage system get saturated and the excess iron get deposited in the liver, heart, pancreas, and endocrine organs such as pituitary, thyroid, parathyroid and adrenal glands leading to tissue toxicity (4, 5). Iron overloading in endocrine organs leads to cellular dysfunction, cytotoxicity and ultimately cellular death. Apart from iron overload, chronic hypoxia and viral infections are also thought to play an important role in endocrine dysfunction of these patients (6). Commonly encountered endocrine complications are growth hormone deficiency, delayed puberty, hypogonadotrophic hypogonadism, hypothyroidism, hypoparathyroidism, diabetes mellitus, osteoporosis and adrenal insufficiency.

**Evaluation and management**

**Growth assessment and growth hormone (GH) deficiency**

Growth retardation or failure is commonly seen in patients with thalassaemia and the causes are multifactorial. Usually, this is attributed to the chronic anaemia, iron overload, and chelation toxicity. However, co-existing factors like hypothyroidism, GH deficiency, hypogonadism, zinc deficiency, chronic parenchymal liver disease, poor nutrition, and psychosocial stress contribute to this problem (6) and need to be evaluated and treated properly.

Growth of a patient is assessed by plotting weight, height and head circumference (during first 2 years of life) in a standard growth chart and calculating the annual growth velocity (GV) and the mid parental height (MPH). The average height velocity varies at different developmental phases (6).

- **Infancy:** 23-28 cm/year
- **Childhood:** 5-6.5 cm/year
- **Puberty:** 8.3 cm/year (girls), 9.5 cm/year (boys)

A child is considered short if any one of the following is seen (6).

- Height is less than the 3rd percentile or 2 SD below the mean height for age and sex.
- Height is within normal but GV is consistently <25th percentile over 6 - 12 months.
- Excessively short for his or her MPH.

Annual screening for endocrine related growth evaluation should be started at the age of 9 years. However, earlier screening can be considered if indicated. Significant GH deficiency can be diagnosed by impaired response of GH stimulation in two different occasions with two provocative tests or reduced response of GH in one test plus low IGF-I and IGFBP3 concentrations. Interpretation of IGF-I levels needs careful consideration in the context of malnutrition and chronic liver disease in patients with thalassaemia.

Serum free T4, TSH, 9 am cortisol and bone age assessments are also essential in the evaluation of short stature. MRI of the pituitary gland is useful in evaluating iron overload and size of the pituitary.

Although children with GH deficiency are recommended recombinant GH (rhGH) treatment (6, 7), there are no clear guidelines for the rhGH treatment in adult GH deficient patients with thalassaemia. Recombinant GH is given 0.025-0.05 mg/kg/day (0.5-1.0 units/kg/wk) subcutaneously daily at night and it is started with low doses and titrated according to clinical response.

**Hypogonadism**

Iron deposition in the pituitary gland leads to pituitary hormone deficiencies. Impaired production of gonadotrophins is the commonest endocrine complication encountered in patients with thalassaemia, which will lead to hypogonadotrophic hypogonadism (HH) as well as delayed and arrested puberty. Most of the well-chelated patients have normal gonadal function. Occasionally, gonadal iron deposition can occur, leading to primary gonadal failure.

Delayed puberty in girls is defined as complete lack of pubertal development by the age of 13 years and in boys by the age of 14 years. Hypogonadism in boys is defined by the absence of testicular enlargement (less than 4 ml) and in girls by the absence of breast development by the age of 16 years (10). Arrested puberty is characterized by the lack of pubertal progression over a year or longer. Tanner staging should be determined every 6 months, starting from the age of 12 years. Girls without evidence of puberty by 13 years and boys by 14 years will need a hormonal assessment that includes serum LH, FSH, and estradiol or testosterone. Pelvic ultrasound scan can also be carried out in females to determine the uterine and ovarian maturation.

Treatment of delayed puberty needs a multidisciplinary approach. In boys, treatment is usually initiated with IM depot testosterone in doses of 50-100 mg per month. This is followed by clinical and hormonal reassessment every 3 months. In patients with hypogonadotrophic hypogonadism, low dose testosterone therapy (50 mg) can be continued until the growth rate wanes. However, for proper virilization, 75-100 mg of IM depot testosterone every 10 days may be required (6).

Treatment for girls can be initiated with the oral ethinyl estradiol (EE) 2.5-5 ug daily for 6 months, followed by clinical and hormonal reassessment. If spontaneous
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puberty does not occur within 6 months after stopping the treatment, oral estrogen is re-introduced with higher doses of EE (5 to 10 ug daily) for another 12 months and to 20 ug for additional 12 months. Once EE reaches 20 ug/day or if breakthrough bleeding occurs, norethisterone or medroxyprogesterone acetate 5 mg/day from the day 10-21 and EE for 21 days should be taken (6).

Hypothyroidism

Primary hypothyroidism is commoner than secondary hypothyroidism in patients with thalassaemia (8, 9). Annual screening for hypothyroidism with serum TSH and free T4 should be obtained from 9 years of age if detected to be mild or overtly hypothyroid, Levo-thyroxine treatment is initiated. Patients with subclinical hypothyroidism need regular monitoring and optimization of chelation therapy (11, 12).

Hypoparathyroidism

Hypoparathyroidism in thalassaemia is mainly due to iron deposition in the parathyroid glands. However, the suppression of parathyroid secretion can occur due to the increased bone reabsorption with increased hematopoiesis secondary to the chronic anaemia. This complication is usually seen after 16 years of age. The majority has mild disease and severe hypocalcaemia is rare (13). The diagnosis is based on low serum calcium, high phosphate and low PTH levels.

Diet rich in calcium and low in phosphorus is advised to these patients and the deficiency is treated with calcitriol (0.25-2.0 ug/day) and calcium (1 g of calcium per day) with frequent monitoring of serum and urine calcium levels (6).

Diabetes mellitus (DM)

DM in thalassaemia has multiple causes and includes genetic factors, insulin deficiency, insulin resistance, and liver dysfunction due to viral hepatitis. Insulin-dependent diabetes in these patients has some unusual characteristics compared with type 1 diabetes and they are,

• Ketoacidosis is a rare presenting symptom
• Renal glucose threshold is high
• Islet cell antibodies are negative
• There is no association with HLA haplotypes B8-DR3, BW15, and DR4 (6).

Diabetes mellitus is seen after the age of 10 years, therefore monitoring for blood glucose levels are indicated from this age. A 2 hour oral glucose tolerance testing (OGTT) should be performed at 10, 12, 14, and 16 years of age and annually thereafter. If fasting serum glucose is >110 mg/dl, OGTT is performed (6). HbA1C is dependent on normal hemoglobin concentration and usage of HbA1C for diagnosis and monitoring has limitations in thalassaemia. Altering of the normal process of glycation of HbA to HbA1C causing an abnormal peak on chromatography, making estimation of A1C unreliable (14).

Insulin should be initiated, when the diagnosis of DM is confirmed and the benefits of oral hypoglycemic agents are undetermined.

These patients also should be screened for end organ damage similar to other patients with diabetes. However, retinopathy and nephropathy are less documented in these patients and is thought to be due to absence of dyslipidaemia and commonly co-existing hypogonadism (14).

Bone disease (osteopenia and osteoporosis)

Aetiology of bone mineral loss in thalassaemia is multi-factorial (15). Medullary expansion due to anaemia, patient age, and duration of the disease, chronic liver disease, vitamin D deficiency, hypogonadism and hypothyroidism are the main causes. Osteopenia and osteoporosis are the commonest bone diseases encountered in these patients (16).

Bone profile (serum calcium, phosphorus, alkaline phosphatase) should be obtained and 25-hydroxy vitamin D and parathyroid hormone level should be carried out, if indicated. Dual-energy X-ray absorptiometry (DEXA) needs to be done to assess the bone mineral density. Standard cut off values are used to for the diagnosis.

• Bone density T-score >1.5 SD below the mean - osteopenia
• Bone density T-score >2.5 SD below the mean - osteoporosis

Diagnosis of osteoporosis in children requires the presence of both a clinically significant fracture history and low bone mineral density. DEXA should be performed at 10-12 years for girls and boys annually and every 2 years thereafter.

Thalassaemia patients should be supplemented with calcium 500-1000 mg/day starting at age 12 years and vitamin D 400-800 units/day for patients with low levels or those at high risk to develop vitamin D deficiency. For patients with established osteoporosis, treatment with bisphosphonates should be considered (16).

Adrenal insufficiency

Iron overload has the potential to disrupt adrenal function by affecting the hypothalamic-pituitary adrenal axis at the hypothalamic or pituitary and/or adrenal level. However, clinical adrenal insufficiency such as an adrenal crisis is extremely rare (17).
Measurement of both basal 9 a.m. serum cortisol and cortisol response to stimulation by ACTH or insulin stimulation (ITT) is used for assessment of adrenal function. Adrenal function should be tested every 1-2 years, especially in growth hormone deficient patients during rhGH therapy.

Patients with subclinical impairment of adrenocortical function should be advised to have the steroid cover during the stressful situations (17).

Conclusion

Multiple endocrine complications in thalassaemia warrant a comprehensive approach in their management. Intensive chelation therapy has shown to reverse some of the endocrine complications such as diabetes, hypothyroidism and hypogonadism (18). Each patient should be evaluated separately and treatment should be individualized and tailor made as regimented approaches are usually unsuccessful. Aim of treatment is to provide the best quality of life, as much as possible to these patients, who are victims of a genetic disorder.

References

Surgery for obesity and “metabolic syndrome” in Asia
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Obesity and associated complications are increasing at an alarming rate in South Asia. The relatively higher incidence of central obesity, increasing incidence of type 2 diabetes, hypertension, coronary heart disease and fatty liver disease makes obesity a significant risk factor associated with high morbidity and early mortality in our region. The increasing trend of childhood obesity is also alarming (1).

It is proven beyond doubt that bariatric surgery is the most effective option in treating morbid obesity with sustained weight reduction and reversal of associated morbidities (8). The field of bariatric and metabolic surgery has shown considerable improvements and development all over the world with new surgical procedures being developed constantly to make this a safe, acceptable and durable treatment option for obesity and metabolic syndrome. The main new trends in the advances of surgical field are making surgery total laparoscopic (or even endoscopic), limiting usage of severe malabsorptive procedures and designing new procedures which cause minimal long term nutritional issues. This is achieved by adding a restrictive procedure to almost all surgeries and increasing usage of pure restrictive procedures for low risk patients. Recommendations on various types of operations are emerging for different target populations.

Obesity and metabolic surgery in south Asia – what is the difference?

The obesity in south Asia has become a separate clinical issue for the bariatric specialists and researchers in the field. Asia Pacific region is exposed to the most rapid socioeconomic and lifestyle changes with resultant effects on calorie imbalance, Today 31 million adults in China are found to be obese with many South Asian countries such as India, Pakistan and Sri Lanka showing adult obesity prevalence over 20%. The rapidly increasing incidence of diabetes and “metabolic syndrome” in the region has led to the coining of the new term “diabesity”. Highly imbalanced diet with excess refined carbohydrates, fast foods and too rapid change of lifestyle to a sedentary one with low physical activities are recognized as main contributing factors for this explosive increase in adult and childhood obesity. In making recommendations on type of operations suitable for the region, these factors have been taken into account (2).

Selecting a patient for a surgical procedure has to be done with much more caution than in the west. Although indicated medically, these procedures should not be offered to anyone who requests or gets referred to the surgeon. The concept of metabolic and bariatric surgery is still novel to our region and morbid obesity is still not considered a disease entity even by some of the medical professionals. Surgical complications are highly sensitive issues in this field and a single death can shut down an established bariatric surgical program completely. Therefore the psychosocial background, the absolute necessity, the will and commitment of the patient and relatives to surgery and proper understanding of possible complications and ability to accept them should be very well established prior to embarking on surgery. The patient should be willing and committed to long term regular follow up and lifestyle changes including dietary modifications that are essential for long term success and safety of the procedure.

The following list highlights the BMI cut off points for surgical intervention and other selection criteria (3)

Indications based on BMI

- BMI 37.5 kg/m² without co-morbidities
- BMI 32.5 kg/m² with obesity associated co-morbidities
- BMI 30 kg/m² if there is associated central obesity and at least 2 established criteria of metabolic syndrome
- Less than BMI 30 kg/m² – strictly under a research / study protocol with special consent.

However, even lower cutoffs are considered as indications for bariatric surgery according to the latest guidelines published by the Endocrine Society of Sri Lanka (ESSL).

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Other factors to consider

- Age between 16-65 years
- Documented evidence of failure of non-surgical methods in weight loss
- Acceptable operative risk
- Well informed and motivated patient
- Commitment to prolonged lifestyle change
- Supportive family/social environment
- Resolution of alcohol or substance abuse
- Psychologically stable patient with realistic-expectations
- Absence of active psychosis and untreated severe depression

Restrictive vs malabsorptive procedures

Restrictive bariatric surgical procedures cause overall reduction of calorie intake whereas malabsorptive procedures work mainly on the principle of reduction of absorption of nutrients across small bowel achieved by various types of anatomical alterations in the small bowel with bypasses and anastomoses. However the real picture is more complex than this simple description of restriction or malabsorption. Restrictive procedures such as Sleeve Gastrectomy (SG) show hormonal effects affecting the desire to eat excessively and many malabsorptive procedures consist of a gastric restrictive component causing reduction of calorie intake as well. Recognition of the endocrine aspect of small bowel and alterations of action of gut hormones due to bypass surgical procedures are well recognized now.

Roux en Y gastric bypass

This is the “gold standard” operation against which the outcome of other bariatric operations is often compared. This is the longest-standing surgical procedure which was most frequently performed globally. At present its place is rapidly replaced by LSG which is emerging as the number one surgery performed worldwide for morbid obesity.

The main principle is creation of gastric restriction by formation of a 20cc-30cc gastric pouch just below the gastro-oesophageal junction. After that a measured length of upper jejunum (usually about 150-200cm from DJ flexure) is divided and distal bowel anastamosed to create a gastric pouch forming the alimentary limb. The bypassed bilio-pancreatic limb is anastamosed to this causing the common limb which would now absorb much less amount of nutrients due to the proximal jejunum being bypassed. The surgery is very effective in metabolic syndrome as effects of proximal foregut bypass are seen within 24 hours. The patients adapt to new eating patterns much easier than in sleeve gastrectomy and post-procedure regurgitation is much less. Unlike more extensive bypasses such as duodenal switch (DS), this procedure rarely causes diarrhoea or steatorrhea and severe vitamin deficiencies. However, the relatively carbohydrate-rich protein-poor Asian diet can push a proportion of patients into protein calorie malnutrition, significant vitamin and mineral deficiencies or even chronic liver cell disease long term. These patients need lifelong very close follow up with periodic assessments of vitamin and mineral levels and appropriate replacement. With the high rate of poor compliance in follow up of surgical patients in the Asian community, this surgery can have devastating results on those who do not comprehend the importance of lifelong follow up and supplementation. On the other hand, in a proportion of patients the malabsorptive component may become ineffective due to long term adaptations of small bowel. In them the procedure will function essentially as a restrictive operation with resultant weight gain and even recurrence of some of the associated illnesses. Stomal ulcers at gastric anastomotic site, anastomotic strictures and internal herniations causing small bowel obstruction are some of the other recognized complications of this procedure.

Mini gastric by-pass (MGB)

This is a relatively novel malabsorptive procedure which is now highly recommended for Asian population especially for patients with obesity associated “metabolic syndrome” who comparatively have a higher amount of visceral fat (9). It is also recognized that it is more suited for the Asian dietary pattern which is high in carbo-
hydrates and vegetables. The surgical technique encompasses a gastric restrictive procedure in the form of a 20-30cc vertical gastric pouch along the lesser curve which is disconnected from the remainder of stomach and a single Gastro-Jejunal bypass created between the gastric pouch and the proximal loop of small bowel at 200 cm from the DJ flexure. This is a highly effective malabsorptive procedure with patients enjoying a wide range of food choices compared to pure restrictive operations. It can be performed laparoscopically and only one small bowel anastamosis is created. The main drawback of the procedure is bile reflux into the stomach which can be troublesome in about 6% of patients and may require creation of a jejuno-jejunostomy between the limbs of the bypassed small bowel loop. Stomal ulcers at anastamotic site and strictures can also occur. Stringent follow up and replacements are essential as this is a highly efficacious malabsorptive operation (10). This is also regarded as one of the surgical procedures of choice in failed sleeve gastrotomies and laparoscopic adjustable gastric bands (LAGB). As there is only one small bowel anastomosis, the procedure is reversed with ease using laparoscopic technique.

Other by-pass (malabsorptive) operations – the role in Asia

Other main malabsorptive procedure is Bilio-Pancreatic Diversion with Duodenal Switch (BPD-DS) which perhaps is the “most effective” bariatric surgical procedure ever. This causes severe malabsorption leading to rapid weight loss and maintenance of sustained low weight. Even in the West this procedure is often selectively offered to the super-obese patients only (BMI >50 kg/m²). In Asian setting this is performed very rarely and only in a highly selective basis in a high-volume center. The ileal interposition, on the other hand shows very promising results with regard to reversal of metabolic syndrome rapidly with minimal nutritional disturbances. However, the extreme high level of skill in laparoscopic surgery in performing this complex bypass makes it a less popular overall option in the region.

Restrictive surgical procedures in Asia – the current status

Laparoscopic adjustable gastric band (LAGB) – why we are moving “away” from it?

LAGB used to be the most popular restrictive bariatric surgical procedure in the world and still there are centers in Europe, USA and Australia which perform this operation in high numbers. This is probably the short term “safest” surgical procedure (as there are no resections or anastamoses involved; thus minimizing risks of leaks) and perhaps the only bariatric surgical procedure which is 100% reversible. The principal of the procedure involves placement of a silicone adjustable band just below gastroesophageal junction forming a 20-25cc gastric pouch above it. The band is connected to an injection port placed subcutaneously in anterior abdominal wall via tubing and by injecting or withdrawing saline into the port; the band pressure or tightness across gastric pouch can be adjusted. However, over the past decade the popularity of LAGB has drastically reduced all over the world and especially in Asian setting and it is no longer offered as a first line procedure of choice.

One of the main reasons for LAGB becoming unpopular is the pure restrictive nature of the procedure. With the increasing band pressure the restriction increase making it more and more difficult to eat a modest meal. With special reference to Asia, the choice of food also becomes rather restricted with increasing gastric band pressure. Frequent adjustments of the band is required when its filled to near total volume as at high band pressure complications such as band erosions into stomach, food impaction, regurgitation and resultant upward herniation of stomach across band causing gastric wall ischaemia and perforation can occur. In our setting early and delayed band infections and port site infections are also common problems.

Although very safe in the peri-operative periods failure of band mechanism and above listed complications can occur in about 20% of LAGB patients within first 10 years of procedure making it necessary to remove the band and perform a revision procedure. This high rate of revisions (one in five) and the risk of re-operating on already scarred upper stomach with increased incidence of leaks make this a less suitable long term option especially for the Asian patient where the cost of a bariatric operation
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is often very high. The place of the LAGB as the restrictive procedure of choice is rapidly being replaced by LSG all over the world today.

Laparoscopic sleeve gastrectomy (LSG)

Sleeve gastrectomy was initially described as a part of the biliopancreatic diversion with duodenal-switch operation (BPD-DS); where the gastric resection component was performed first in high risk or super-obese patients with completion of the small bowel by-pass components at a later setting (7). With the improvement of laparoscopic techniques Gagner et al introduced the sleeve gastrectomy component of the operation as a totally laparoscopic restrictive surgical procedure in managing morbid obesity (4). This operation which was initially considered “experimental” due to lack of long term data; is accepted today worldwide as an effective and safe stand-alone bariatric surgical procedure.

As a stand-alone surgical option for managing morbid obesity, sleeve gastrectomy has several advantages over other surgical procedures. It is an attractive feasible and effective surgical option for many bariatric surgeons adopting this procedure over the past decade.

Firstly the procedure can be performed as a 100% minimal access or a total laparoscopic manner, with many advantages compared to an open operation which should especially be noted in a morbidly obese patient. It is technically a demanding operation; but can be learned by any surgeon who is competent with laparoscopic upper GI surgery and the total anaesthesia time and procedure time is less than a more complex laparoscopic by-pass surgical procedure. The patients generally enjoy a wide variety of food postoperatively compared to other restrictive operations such as adjustable gastric band (LAGB) and are free of other gastrointestinal disturbances secondary to various types of by-pass operations.

Although considered mainly as a restrictive operation, it has several hormonal advantages as compared to other restrictive procedures, e.g. LAGB. As an essential component of the surgery, complete gastric fundus mobilization and resection is carried out, which is rich in receptors for “Ghrelin” an orexigenic GI hormone which drives hyperphagia (desire to eat excessively) in morbidly obese patients. The combined effect of restriction and volume reduction in stomach causing “fullness” with a small meal and the reduction of desire to overeat due to hormonal effects have made it a very effective weight reduction surgery with minimal alterations in gastrointestinal function.

LSG has been recognized as one of the two main operations that should be recommended as first line surgical options for Asian patients with morbid obesity (5,6). Especially in south east Asia, the rapidly rising incidence of morbid obesity and metabolic syndrome are attributed mainly to high volume carbohydrate consumption and LSG provides a direct and a drastic reduction of volume eating. Once the perioperative period is over, medium-term data (up to 10 years) suggests that the nutritional deficiencies common to many by-pass procedures are minimal or absent in LSG (5); therefore a stringent lifelong follow up which is required in most other complex bariatric operations (e.g. Roux en Y by-pass) is not needed; patients can somewhat be relaxed with LSG.

In many studies which compared outcome and resolution of co-morbidities of LSG with the gold standard bariatric surgical procedure (i.e. Roux-en-Y Gastric bypass), the initial weight loss and resolution of co-morbidities seem more rapid with Roux-en-Y by pass; but over a period of 1-2 years the reversal of co-morbidities and sustained excess weight loss show no statistical difference in the two procedures (5).

The surgical procedure encompasses mobilization of greater curve of stomach upto gastro-oesophageal junction (GOJ) and a vertical resection of stomach against a gastric bougie placed along the lesser curve of the stomach. This results in a narrow gastric tube with complete resection of gastric fundus and most of the greater curve of the stomach preserving the antro-pyloric mechanism.
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The main perioperative complications of this operation are staple line leaks and bleeding. Reported mortality is 0.5-1%. Reflux at gastro-oesophageal junction due to increased gastric pressure occur in 20-30% of patients but this settles gradually over time with antacids and anti-reflux medications. Both narrowing of gastric tube and dilatation can occur over years requiring revision surgery.

In summary, the surgery for morbid obesity and metabolic syndrome in Asian population has many differences and considerations with regard to matched populations of rest of the world. Clear understanding of these differences by all health care professionals who handle this specific group of patients helps to minimize confusions and mistakes that can give rise to medical and medico-legal problems that are common in this highly specialized and sensitive surgical field.

References

Glycogen synthase deficiency (GSD0)
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Abstract
Hypoglycaemia is a common presentation in paediatric practice. It is challenging at times to arrive at a definitive diagnosis with the limited facilities available. These are uncommon clinical conditions which can present with common symptoms. Glycogen storage disease type 0 presents with fasting hypoglycaemia associated with ketosis and post prandial hyperglycaemia. Molecular genetic studies have improved the diagnosis of this condition and there are 18 different mutations identified to date. The treatment includes a high protein diet with complex carbohydrates to prevent hypoglycaemia. Here we present a child with a possible diagnosis of glycogen storage disease type 0.

Introduction
GSD0 is a rare cause of fasting hypoglycaemia in infancy and early childhood (1, 2) due to deficiency of the hepatic isoform of glycogen synthase (3). GSD0 is not considered as a true glycogen storage disease as liver glycogen content is markedly reduced. Until recently the gold standard for the diagnosis was liver biopsy showing a low glycogen content and glycogen synthase activity (1). However the advancement of molecular genetics has resulted in improved diagnosis and further awareness of this condition.

In the healthy state following a carbohydrate load, glucose is deposited in the liver as glycogen by the activity of glycogen synthase. In the absence of this enzyme there is postprandial hyperglycaemia and glycosuria. The unutilized glucose, through the alternate glycolytic pathway cause postprandial hyperlactatemia and hyperlipidemia (1,2,4). During a fast, as glycogen is deficient there is hypoglycaemia associated with ketosis. Both the intact gluconeogenesis and ketogenesis via alanine, the major gluconeogenic substrate in the skeletal muscle, reduces the degree of blood glucose reduction initially. However prolonged fasting with hyperketonemia inhibits the release of alanine from skeletal muscles and subsequently leads to hypoglycaemia (5).

GSD0 has a wide variety of symptoms such as lethargy, pallor, nausea, vomiting and sometimes seizures. Long term complications seen in other types of glycogen storage diseases are not seen in this disorder as gluconeogenesis and fatty acid oxidation are not defective (6) and provide the brain with ketone bodies which is an alternate source of fuel (7). Most children are diagnosed incidentally when they present with lethargy or weakness following a minor illness. Postprandial hyperglycaemia and fasting ketonuria may be confused with diabetic ketoacidosis.

Diagnosis is based on demonstration of postprandial hyperlactatemia in a child presenting with ketotic hypoglycaemia. An oral glucose tolerance test can result in postprandial hyperlactatemia. The gold standard for the diagnosis at present is mutation analysis.

Here we present a possible case of GSD0.

A girl aged one year and three months was referred to the University Paediatric Unit at Lady Ridgeway Hospital with the complaint of repeated hypoglycaemic events onset at the age of 11 months. Those episodes had been associated with drowsiness and sweating. Two of the episodes were noted 2-3 hours after lunch. The patient’s blood sugar level had been 29 mg/dl on one such occasion.

She was born to consanguineous parents was the younger of the two children. Her birth weight was 4.6 kg in spite of the pregnancy being complicated by pregnancy induced hypertension. Mother has had a normal oral glucose tolerance test during the antenatal period. On day 9 after birth, the child had symptomatic hypoglycaemia with convulsions; during which time her blood sugar was found to be low. Until 11 months of age she did not have a history suggestive of hypoglycaemia. She had normal developmental milestones. Her growth chart revealed faltering weight gain at the age of 6 months. On presentation she was mainly fed on breast milk and a small quantity of weaning food.

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On examination she had a round cherubic face. She weighed 10 kg (median +1SD and was 72 cm (-1SD, -2SD) in length. No midline defects or dysmorphic features were noted. There was no hepatomegaly. Cardiovascular, respiratory and neurological systems were normal.

The investigations performed revealed normal liver function tests and ultrasound scan of the abdomen. Urinary ketone bodies were not detected at the time of hypoglycaemia.

Given the history of hypoglycaemia within a few hours of meals raised the possibility of type 0 glycogen storage disease. Chubby round face with absent hepatomegaly further supported the possibility of this rare condition. Other possibilities of hypoglycaemia at this age were ketotic hypoglycaemia, cortisol deficiency and rarely hyperinsulinaemia or fatty acid oxidation defects. Ketotic hypoglycaemia usually occurs in children with poor growth with prolonged fasting.

Her blood sugar was checked 2 hours after lunch which was a small amount of rice followed by breast milk. It revealed a blood sugar level of 180 mg/dl; unusual for a non-diabetic child. She was kept fasting from that point. Within 4 hours she became symptomatic with a blood sugar level of 33 mg/dl. Urine checked at that time revealed ketone bodies. With the presence of ketone bodies rare conditions like hyperinsulinaemia and fatty acid oxidation defects were excluded. The presumptive diagnosis of glycogen storage disease was more favored with fasting hypoglycaemia and fed state hyperglycaemia. This phenomenon was confirmed on two occasions. Urine sugar was positive on one occasion when blood sugar was 269 mg/dl, just 1 hour after a breast feed.

Unfortunately we did not have the facilities to do enzyme assays on liver biopsy specimens or facilities to do lactate levels after meals.

She was advised on a high protein diet and low glycaemic index carbohydrates (complex carbohydrate) to maintain normal blood sugar. In the ward we demonstrated normoglycaemia with this regime.

**Discussion**

GSD0 is an autosomal recessive disorder due to mutation at GYS2 gene located on chromosome 12p12.2 (3,8). This was first described in 1963 (2). So far 18 different mutations have been identified (9). Children are usually asymptomatic until they are weaned from breast milk. Even with low blood sugar levels these children may not become symptomatic because the ketone bodies provide an alternative fuel for the brain (7). Only a small percentage of children present with seizures or developmental delay(10) explaining the brain protective nature of ketone bodies (4). The subtle nature of the clinical picture in this condition delays the diagnosis. Therefore any child presenting with fasting hypoglycaemia and postprandial hyperglycaemia with glucosuria should be evaluated for GSD0 (4).

There were few case reports of adults being diagnosed with GSD0 (3). All those patients had shown good outcome.

Treatment goal is to prevent hypoglycaemia and postprandial lactic acidosis. Protein rich meals and low glycaemic index complex carbohydrates prevent repeated episodes of hypoglycaemia. Intact gluconeogenesis will provide glucose from protein rich food. This will prevent lactic acidosis and ketosis. When hyperketonemia is prevented more alanine will be released from skeletal muscles for gluconeogenesis (11). Young children will benefit from uncooked cornstarch at bedtime or more frequently when they fall ill. Frequent snacks are used to prevent day time hypoglycaemic episodes. Improved physical activity is seen in children who are given uncooked corn starch an hour before physical activity. It is important to understand that simple carbohydrate can increase blood lactate levels and should be avoided.

This highlights the importance of a thorough evaluation especially by a comprehensive clinical history to arrive at a clinical diagnosis even in a resource limited setting. With limited facilities available, the awareness of this condition will help the physician to arrive at a tentative diagnosis with the use of fasting and postprandial blood glucose levels and provide appropriate treatment. We note that we do not have the confirmation of the diagnosis with the genetic tests or lactate levels; however we thought it would be useful to share this case history with clinicians.

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Managing a patient with resistant Graves’ disease

S Pathmanathan¹, Noel P Somasundaram², S Kollure³


Abstract

Antithyroid drugs have been a mainstay in the management of Graves’ disease for a long time. They are generally safe, effective and well tolerated. However, some patients may not respond to this conventional treatment and may require additional treatment modalities to achieve a euthyroid state. We describe a case of Graves’ disease which was resistant to usual antithyroid drugs requiring addition of lithium, high dose steroids and lugol’s iodine to control her thyrotoxicosis before undergoing the definite treatment – total thyroidectomy.

Introduction

Management of thyrotoxicosis includes antithyroid drugs, radioactive iodine, and surgery. In Graves’ disease, antithyroid drugs are the first line treatment, used as the only modality for a first episode, or as a bridging therapy to decrease high thyroid hormone levels prior to definitive treatment of either radioactive iodine (RAI) or surgery. They are generally safe and effective (1). However, a few cases may show resistance to these antithyroid drugs requiring additional treatment options to achieve euthyroid state.

We describe a case of thyrotoxicosis in a patient with Graves’ disease who was resistant to antithyroid drugs. High-dose steroids, lithium and lugol’s iodine were additionally administered to control her thyrotoxicosis and she underwent total thyroidectomy. This case was written in the best interest of sharing our experience in managing a resistant Graves’ disease.

Case presentation

An 18-year-old student from Elpitiya was referred to our institution for further management of uncontrolled hyperthyroidism. She had presented to the local hospital with typical symptoms of hyperthyroidism 8 months back and was started on carbimazole 40mg daily. Two months later a dose increment was made as there was a poor response to the initial doses. Since then she was on the recommended maximum doses of carbimazole (60 mg daily) without much clinical and biochemical improvement. Physical examination showed signs of Graves’ ophthalmopathy, a diffusely enlarged thyroid gland and thyroid bruit. Thyroid function tests showed severe thyrotoxicosis with a free T4 level of 7.77ng/dl (normal range: 0.9-1.7) and TSH of <0.01?IU/mL (normal range: 0.4-4.0). A diagnosis of Graves’ disease was made based on the presence of Graves’ ophthalmopathy. In addition, the presence of a thyroid bruit was also considered pathognomonic for Graves’ disease. Ultrasound of the neck showed heterogeneously enlarged thyroid gland with increased vascularity. No discrete nodules were identified.

It was planned that the patient be made euthyroid with free T4 values as near normal as possible, so that she should be able to undergo surgery without the risk of precipitating a thyrotoxic crisis. Radioactive iodine (RAI) was not considered as an option for her because of the presence of Graves’ ophthalmopathy. As the patient was already on 60mg per day of carbimazole, lithium (LiCO₃ 500 mg bid) was added on to her regime. Six weeks later her free T4 still failed to normalize although there was a slight improvement (free T4-4.92 ng/dl) in comparison to her initial values. Her antithyroid drugs were switched to propylthiouracil (PTU) 200mg tds and lithium was continued. Administering maximum doses of PTU (200 mg qid) had minimal benefit with free T4 values still elevated at 4 ng/dl. The patient was accompanied by her mother at every visit. The issue of compliance was thoroughly ascertained through direct questioning and visual inspection of pill bottles at every clinical visit. The patient appeared to be compliant in taking her medications.

She was then started on high doses of prednisolone (1 mg/kg/day) along with lithium (500 mg bid) and PTU (200 mg qid) to make her euthyroid so that she could undergo surgery safely. Four weeks later the patient showed only a mild response to these treatment modalities, and her free T4 still remained at 3.25 ng/dl. As the response to medical management was inadequate, in discussion

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with the surgical team we admitted her to ward for preoperative stabilization before surgery. Administration of Lugol’s iodine and arranging for plasmapheresis immediately prior to surgery were the two options we considered for rapid preoperative stabilization in this case of refractory Graves’ thyrotoxicosis. She was started on Lugol’s iodine 4 drops qid. Four days later her free T4 further reduced to 2.5ng/dl and 7 days later to 2ng/dl. She underwent total thyroidectomy with preservation of parathyroid glands. Postoperatively she was kept under closed monitoring for development of thyrotoxic crisis. Steroids, lithium and PTU were stopped on the day of surgery while beta blockers were tailed off and discontinued over 2 weeks. She did not develop any peri-operative complications and currently remains well on replacement doses of levothyroxine at follow-up.

Discussion

Antithyroid drugs have been prescribed routinely for the treatment of thyrotoxicosis and are found to be very effective in controlling hyperthyroidism due to Graves’ disease. They inhibit thyroid hormone synthesis leading to a gradual decrease in the serum thyroid hormone level. Carbimazole is regarded as more potent and rapidly effective than PTU. (1) The usual dosage is 20-60 mg of carbimazole or 300-600 mg of PTU per day. (1) But some patients fail to respond to these usual doses thereby requiring higher doses. There are reported cases where in some patients doses of PTU as high as 2000 mg daily (2) and carbimazole above 150 mg have been administered (3,4). Rarely some patients fail to show any response to even increment doses of antithyroid drugs thereby forcing the managing physician to look for other prospects to control the disease. In our patient, resistance to both carbimazole and PTU was noted.

The possible mechanisms mediating resistance in cases refractory to conventional treatment are malabsorption, accelerated drug metabolism, existence of antithyroid antibodies, impaired intrathyroidal drug accumulation or action of antithyroid drugs, predominant elevation of T3 rather than T4 levels and the severity of the disease. As noncompliance is the commonest reason for treatment failure, evaluation of patient compliance should be first undertaken before deciding on further investigations (4). Our patient was compliant in taking her medications. This compliance was ascertained through direct questioning at each clinic visits and by inspecting her pill bottles. Malabsorption was ruled out in our patient through careful history taking and physical examination. She did not have any remarkable history or physical examination findings to suggest malabsorption as a potential cause for drug resistance. The measurements of drug levels or anti-drug antibodies were not undertaken due to non-availability of these investigations. Similarly tests to check for drug resistance were also not performed in our patient.

The treatment approach for the management of resistant thyrotoxicosis is to achieve a euthyroid state and to offer surgery or radioactive iodine ablation as the definitive treatment. Achieving euthyroidism before definitive treatment is recommended in order to minimize potential complications such as precipitation of thyroid crisis (1). The treatment options include addition of lithium, steroids and iodine. Cholestyramine, a bile acid sequestrant, has also been shown to cause a dramatic decline in serum thyroid hormone levels in patients who are resistant to conventional treatment (5).

Lithium carbonate which is widely used to treat bipolar affective disorder and acute manic depressive disorders, significantly changes the iodine kinetic in thyroid tissue through the inhibition of the release of organic iodine from the thyroid gland. When administered (800-1200 mg daily) to patients suffering from Graves' thyrotoxicosis, the serum T 4 and T 3 levels have been shown to decrease by as much as 35% and most patients become clinically euthyroid within 2 weeks of treatment (6,7). In our patient although euthyroidism was not achieved lithium helped to reduce the free T4 levels.

Corticosteroids have traditionally been used in the management of thyroid crisis, but they are not used as a mode to achieve euthyroidism in thyrotoxicosis. They inhibit the conversion of thyroxine to triiodothyronine in the peripheral tissue as well as block the release of thyroxine from the thyroid. There is some limited evidence for the use of steroids in the management of resistant Graves’ disease. As Graves’ is an autoimmune disorder, steroids may lead to suppression of the immune response and hence decrease stimulation of the thyroid gland by the altered immune response. Clearly, further studies are needed to examine the effect of such immuno suppressive therapy in Graves’ disease because it has been found not all patients respond to steroid therapy (8). Our patient’s response to steroid was moderate.

Lugol’s iodine for 7-10 days has been used safely to reduce the vascularity of the thyroid gland preoperatively. Iodine has several effects on thyroid function. It acutely inhibits hormonal secretion within hours which occurs within one to two days of the start of therapy. Iodine also causes inhibition of iodine organification in the thyroid gland, thereby diminishes thyroid hormone biosynthesis, a phenomenon called the Wolff-Chaikoff effect. However, within two to four weeks of continued exposure to excess iodine, organification and thyroid hormone biosynthesis resume in a normal fashion. This is called escape from the Wolff-Chaikoff effect. Patients with Graves’ hyperthyroidism are more sensitive to the inhibitory effect of
Case report

pharmacologic doses of iodine than normal subjects. We used Lugol’s iodine in our patient preoperatively to reduce her free T4 levels to near normal which enabled her to undergo the surgery effectively.

When all the above measures fail to normalize the free T4 level, plasmapheresis can be used in preoperative stabilization. It is relatively an effective and safe procedure which causes rapid improvement in thyroid hormone levels. Therefore when medical therapy fails, plasmapheresis should be considered earlier in the pre-operative management of severe thyrotoxicosis (9,10). Although we planned for plasmapheresis, administration of Lugol’s iodine together with steroids, lithium and PTU helped to achieve a near normal FT4 so plasmapheresis was not performed in our patient.

RAI and surgery are the definitive treatment options for thyrotoxicosis (1). Thyroidectomy is more preferable when patients have large goiters, intolerant of antithyroid drugs, refuse RAI therapy, or when there is associated thyroid ophthalmopathy and a concern of worsening of it following RAI (1,10). In our patient surgery was the preferred option because of the concerns of withdrawing the drugs before RAI and the presence of associated ophthalmopathy.

Conclusion

This case highlights the difficulties in medical management of resistant thyrotoxicosis. Our patient was resistant to the conventional antithyroid drugs. In this report we have discussed the possible management options in patients with resistant Graves’ disease and our experience in treating a patient with resistant Graves’ disease. Radioactive iodine or surgery are the definitive modes of treatment in such complex cases while steroids and lithium may play an important part in preparing them for the more definitive forms of treatment. Plasmapheresis can be rarely used in preoperative stabilization, though it was not required in our patient.

References

Leiomyoma: a rare cause of adrenal incidentaloma

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Abstract

A 66 year old woman was incidentally found to have a left adrenal mass while investigating for chronic lower abdominal pain. It was 13.8 cm x 10.1 cm x 7.3 cm in size and heterogeneously enhancing. Radiological differential diagnoses included adrenal carcinoma or malignant phaeochromocytoma. Laboratory results revealed the mass to be non-functioning. She underwent left sided adrenalectomy along with splenectomy as the mass was attached to the spleen. She had an uneventful recovery. Pathological examination revealed a leiomyoma which is a rare form of adrenal tumours.

Key words: adrenal incidentaloma, adrenal leiomyoma

Introduction

An adrenal incidentaloma is a mass lesion greater than 1 cm in diameter, serendipitously discovered by radiologic examination (1). This entity is the result of technological advances in imaging such as computed tomography (CT) and magnetic resonance imaging (MRI) and their widespread use in clinical practice. The finding of an adrenal incidentaloma requires concurrent testing to determine the tumour functional status of the tumour as well as its potential for malignancy. Nonfunctioning adrenal masses ≥4 cm should be considered for surgical resection.

Case report

A 66 year old lady presented with a history of a dull, mild left sided abdominal pain for 2 years worsening over the last two months. Apart from the abdominal pain she did not have any other symptoms and her appetite, weight and her bowel habits were unaltered. She was diagnosed with hypertension for 5 years with no paroxysms of sweating, palpitations and headache.

Physical examination revealed a physical habitus with a normal she was not cushinoid and did not show signs of virilization, abdominal examination was normal.

Abdominal sonography revealed a hetero-echoic solid mass of 7.3 cm x 13.4 cm x 9.2 cm size in the left supra renal region.

Computed tomography was also performed which showed a 13.8 cm x 10.1 cm heterogeneously dense left supra renal mass lesion with retrocrural lymphadenopathy. There were multiple hypodense areas seen within the lesion suggestive of necrosis.

Figure 1a.
Contrast enhanced computed tomography of the abdomen showing a large heterogeneously dense left supra renal mass (Arrow) with multiple hypodense lesions.

Figure 1b.

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Case report

Radiological differential diagnoses were adrenal carcinoma or malignant phaeochromocytoma.

Laboratory investigations revealed the tumour to be non functioning. Her 24 hour urinary vanillylmandelic acid (VMA), testosterone and dehydroepiandrosterone levels were within normal limits. Overnight dexamethasone suppression test was suppressed to less than 1.00 micrograms/dl.

She underwent left side adrenalectomy along with splenectomy as the tumour was attached to the spleen. Macroscopically the mass was 15.0 cm × 12.8 cm × 7.5 cm with attached to the spleen and surrounding fatty tissue. Cut section showed a solid, yellowish tumour with small cystic areas. Histological examination revealed a circumscribed lesion composed of interlacing bundles of smooth muscle cells separated by vascularized connective tissue which is consistent with adrenal leiomyoma.

Discussion

Leiomyomas are benign, smooth muscle tumours that can originate anywhere in the body where smooth muscle layers exist. They occur most frequently in the uterus and gastrointestinal tract but can be identified in different places, including the adrenal glands.

An adrenal leiomyoma is a rare cause of an adrenal mass. There are less than 20 reported cases in the literature worldwide (2).

The adrenal leiomyomas reported in the literature were large (3.0-11.0 cm in diameter), tended to occur more frequently in females (61%), and affected subjects over a wide age range, from early childhood to late adulthood (an age range from 2-72 years). Most were solitary (unilateral) adrenal masses (2).

There are several reported cases of adrenal leiomyomas in patients with acquired immunodeficiency syndrome (AIDS) (3-5). The association of leiomyoma and HIV/AIDS is not restricted to the adrenal gland as these tumours have been found in various sites in children and adults (6). The pathologic reason for this association is not clear. However HIV antibodies were negative in our patient.

Conclusion

This case illustrates that benign tumours such as leiomyomas, when large and heterogeneous on imaging, can mimic adrenal cortical carcinomas or phaeochromocytomas and should be included in the differential diagnosis of adrenal incidentalomas.
References


Morbidity pattern of adrenocortical tumours presenting to a tertiary care paediatric center and a specialized cancer unit

N Ginige¹, D S Gunasekera², D C Pieris³, K S H De Silva⁴, C S Perera⁵


Abstract

Adrenal cortical neoplasms in paediatric patients are rare. The clinical manifestations and behaviour of these lesions can be different from the adult population. At times pathologic criteria for distinguishing benign from malignant tumours are equivocal. We undertook a descriptive study of adrenal cortical neoplasms in 11 children to describe the presentation and clinicopathologic behaviour of these lesions and, to determine the prognostic indicators in children. Our data indicate that adrenal cortical neoplasms in childhood may not be as uniformly fatal as they are in adults, even with histologic evidence of malignancy. But at the same time when they are clinically malignant and complete surgical resection cannot be achieved, they behave aggressively. Therefore we conclude that histology alone is not a reliable prognostic indicator; tumour size, weight and extent of surgical resection taken together are more predictive. More prospective studies to evaluate the long term outcome of the patients with a database for this rare tumour are a need.

Key words: adrenal, neoplasm, carcinoma, paediatric, prognosis

Introduction

Adrenocortical tumours (ACT) are rare in children with adrenal cortical carcinomas (ACC) accounting for the majority of the tumours (1). Patients can present with features of excess hormones of adrenocortical origin (cortisol, androgens and aldosterone). The prognostic significance of tumour size, capsular invasion and histological grade are debatable. Adrenocortical tumours (ACT) are very rare in children with a worldwide annual incidence of 0.3 per million children below the age of 15 years (1). The incidence in girls under the age of 3 years is higher than in boys (2:1), whereas in adolescence the sex ratio is equal (2).

Disease staging criteria for childhood ACTs generally have not been agreed on, because definitive pathologic criteria for malignancy in adrenal cortical neoplasms in the paediatric age group remain uncertain. Most pathologists use a classification which is extrapolated from adult staging systems. This is due to the rarity of tumours in this age group as well as the lack of clinicopathologic correlation of the patients' outcomes. It has been noted that some children with adrenal cortical neoplasms with apparently poor prognostic features (based on adult criteria) have a good clinical outcome during the follow up.

Objectives

To describe the morbidity pattern in a group of children who presented to a tertiary care children’s Hospital and the National Cancer Institute in the country.

To determine disease free survival in relation to the surgical resection, at the maximum follow up period.

To determine prognostic indicators of adrenal neoplasms on children.

Method

Here we provide a descriptive analysis of 10 patients who were registered at the clinics of Paediatric oncology at the National Cancer Institute and the Children’s Hospital in Colombo. The 11 patients with adrenocortical tumours initially recruited in our study represented 2.7% of all benign and malignant primary adrenal gland neoplasms diagnosed during the period January 2006-August 2013.
We retrospectively analysed these patients with histologically proven adrenocortical tumours during past 7 years between January 2006 and August 2013. Eleven patients younger than 11 years of age with newly diagnosed or previously treated ACTs were included in the study.

Inclusion in this study required the presence of an adrenal cortical neoplasm. Adrenal medullary tumours such as pheochromocytoma, neuroblastoma and ganglioneuroma were excluded. The macroscopic pathological features of the tumours were obtained from descriptions of the pathologists as reported in their surgical pathology reports. Furthermore we evaluated these tumours based on macroscopic and microscopic features, immunohistochemical reactivity (if and when available), clinical behaviour, and treatment outcomes. Those patients who were registered both at the Cancer Institute and the Children’s Hospital were recruited only once. The records of 11 pediatric patients with tumours diagnosed as adrenal cortical adenoma, adrenal cortical neoplasm of uncertain malignant potential, adrenal cortical carcinoma were identified from the clinical records. These records also supplied the information regarding demographics (gender and age) symptoms at presentation (including duration) and past history (specifically, any syndrome association such as hemi hypertrophy, café au lait spots, Beckwith-Weidman syndrome). In addition, surgical pathology and operative reports of these patients were reviewed.

Follow-up information was retrieved from the clinic records and bed head tickets of both hospitals as well as by direct communication with the oncologist or the patient. One patient had the histology of a Wilms tumour secreting ACTH which was also confirmed by immunohistochemistry. Hence he was excluded from the study.

Therefore, the remaining 10 patients with adrenal cortical tumours constituted the subjects of this study based upon histological diagnosis. The review of 402 cases with masses of adrenal origin from both institutes identified 10 cases of adrenocortical tumours, 4 pheochromocytomas, and 392 of both neuroblastomas and ganglioneuromas.

Results

The clinical features of the 10 patients are summarized in Table 1. Out of these tumours 7 were adrenocortical carcinomas while two were tumours with uncertain malignant potential. Interestingly only one patient had histology of adrenocortical adenoma. But this was the only occasion where the histopathological diagnosis was supported by immunohistochemical tests of the tumour material.

There were 6 girls and 4 boys (1.5:1) ranging in age at presentation from 2 months to 11 years. Their median presenting age was 2 years 8 months.

Summary of study findings

<table>
<thead>
<tr>
<th>Endocrine abnormality</th>
<th>Female</th>
<th>Male</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Virilization</td>
<td>+</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Cushing syndrome</td>
<td>+</td>
<td>+</td>
<td>4</td>
</tr>
<tr>
<td>Hypertension + Virilization</td>
<td>+</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Cushing syndrome +</td>
<td></td>
<td>+</td>
<td>2</td>
</tr>
<tr>
<td>Hypertension</td>
<td>+</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>Cushing syndrome +</td>
<td>+</td>
<td></td>
<td>2</td>
</tr>
</tbody>
</table>

One female patient presented at the age of 7 years with isolated virilizing symptoms with the appearance of pubic hair for one year and appearance of acne, clitoromegaly, height spurt and voice change for 5 months. Upon complete resection of her tumour which had features favouring adrenocortical carcinoma, most of her virilising signs regressed. But with the advancement of bone age (bone age was 14 years at a chronological age of 7 years) and altered pituitary gonadotropin profile, she subsequently went in to central precocious puberty and was started on GnRH analogue therapy.

Nine patients (90%) had cushingoid symptoms. These patients showed rapid weight gain, increased body hair, typical moon face and thinning of skin although striae were not observed. Linear growth arrest was not demonstrated as previous values of height were not available. Following complete surgical excision three patients with Cushing syndrome and virilisation had their Cortisol normalised within six months during a median follow up of two years (range, 8 months - 7 years). In other patients hormonal investigations were not done consistently. Two had only pre-op cortisol levels and other four had not undergone hormonal assessment. However their cushingoid symptoms improved clinically during the follow up.

Three patients (30%) with cushingoid symptoms also had hypertension requiring one or two antihypertensives. One patient presented with hypertensive encephalopathy that took a refractory course with difficulty in maintaining normal blood pressure but recovered remarkably soon after surgery.
Details of the resected tumours and follow up are given in table 2 and figure 1. In the study group, 8 patients (80%) had complete surgical resection whereas 2 patients had residual disease. The latter two patients aged 2 months and 11 years had adrenocortical carcinomas with capsular and vascular invasion confirmed by the imaging studies with ultrasound and CT scans at diagnosis. Both received adjuvant chemotherapy following incomplete excision of the tumour. The two month old infant girl had a tumour which had invaded the inferior vena cava (IVC) with an atrial thrombus which weighed 90 grams. She died during the first cycle of chemotherapy due to septic shock within 2 months of diagnosis. The eleven year old boy had a tumour which showed a heterogenous echogenesity and calcification on ultra sound with capsular and intra tumour lymphatic invasion. His excised tumour weighed 104 grams. He presented with recurrence of original mass with liver metastases after three cycles of chemotherapy and died 11 months after diagnosis due to the disease process while on palliative care.

<table>
<thead>
<tr>
<th>Patient number</th>
<th>Age at presentation</th>
<th>Tumour weight in grams</th>
<th>Follow up in months</th>
<th>Histology</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2 months</td>
<td>90 (incomplete resection)</td>
<td>2 (Died)</td>
<td>Adrenocortical carcinoma. Atrial thrombus. Capsular, vascular invasion</td>
</tr>
<tr>
<td>2</td>
<td>8 months</td>
<td>135</td>
<td>9</td>
<td>Adrenocortical carcinoma. No capsular vascular invasion. Complete resection</td>
</tr>
<tr>
<td>3</td>
<td>11 yrs</td>
<td>104 (incomplete resection)</td>
<td>13 (Died)</td>
<td>Adrenocortical carcinoma with calcification and capsular and lymphatic invasion. Liver metastasis</td>
</tr>
<tr>
<td>4</td>
<td>1 yr 10 mo</td>
<td>140</td>
<td>12</td>
<td>Adrenocortical tumour with uncertain malignant potential. No invasion. Complete resection</td>
</tr>
<tr>
<td>5</td>
<td>9 yrs 3 mo</td>
<td>190</td>
<td>12</td>
<td>Adrenocortical carcinoma. No capsular vascular invasion. Complete resection</td>
</tr>
<tr>
<td>6</td>
<td>5 yrs</td>
<td>30</td>
<td>13</td>
<td>Adrenocortical carcinoma. No capsular vascular invasion. Complete resection</td>
</tr>
<tr>
<td>7</td>
<td>8 yrs 3 mo</td>
<td>160</td>
<td>18</td>
<td>Adrenocortical tumour with uncertain malignant potential. No invasion. Complete resection</td>
</tr>
<tr>
<td>8</td>
<td>7 yrs</td>
<td>170</td>
<td>25</td>
<td>Adrenocortical carcinoma. No capsular vascular invasion. Complete resection</td>
</tr>
<tr>
<td>9</td>
<td>1 yrs 3 mo</td>
<td>Not recorded</td>
<td>52</td>
<td>Adrenocortical adenoma</td>
</tr>
<tr>
<td>10</td>
<td>1 yr</td>
<td>Not recorded</td>
<td>84</td>
<td>Adrenocortical carcinoma. No capsular vascular invasion. Complete resection</td>
</tr>
</tbody>
</table>
In this study group mean tumour size was 5 cm in diameter and the mean weight was 127.3 grams, the largest being a tumour 8cm in diameter weighing 190 grams. In two patients, weight of the tumour was not documented.

All eight patients in this group were managed by unilateral adrenalectomy alone. The eight patients who had complete surgical excision had their cortisol levels normalized within six months post op. All were given hormone replacement (hydrocortisone) therapy for a few months (range 1-3 months). In five patients who were followed up at the paediatric endocrinology clinic, the recovery of contra-lateral adrenal gland was established by ACTH stimulated cortisol levels and endocrine review was continued at 3-6 monthly intervals. These patients had a good clinical outcome and were alive without evidence of disease at the last follow-up at a median follow up of 24.8 months (range, 7-84 months).

None of the patients had congenital syndromic associations (E.g. Beckwith Weidman).

Discussion

Adrenocortical tumours (ACT) are rare in childhood and they may present with features of hypersecretion of adrenal steroids. Complete surgical resection can reverse most features of steroid hypersecretion. The commonest presenting clinical feature is virilisation, manifesting as early onset appearance of pubic hair, hypertrophy of the clitoris or penis, accelerated growth, gynaecomastia or acne. The second most common manifestation is cortisol excess (Cushing’s syndrome). Cushing’s syndrome is a relatively more common presentation in older children. The most important clinically significant feature of paediatric adrenocortical tumours is that they behave differently to the adult counterparts of similar tumours. In contrast to ACT in adults, non functioning tumours are rare in children (5).

Some case series have described hypertension occurring at an incidence of 43%. However in our study only 3 patients (30%) had hypertension. There may be several reasons for the hypertension found in association with ACT, e.g. increased production of mineralocorticoid and glucocorticoid or the compression of renal artery by the tumour (6). Hypertension associated with adrenal tumours is completely resolved with the successful resection of the tumour which was evident in the three patients in our study group.

Hormonal profile relevant to ACT could be supportive in identifying the tumour origin. In functioning tumours, assessment of post-operative residual disease is best undertaken by steroid tumour markers and therefore it is used as a monitoring tool to detect tumour recurrence during the follow up. These hormone assays may detect raised levels of androstenedione, dehydro-
epiandrosterone sulphate (DHEAS), testosterone, and urinary steroids (7, 8). Most of the patients in this case series had not undergone a hormonal assessment due to the financial constraints and unavailability of the facilities although it could have been used as a follow up marker.

Therefore all the patients were followed up with abdominal ultrasound scanning every three months until one year and every six months afterwards. Ultrasound (US) scanning is the commonest and the most widely used first line investigation. This is particularly useful in identifying tumour invasion in of the IVC. When the ultrasound scan is negative in the presence of strong clinical or biochemical suspicion of an adrenal neoplasm, a magnetic resonance imaging (MRI) should also be performed as some adrenal masses may be difficult to visualise with ultrasound scanning alone (9). Since MRI is not widely available in our setup, a contrast CT may be performed along with a chest CT to exclude or detect pulmonary metastases.

Paucity in numbers of ACT in children may dampen mastering the pathological expertise needed to confirm histological diagnosis. This is further compounded by not having a central review system of ACT in our country. Retrieving data of patients and their histopathological features of tumour were made difficult by not having a cancer registry or a database maintained for adrenal tumours of children in Sri Lanka. Data collection and larger outcome based studies of this rare endocrine tumour in children will be of utmost importance for future reference.

The classification of benign from malignant ACTs is not clear cut. Differentiation between adenoma and carcinoma depends on arbitrary demarcations, and all patients (even those with histologically proven benign adenoma) require close follow-up initially. In many occasions they are named “adrenocortical neoplasms of uncertain malignant potential”. The majority of ACTs in children are interpreted pathologically as malignant in most studies. Factors favouring malignancy include size over 5-10 cm, weight over 200 g, invasion into the periadrenal soft tissues or IVC (10).

More extensive use of immunohistochemistry in the pathological diagnosis of disease also may help differentiate adrenocortical adenomas from carcinomas. This may prevent over treatment of some patients especially during their follow up. It is also of value in diagnosis and differentiating adrenal cortical neoplasms from other neoplasms of supra renal region in the differential diagnostic workup as in the case of the child with the supra renal (Wilms) tumour which secreted ACTH in this case series.

The management of these patients requires a multidisciplinary expertise in a specialized center which has the experience in managing adrenal tumours. Surgical resection is the mainstay of treatment. The role of radiotherapy is uncertain. Similarly the place of chemotherapy is limited. The first choice of chemotherapy in Sri Lanka is cisplatin, doxorubicine combination although efficacy in children is not well established (11).

A number of congenital associations have been reported in children diagnosed with adrenal cortical neoplasms, including hemi hypertrophy and urinary tract abnormalities. Li-Fraumeni syndrome which is caused by mutations of the p53 gene, and Beckwith-Weidman are two well known syndromes which have shown a clear association with ACT (12, 13). The reason we did not encounter such association in our case series may be due to the small number of the study group.

The overall disease free survival rate of 100% was achieved at an average of 22.8 months following complete surgical resection. In the incompletely resected group there was a 100% mortality with the maximum period of survival of 8 months.

Only 22% of histologically malignant tumours behaved in a clinically malignant fashion. Features associated with an increased probability of a malignant clinical behaviour in this case series included tumour weight, atrial thrombus and capsular and/or vascular invasion.

Conclusion

Accurate diagnosis of adreno cortical tumours depends on detailed endocrine biochemistry in addition to the imaging modalities for characterizing the tumour and directing appropriate specific treatment of any endocrine complication (eg hypertension).

Histology alone is not a reliable prognostic indicator; tumour size, weight and extent of surgical resection taken together are more predictive.

The patients with unresectable residual disease carry a poor prognosis.

Our data indicate that although adrenal cortical neoplasms in childhood may not be as uniformly fatal as they are in adults, even with histologic evidence of malignancy, when they are clinically malignant, they are relatively aggressive, resulting in death within a relatively a short period of time (<1 year).
References


A 12 year old girl presented with crooked legs and a painless limp since 1 year duration. Bilateral genu valgus deformity of knees was present without other skeletal manifestations of Rickets.

Radiology revealed bilateral slipped upper femoral epiphyses (SUE) and early epiphyseal displacement in both humeral heads. There was marked reduction in bone density with osteodystrophy involving the spine (rugger jersey appearance). There was no radiological evidence of rickets or primary hyperparathyroidism. Investigations revealed vitamin D deficiency with secondary hyperparathyroidism and normal liver and renal profile.

SUFE occurs in children and young adolescents. Although the etiology remains unclear, SUFE is associated with trauma, obesity, renal failure and endocrinopathies like hypothyroidism, growth hormone deficiency, growth hormone treatment and hypogonadism causing abnormal growth and mineralization of cartilage (1). Vitamin D deficiency which is prevalent in Asian countries has also been linked to SUFE (2,3). The radiological evidence of early epiphyseal displacement of bilateral humeri apart from SUFE in our patient may also be due to the same etiology. However published literature in this regard was unavailable.

Vitamin D deficiency may have played a causative role in our patient’s epiphyseal displacement. She was commenced on mega doses of vitamin D followed by daily replacement and underwent initial corrective surgery at the hips. It was planned to review her in three months with repeat metabolic and radiological investigations to observe for progression or regression of her disease condition.

References
Management of obesity

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Introduction

Obesity is defined as accumulation of excess fat in body, which is associated with adverse health outcomes (1). Obesity has become a global problem affecting all societies and age groups. There is an increased prevalence of obesity among adults, adolescents and children in developed as well as developing countries. Increased prevalence of obesity gives rise to increase in obesity associated morbid factors such as hypertension, diabetes, dyslipidaemia, obstructive sleep apnoea, degenerative arthritis and cancers. These associated co-morbid factors invariably increase the healthcare expenditures of subjects with obesity and complications associated with obesity.

Epidemiology

The World Health Organization (WHO) estimates, that more than 1.7 billion of the world population is overweight and 310 million are obese (2). The rates of obesity have tripled in the last 10 years in developing countries. These increased rates were observed especially in the Middle East, Pacific islands, China and south east Asia. The epidemic of obesity has spread rapidly through the South Asian region (3). Ten percent of children are obese in the world according to the WHO sources. Local data shows that the prevalence of overweight and obesity in Sri Lankan adults is also increasing. In 2010, it was reported that the prevalence of overweight, obese and centrally obese people in Sri Lanka were 25.2%, 9.2% and 26.2% respectively (4).

The overall prevalence of overweight among children in Sri Lanka was found to be 2.2% (5). The same survey found that the overweight among urban school children was 3-5% and among rural children was 1.7%. The prevalence of overweight/obesity among 8 to 12 years old school children in Colombo metropolitan area is 14-15% (6).
In Asians the distribution of body fat is as important as the BMI itself. It has been shown that abdominal obesity is higher among Asians than Caucasians for a given body mass index (7). Therefore, Asians develop obesity related complications at a lower BMI (8). Additionally, Sri Lankan adults have been found to develop obesity related cardiovascular disease at a lower BMI and waist circumference (9).

Classification

Obesity is classified based on the BMI. The BMI is correlated with body fat mass. However, BMI may overestimate the degree of obesity in individuals who are muscular as much as it will underestimate in individuals with a low lean mass and relatively high fat mass. The BMI is calculated using a standard formula (Annexure 1).

Table 1. Classification of obesity according to the BMI

<table>
<thead>
<tr>
<th></th>
<th>Sri Lanka*</th>
<th>Caucasians</th>
</tr>
</thead>
<tbody>
<tr>
<td>Underweight</td>
<td>&lt; 18.5</td>
<td>&lt;18.5</td>
</tr>
<tr>
<td>Normal</td>
<td>18.5 – 22.9</td>
<td>18.5 – 24.9</td>
</tr>
<tr>
<td>Overweight</td>
<td>23 – 24.9</td>
<td>25 – 29.9</td>
</tr>
<tr>
<td>Obesity – class 1</td>
<td>25 – 30</td>
<td>30 – 34.9</td>
</tr>
<tr>
<td>Obesity – class 2</td>
<td>30 – 35</td>
<td>35 – 39.5</td>
</tr>
<tr>
<td>Obesity – class 3</td>
<td>≥35</td>
<td>≥40</td>
</tr>
</tbody>
</table>

*Adopted from available Asian data and modified by the Sri Lankan guideline committee.

The waist circumference is a clinical indicator of abdominal obesity, which increases the risk of coronary heart disease, diabetes, hypertension and dyslipidaemia (8). The WHO technique for measurement of waist circumference is given in Annexure 2.

Table 2. Abdominal adiposity according to the waist circumference

<table>
<thead>
<tr>
<th></th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sri Lankan</td>
<td>≥90 cm</td>
<td>≥80 cm</td>
</tr>
<tr>
<td>Caucasians</td>
<td>≥102 cm</td>
<td>≥88 cm</td>
</tr>
</tbody>
</table>

Evaluation

Obesity is a complex disease resulting from the interactions of a wide variety of hereditary and environmental factors.

However, excess energy intake and/or reduced energy expenditure due to physical inactivity over a long period of time are the major determinants of obesity. In humans, genetic background explains only an estimated 40% of the variance in body mass (10). A growing body of evidence supports the notion that epigenetic changes such as DNA methylation and histone modifications, both involving chromatin remodeling, contribute to fetal metabolic programming and suggests that adverse uterine environments can “permanently” alter the metabolic, endocrine, and immune function parameters of individuals well into adulthood.

Table 3. Causes and associations of obesity (11)

<table>
<thead>
<tr>
<th>Environmental causes</th>
<th>Excess calorie intake</th>
<th>Physical inactivity</th>
<th>Major determinants of obesity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genetic causes</td>
<td>Monogenic (rare)</td>
<td>Leptin deficiency/ resistance</td>
<td></td>
</tr>
<tr>
<td>Chromosomal rearrangements (rare)</td>
<td>Prader-Willi Syndrome</td>
<td>Lawrence-Moon-Biedl Syndrome</td>
<td></td>
</tr>
<tr>
<td>Polygenic (common)</td>
<td>A large number of human genes show variations in DNA sequences that might contribute to obesity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Secondar causes</td>
<td>Cushing syndrome</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypothalamic lesions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Polycystic varianyndrome</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medications: E.g. Steroids</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Obesity causes many serious medical complications that impair quality of life and lead to increased morbidity and premature death (12). Thus the complete diagnosis of obesity does not simply depend upon the BMI level but also on the impact of weight gain on health.

Individuals who fulfill the anthropometric criteria of obesity require evaluation for the presence and severity of specific obesity-related complications to complete the diagnostic process.
Table 4. Additional co-morbidities and complications that need to be considered in the management of obesity

<table>
<thead>
<tr>
<th>System</th>
<th>Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endocrine and metabolic diseases</td>
<td>Metabolic syndrome, Dyslipidemia—(hypertriglyceridaemia, reduced HDL)</td>
</tr>
<tr>
<td>Cardiovascular diseases</td>
<td>Hypertension, Coronary heart disease, Cerebrovascular and thromboembolic disease</td>
</tr>
<tr>
<td>Pulmonary disease</td>
<td>Restrictive lung disease, Obesity hypoventilation syndrome, Obstructive sleep apnea</td>
</tr>
<tr>
<td>Gastrointestinal disease</td>
<td>Gastro-esophageal reflux disease, Gallstones, Pancreatitis, Liver disease</td>
</tr>
<tr>
<td>Neurological disease</td>
<td>Stroke</td>
</tr>
<tr>
<td>Genitourinary disease in women</td>
<td>Polycystic ovarian disease, Complications during pregnancy, Urinary incontinence</td>
</tr>
<tr>
<td>Musculoskeletal disease</td>
<td>Gout, Osteoarthritis</td>
</tr>
</tbody>
</table>

Figure 1. Clinical assessment of an overweight or obese patient

**History**
- A weight history from birth onwards
- Current eating habits and activity levels e.g. food diary
- Triggers of eating
- Previous treatment/management strategies and their success
- Drug history (e.g. anti depressants, anti-psychotics, anti-epileptics, steroids)
- Family history of obesity (may suggest genetic syndromes)
- The weights of partner and children will give a clue on shared dietary habits and lifestyle
- Psychological aspect of eating behavior
- Assessment of patient’s motivation, readiness for change and expectations
- Presence of obesity related complications such as cardiovascular disease, diabetes, hypertension, psychological issues and obstructive sleep apnoea
- Assess co-existent cardiovascular risk factors such as smoking, family history of diabetes

**Physical examination**
- Correct anthropometric measurements of weight, height and waist circumference
- Features of insulin resistance (acanthosis nigricans, skin tags)
- Features of any underlying disease and associated conditions
  - E.g. bradycardia in hypothyroidism, purple striae in Cushing syndrome, hirsutism in polycystic ovarian disease, features of genetic syndromes in children
- Presence of complications
  - E.g. elevated blood pressure, eruptive xanthoma in hypertriglyceridaemia, osteoarthritis

- Basic investigations for screening such as glucose, lipid profile, liver function tests should be done to identify common metabolic complications.
- Specific investigations to detect secondary causes for obesity should be done only in clinically suspected situations.
Management of overweight and obese patients

- Overweight and obese individuals ideally should be managed by a multidisciplinary team which includes a physician, nutritionist, exercise therapist and in certain situations psychiatrist/psychologists or other specialists.

- Combined intervention offers the highest result on both weight loss as well as maintenance of the new weight (13).

- The primary care physician can play a vital role in the early detection of patients who are overweight or obese.

- Weight loss is achieved by negative energy balance. This in turn is attained in most by reduction in calorie intake rather than an increase in physical activity (13).

- It is very important to balance the potential risks and benefits of any treatment modality for a specific individual as all obesity treatments involve some degree of risk (14).

Figure 2. Approach to an overweight or obese patient
**Intervention thresholds**

<table>
<thead>
<tr>
<th>BMI class</th>
<th>Normal</th>
<th>Over weight</th>
<th>Obese I</th>
<th>Obese II</th>
<th>Obese III</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diet</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Physical activity</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Behavioural therapy</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Pharmacotherapy</td>
<td>+</td>
<td>(with presence of severe complications)</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Surgery</td>
<td>may be beneficial in the presence of severe complications</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Dietary modifications in the management of obesity**

- The main requirement of a dietary approach to weight loss is that total energy intake should be less than energy expenditure.
- At least a calorie deficit of 500 Kcal/day is needed to lose weight.
- Prescribing an energy-restricted diet may require the intervention of a clinical nutritionist.
- Dietary changes should be individualized, tailored to food preferences and allow for flexible approaches to reducing calorie intake.
- Unduly restrictive and nutritionally unbalanced diets are not recommended, as they are ineffective in the long term and can be harmful.
- Total caloric intake should be distributed throughout the day (Figure 3), with the consumption of 4 to 5 meals/snacks per day, including breakfast.
- Greater energy intake during the day is preferable to evening overconsumption and night grazing behaviors.

**General advice**

- Encourage healthy eating
- Increase consumption of healthier food
  - Increase non-starchy vegetables, green leaves, low calorie fruits
  - Substitute low-fat dairy products and meats for full-or high-fat alternatives
- Decrease total energy intake
  - Lower the intake of highly refined carbohydrates
  - Replace these with complex carbohydrates
- Do not skip main meals specially breakfast
- Alcohol intake should be discouraged
- Self monitoring of calorie intake – various methods are available for self monitoring for patients who are motivated (food diary, electronic applications e.g. My Fitness Pal, Noom)
- Recognition of maladaptive eating patterns should be encouraged i.e.
  - Eating while watching television
  - Drinking fizzy drinks while eating
  - Self-rewarding with food

**Specific advice**

Fruits and vegetables: Atleast five portions of fruits and vegetables should be consumed each day. A variety of green salads, ‘Mallum’, vegetables and low calorie fruits should be consumed. Including vegetables is the best method to lower calorie density of the main meals. Fruits should be best consumed as a snack (in between main meals) rather than desserts.
Reduced carbohydrate intake: In Sri Lankan diet the main nutrient source is carbohydrates, which provide over 70% of total calorie intake. Therefore, controlling the starch portion and replacing it with non-starch vegetables is very important. It is advisable to use a model such as the ‘Plate Model’ (Figure 4) which consists of mainly vegetables (half of the plate), with only a ¼ plate of starch and rest protein. All starchy meals should be accompanied with vegetable portions. Although the main priority must be to control total carbohydrate intake, un-refined and low glycaemic index carbohydrates consumption should be encouraged.

Sugar containing drinks such as fizzy drinks, cordials, bottled fruit juices (including no-added sugar drinks), energy drinks and flavored milk and malted milk packets should be limited. Sweets and desserts should be limited including diet products (e.g. diet ice cream and diet jams). However, artificial sweeteners can be added to enhance sweet taste.

Lower fat intake: Total fat intake can be reduced by lowering the consumption of coconut milk and oil. All types of oil contain more or less same amount of calories. Therefore, frying, tempering and oiling should be minimized and alternative cooking methods should be used. Choose lower fat dairy products and lean cuts of meat, skinless chicken, and trim any visible fat before cooking. Reduce high fat processed foods such as sausages.

 Adequate protein intake: It is very important to consume high quality protein containing foods such as fish, lean meat, egg (white), and soya as part of healthy meal plan.

It should be made aware that most pulses contain a high carbohydrate content rather than protein (e.g. Dhal, Mung bean).

Physical activity in the management of obesity

- Main role of exercise is the prevention of weight regain rather than causing weight loss (15).
  
  E.g. To lose 500g, an obese person has to run 7 km every day for a week or consume 500 kcal/ day energy deficit diet for a week.

- The importance of sustained physical activity should be stressed.

- Advice should be given on a structured exercise program and patients should also be encouraged to increase “every day” activities such as walking rather than using a vehicle for short distance travel.

- Benefits of exercise
  
  - Modest contribution to weight loss in overweight and obese adults (16).

  - May reduce abdominal fat (16).

  - Increases cardiorespiratory fitness (16).

  - Reduces cardiovascular and diabetes risks beyond that produced by weight reduction alone.

  - May reduce loss of muscle mass associated with diet.

- Cardiovascular and respiratory adequacy should be assessed prior to making a plan for exercise.

- Aerobic exercise is of greater value than other forms of exercise.

- Exercise is initiated slowly, and the intensity increased gradually.

  - Initial goal – moderate levels of physical activity for 30 to 45 minutes, 3 to 5 days a week.

  - Long-term goal – accumulate at least 30 minutes or more of moderate intensity physical activity on most, and preferably all days of the week.

- Resistance training (anaerobic exercises) e.g. Weight lifting can be cautiously added as an adjunct after the aerobic goal is achieved. Resistance training is valuable in minimizing muscle mass loss and is particularly beneficial in patients with diabetes, as it increases glucose uptake by muscles.
Follow up and re-assessment

• Patients should be reevaluated at predetermined intervals to assess the progress in the weight loss.
• The target weight as well as the rate of weight loss helps to assess the effectiveness of interventions.
• When an exercise program is started fat mass may be replaced by muscle and bone mass. In such a situation weight loss may not be observed in the initial stages.
• Patients should be assessed for possible complications of interventions as well.
• Reasons for failure should be identified and remedial measures should be taken at this stage after reinforcing the patient’s motivation for change.

Behaviour modifications in the management of obesity

Behaviour therapy in weight control refers to a set of principles and techniques for obese individuals to help them modify eating, activity, and thinking habits that contribute to their excess weight (17). Information can be delivered to them individually or within groups, face to face and also through written, web-based or audiovisual materials.

Behavioural change techniques

1. Self-monitoring of behaviour and progress
   Self-monitoring with recording one’s behaviour, is one of the most important components of behavioural treatment. Patients keep detailed records of their food intake such as food diaries to record total caloric intake, total fat grams consumed and food groups used and also of physical activity by recording duration and intensity of exercise, and body weight with weight scales or body composition measures. Patients review the records with their health care provider to identify areas of success and areas that need improvement (18).

2. Goal setting
   When setting goals, clear and realistic goals should be set and specific goals facilitate a clear assessment of success as most patients have unrealistic goals, which will lead to patient being discouraged of life style intervention.

3. Stimulus control (e.g. recognizing and avoiding triggers that prompt unplanned eating)
   Stimulus control includes, examining the environmental cues and events that lead up to an overeating episode. By learning to avoid such stimulus will help to break the chain of events, which will proceed thereafter. Suggestions for ways patients can implement this strategy include eating only at the kitchen table without watching television, keeping no snack foods stacked in the house (19).

4. Cognitive restructuring (modifying unhelpful thoughts or thinking patterns)
   Cognitive reconstructing increases patient awareness of their self-perceptions and their
weight as many obese patients have poor self-esteem and a distorted body image.

5. Problem solving
Problem solving includes stress management in these patients, as stress is a primary predictor of relapse and overeating (20). Problem solving strategies will enable a patient to cope with the problems encountered during the process of life style modifications.

**Psychological therapies**
When combined with life style interventions, psychological therapies such as behaviour therapy and cognitive behaviour therapy have shown to be more beneficial.

Teaching patients various methods for reducing stress and tension is crucial. Tension reduction techniques (e.g., diaphragmatic breathing, progressive muscle relaxation and meditation) should be taught to the patients.

**Pharmacological therapy in the management of obesity**
Although, pharmacological therapy of obesity is an area with exciting future advances, currently there are only a handful of approved drugs available for the use of the clinician (Table 7).

Candidates for pharmacological agents for obesity are those with a:

- BMI ≥ 25 kg/m², with one or more obesity related complications.
- BMI ≥ 30 kg/m², without obesity related complications.

All currently approved weight-loss drugs act as anorexiants with the exception of orlistat, which inhibits the absorption of dietary fat (21).

All weight loss medications are contraindicated in patients planning pregnancy or are currently pregnant.

Pharmacological therapy for obesity is far less effective when used alone with poor long-term maintenance of weight loss. Therefore it should always be combined with dietary and lifestyle modifications (21).

Some obese patients do not respond to drug therapy, and long-term success is unlikely if weight loss does not occur within the first 12 weeks of treatment (29).

Maintenance of the weight loss can be achieved by long-term use of the drug, while short-term use can lead to weight regain.

**Treatment of diabetes in obese patients**
Weight gain is an undesirable result of treatment for diabetes, which leads to poor cardiovascular outcomes and increased insulin resistance.

In selecting an anti-diabetic medication for an obese diabetic, one can opt for medications with a favourable effect on weight such as metformin, GLP-1 analogs, DPP-IV inhibitors and SGLT-2 (not registered in Sri Lanka), while trying to avoid medication that aid weight gain, including sulfonylureas, insulin and thiazolidinedione.

**Surgery in the management of obesity**
Bariatric surgery aims to reduce food intake by restricting gastric capacity and/or reducing uptake by reducing exposure to the small bowel absorptive area.

Bariatric surgery has been shown to be the most effective and durable treatment for morbid obesity. Compared to medical therapy, bariatric surgery has resulted in excellent outcomes including remission of diabetes and other co-morbidities and significant improvement in quality of life. It also improves cardiovascular outcomes and survival (30).

**Indications for bariatric surgery** (31-34)
Patients in age groups from 18 to 65 years:

1. With BMI ≥ 35 kg/m² (even when there are no medical problems)
2. With BMI ≥ 30 kg/m² with ≥ 1 obesity related co-morbidities such as:
   - Type 2 diabetes mellitus
   - Hypertension
   - Hyperlipidaemia
   - Obstructive sleep apnoea/obesity
   - Hypoventilation syndrome
   - Non alcoholic fatty liver disease /non alcoholic steatohepatitis
   - Asthma, venous stasis
   - Debilitating arthritis
   - Impaired quality of life

Note:
- BMI criterion may be the current BMI or previously maximum attained BMI of this severity.
- To be considered for surgery, patients should have failed to lose weight or to maintain long-term weight loss, despite appropriate surgical and/or non-surgical comprehensive medical care.
- Patients should have shown their compliance with scheduled medical appointments.
### Table 7. Currently approved weight reducing drugs

<table>
<thead>
<tr>
<th>Obesity drug</th>
<th>Mode of action</th>
<th>Dosage</th>
<th>Effects</th>
<th>Expected weight loss</th>
<th>Common side-effects</th>
<th>Special considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Orlistat (22,23)</td>
<td>Binds to lipases in the GI tract and blocks the digestion of dietary triglycerides</td>
<td>120 mg three times daily With meals</td>
<td>30% of ingested fat is unabsorbed and excreted May improve TC, LDL, TG, HbA1c</td>
<td>5% to 10% of the initial body weight, over one year</td>
<td>Mostly GI-oily spotting, flatus, fecal urgency/incontinence Fat-soluble vitamin malabsorption</td>
<td>Low-fat diet (≤ 30%) required to minimize side effects Supplementation of vitamin A, D, E, K</td>
</tr>
<tr>
<td>Lorcaserin* (24,25)</td>
<td>Selective serotonergic 2C receptor agonist Increases satiety and inhibits hunger effect</td>
<td>10 mg twice daily</td>
<td>May improve HbA1c</td>
<td>5 - 6% over one year</td>
<td>Headache, nausea, dizziness, fatigue</td>
<td>Hallucinogenic properties Serotonin syndrome (do not combine with SSRI or MAOI)</td>
</tr>
<tr>
<td>Phentermine*</td>
<td>Induces central norepinephrine release leading to decreasing food intake</td>
<td>15-30 mg daily</td>
<td>5% over 12 weeks</td>
<td></td>
<td>Dizziness, dry mouth, difficulty sleeping, irritability, nausea, vomiting, diarrhea or constipation</td>
<td>FDA approved for only 12 weeks continuous use.</td>
</tr>
<tr>
<td>Phentermine/topiramate* (26)</td>
<td>In combination greater weight reduction than either agent alone</td>
<td>Low - 3.75/23 mg/d</td>
<td>May improve glycaemic control, dyslipidaemia and hypertension</td>
<td>5 - 11% over one year</td>
<td>Headache, paresthesia, dry mouth, altered taste, dizziness</td>
<td>Avoid pregnancy due to increased birth defects</td>
</tr>
</tbody>
</table>

(Continued)
<table>
<thead>
<tr>
<th>Obesity drug</th>
<th>Mode of action</th>
<th>Dosage</th>
<th>Effects</th>
<th>Expected weight loss</th>
<th>Common side-effects</th>
<th>Special considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liraglutide** (27)</td>
<td>Selective glucagon-like peptide-1 (GLP-1) receptor agonist Regulates appetite by decreasing hunger and increasing satiety</td>
<td>3 mg once daily Sub-cutaneously</td>
<td>May improve prediabetes, systolic BP, triglycerides</td>
<td>5 - 10% over one year</td>
<td>Nausea, diarrhea, vomiting, hypoglycemia when used in combination with sulfonylureas Rarely - acute pancreatitis, acute cholecystitis</td>
<td>Increase heart rate by 2-3 bpm</td>
</tr>
<tr>
<td>Naltrexone (SR)/ Bupropion (SR)* (28)</td>
<td>Dopamine and norepinephrine reuptake inhibitor and opioid receptor antagonist Increases satiety and inhibits hunger effect</td>
<td>Starting dose- 8/90 mg daily Gradually increase upto, 32/ 360 mg/d in 2 divided doses by 4 weeks</td>
<td>May improve triglycerides, HDL, hs-CRP, HbA1c</td>
<td>5% - 10% over one year</td>
<td>Nausea, constipation, headache, vomiting, dizziness, insomnia, dry mouth, and diarrhea Risk for suicidal thoughts associated with bupropion</td>
<td>Contraindicated in patients with seizures, opioid use, abrupt cessation of alcohol, benzodiazepines and barbiturates May increase BP and heart rate</td>
</tr>
</tbody>
</table>

* FDA approved for obesity management but not registered in Sri Lanka at the time of publication.
** Registered in Sri Lanka for the treatment of Diabetes Mellitus.
Contraindications for bariatric surgery

- Absence of a period of identifiable medical management.
- Patient who is unable to participate in prolonged medical follow-up.
- Non-stabilized psychotic disorders, severe depression, personality and eating disorders, unless specifically advised by a psychiatrist experienced in obesity.
- Alcohol abuse and/or drug dependencies.
- Diseases threatening life in the short term- eg. Pulmonary hypertension.
- Patients who are unable to care for themselves and have no long-term family or social support that will warrant such care.

Types of bariatric procedures

Sleeve gastrectomy (SG)
This surgery involves removing the greater portion of the fundus and body of the stomach, reducing its volume from up to 2.5 L to about 200 mL. This procedure provides fixed restriction and does not require adjustment as in LAGB.

Mini gastric bypass
A mini gastric bypass creates a long narrow tube of the stomach along its right border (the lesser curvature). A loop of the small gut is brought up and hooked to this tube at about 180 cm from the start of the intestine. This results in restriction of food intake and modest malabsorption of nutrients.

Laparoscopic adjustable gastric banding (LAGB)
This surgery involves placing a band around the stomach near its upper end to create a small pouch. This restricts intake of food. The band can be tightened or loosened over time to change the extent of restriction.

Roux-en-Y gastric bypass (RYGB)
This is a combination procedure in which a small stomach pouch is created to restrict food intake and the lower stomach, duodenum and first portion of the jejunum are bypassed to produce modest malabsorption of nutrients and thereby kilo joule intake.

Biliopancreatic diversion (BPD)
This is also a combination procedure that involves removing the lower part of the stomach, and bypassing the duodenum and jejunum to produce significant malabsorption. This procedure is no longer recommended for Asians.

Management of obesity in children

Children are in continuous physical growth and behavioral development. Therefore approach to an obese child is different from that of an obese adult with regard to watching TV, computer games etc.

Classification
Sex specific BMI for Age charts available in the Sri Lanka Child Health Development Record (CHDR) can be used. These are based on WHO standards (Annexure 3,4)

- Obese: BMI more than +2SD
- Overweight: BMI between +1SD and +2SD
- Wasting: BMI below -2SD

For children less than 5 years of age the weight for height chart can be used.

- Obese: Weight for height >=+2SD
- Overweight: Weight for height between +1SD and +2SD
  - The ‘weight for age’ and ‘height for age’ should be plotted in the charts and compared.
  - Both ‘weight for age’ and ‘height for age’ are proportionately increased in simple obesity.
  - Any child who shows upward crossing of SD lines in the weight for age chart, should be plotted on the weight for height chart and the correct nutritional status need to be identified.
  - In genetic syndromes and endocrine diseases ‘weight for age’ is increased but ‘height for age’ is not proportionately increased, and therefore their ‘weight for height’ will be high and the ‘height for age’ usually lies below the median line. In other words they are more or less, ‘short obese’ individuals. They need further evaluation for any other underlying cause for the obesity.

Evaluation

- A thorough history and a complete physical examination is the most important step in the evaluation (for details please refer section on Evaluation).
- Routine hormonal or genetic tests are not indicated for the diagnosis unless clinical suspicion of an endocrine disorder or a genetic syndrome is present.
- The basic screening investigations are done to identify metabolic complications including FPG or OGTT, lipid profile and ALT. Imaging of liver may detect non alcoholic steatohepatitis.
Management

- The mainstay of treatment is lifestyle modification, which includes dietary adjustments, increased physical activity and behavioral changes.
- Pharmacotherapy and bariatric surgery are considered as second line options.
- The goals of the management are to achieve a BMI of <85th percentile and to prevent complications.
- The child needs a good support from the family to reach these goals. Therefore it is very important to educate and involve parents and other family members in these interventions.
- Treatment targets should be set based on pubertal stage of the child (35).
- Children who have not undergone pubertal growth spurt (Tanner stage <2 for girls, <3 for boys): maintain weight until the rapid height gain occurs which will reduce the BMI eventually.
- Children who have undergone pubertal growth spurt: attempt weight reduction

Diet

- Food based on portion sizes should be used to control the calorie intake and guide the types of foods that the child can take (38).
- High calorie, low nutrient foods such as sport drinks, fast foods should be avoided and intake of dietary fibre, fruits, and vegetables should be increased.

Physical activity

- Maintain at least 60 minutes per day of moderate to vigorous physical activity
- Reduce time of physical inactivity such as watching TV, computer games etc.
- Limit ‘screen time’ for 1 hour per day.

Behavioural changes

- Educate parents and siblings on psychological support to the child
- Limit availability of unhealthy foods at home
- Encourage in physical activity and avoiding over-dieting
- Explore psychological issues and support where necessary

Pharmacological therapy

- This should be always combined with lifestyle modifications and only be used when lifestyle modifications has failed to control weight gain or in the presence of severe co-morbidities associated with obesity (35,39).
- A specialist should initiate pharmacological therapy.
- Drugs available are orlistat and metformin.
- Orlistat is not FDA approved for less than 12 year olds and can cause vitamin deficiency due to malabsorption.
- Metformin is not FDA approved for treatment of obesity per se in children.

Bariatric surgery

Bariatric surgery can be considered after specialist opinion in severe obesity which fails to respond to above measures or where associated with severe co-morbidities (34).

Prevention of obesity in children

- Preventive measures should begin in-utero. Proper antenatal care should minimize maternal diabetes complications and low birth weight babies.
- Good infant care should focus on avoidance of inappropriate rapid weight gain of these babies and early detection and timely interventions by growth monitoring.
- Breastfeeding should be continued for first six months.
- Clinicians should take every opportunity to detect an obese child and educate on future implications to the child and parents.
- Policy makers should take appropriate measures to promote healthy eating habits and increased physical activity among preschoolers and school children and to restrict availability of “junk foods” and “fizzy drinks” (40).
References


Annexures

Annexure 1: Formula for calculation of BMI

\[ \text{BMI} = \frac{\text{Body weight (kg)}}{\text{Height}^2 \text{ (m)}} \]

Annexure 2: Procedure for measuring waist circumference (WHO Technique)

- Clear the subject’s abdomen of all clothing and accessories.
- Position the subject with feet shoulder width apart and arms crossed over the chest in a relaxed manner.
- Take a position to the right side of the subject’s body on one knee.
- The waist circumference measurement should be taken at the midpoint between the lowermost rib and the top of the iliac crest.
- First palpate the upper right hipbone of the subject until you locate the uppermost lateral border of the iliac crest.
- Mark the top of the iliac crest with a horizontal line drawn at the mid-axillary line.
- Next locate the lower most rib and draw a similar horizontal line at the mid-axillary line.
- The correct place to keep the tape is the midpoint between these two lines.
- Position the tape directly around the abdomen at the midpoint between the two lines.
- Use a cross-handed technique to bring the zero line of the tape in line with the measuring aspect of the tape.
- Ensure that the measuring tape is positioned in a horizontal plane around the abdomen. Apply tension to the tape to ensure it is snug, without causing indentation to the skin.
- At the end of a normal expiration, take the measurement to the nearest 0.5cm.

Annexure 3: BMI for age chart Boys

![BMI for age chart Boys](image)
Annexure 4: BMI for age chart Girls
The current diagnostic status of thyroid neoplasms in Sri Lanka – A histopathological analysis

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Introduction

The current diagnostic status of thyroid neoplasms in Sri Lanka has not been studied.

Objectives

We aimed to describe the current diagnostic status of thyroid neoplasms in patients who have undergone thyroidectomy at National Hospital of Sri Lanka from year 2008 to 2013, and to compare with similar data from year 2000 to 2005.

Methods

This was a retrospective study carried out at the department of histopathology, National Hospital of Sri Lanka. Data were gathered from 2236 postoperative thyroid histopathology reports over a period of 5 years from 2000 to 2005 and compared with 3675 postoperative histopathology reports over a period of 5 years from 2008 to 2013.

Results

In the first group 451 (20.2%) of specimens were neoplasms, of which 110 (4.9%) were benign and 341 (15.3%) malignant. In the second group 652 (17.7%) of specimens were neoplasms of which 187 (15.1%) were benign and 468 (12.6%) malignant. The prevalence of all neoplasms was higher in the second group and this was statistically significant (p = 0.02).

Papillary carcinomas constituted 243 (71.5%) of the malignant tumours in the 1st group and 16% were micro carcinomas. In the 2nd group, 352 were papillary carcinomas and 43% (151) were micro carcinomas. Although the difference in the prevalence of malignant tumours between the groups was not statistically significant (p=0.1) the increased detection of micro-papillary carcinoma in the second group was statistically significant (p<0.05).

Conclusions

Papillary carcinoma was the commonest tumour type in both groups and this diagnostic pattern has not changed since year 2002. However there was no increase in the prevalence of papillary carcinoma. There was also a significant increase of papillary micro carcinomas in the 2008-2013 group compared to 2000-2005.

A case of persistent hyperinsulinemic hypoglycemia of infancy (PHHI)

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Introduction

Persistent hyperinsulinemic hypoglycemia of infancy (PHHI) is relatively rare but one of the very important
Abstracts

causes of severe neonatal hypoglycemia. The onset is from birth to 18 month of age, but occasionally it is first seen in older children. We report a 6 months old girl with PHHI presenting with recurrent seizures.

Case report
A 6-month-old girl of non-consanguineous parents presented with three episodes of seizures during a one-month period. Capillary blood glucose on admission to the hospital was 21 mg/dl and simultaneous venous random blood sugar was 23 mg/dl. Urine ketone bodies were negative. Child developed hypoglycemic seizures despite being on a 12 mg/kg/min of glucose infusion. Serum insulin level performed during a hypoglycemic episode (blood glucose 32mg/dl) was 21 U/ml. This confirmed PHHI.

There were no dysmorphic features and the child had normal milestones and weight for age. Neurological examination was normal.

Blood glucose levels improved with diazoxide treatment. Currently she is on 5mg/kg/day diazoxide with no breakthrough events while on frequent 3 hourly feeds. Genetic testing at Exeter Molecular Genetics Laboratory did not reveal a definitive known mutation. The importance of checking blood glucose on a fitting child and calculating glucose utilization rate is highlighted here.

3

Subclinical hypothyroidism (SCH) in patients with polycystic ovary syndrome (PCOS): prevalence and association with metabolic parameters in a south Asian cohort

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Introduction
Both PCOS and hypothyroidism are common endocrine abnormalities which share similar clinical features. They are reported to occur simultaneously, and hypothyroidism may be underdiagnosed.

Methods
Retrospective data were collected by convenient sampling of records of a large database maintained with consecutive consenting women fulfilling Rotterdam criteria for PCOS, attending an Endocrine Specialist Clinic in Colombo. Pretreatment clinical symptoms, examination findings including height, weight, waist-hip measures, blood pressure and laboratory data including thyroid hormones and biochemical profile were analyzed.

Results
The study included 112 subjects with PCOS out of whom 32 (28.6%) subjects had SCH. Among the participants 20 (18.7%) were already on treatment with thyroxine, mean daily dose 71.74±10.58μg. Mean TSH and free T4 levels of subjects with hypothyroidism were 3.054±0.46μIU/mL and 1.29±0.12 ng/dL respectively.

The prevalence of metabolic risk factors were significantly higher in those with SCH compared to euthyroid women with PCOS: BMI>23 kg/m2 77 (96.4%) versus 50 (65.8%), central adiposity (waist>80cm) 27(96.4%) versus 54 (74.0%), impaired fasting glucose 6 (21.4%) versus 4 (6.6%) and impaired glucose tolerance 13 (46.4%) versus 17(25.8%). Logistic regression analysis showed the presence of SCH was an independent predictor for obesity (OR=14.04, 95% C.I.=1.81-109.22) and central adiposity (OR=9.50, 95% C.I.=1.21-74.78).

Conclusions
There is a high prevalence of SCH coexisting with PCOS. Women with SCH in addition to PCOS appear to have greater cardiovascular and metabolic risks. Therefore appropriate management of co-existing SCH is crucial in women with PCOS.

4

Histopathological analysis of chronic lymphocytic thyroiditis from 2008 to 2013: data from a national referral centre in Sri Lanka

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Introduction
Chronic lymphocytic thyroiditis (CLT) is an autoimmune disease of the thyroid gland, which is predominantly seen, in middle-aged females. The histology is characterized by the presence of diffuse lymphocytic infiltrates and...
lymphoid follicles with germinal centre’s in addition to other features. Studies have suggested that the prevalence of papillary carcinoma is higher in CLT.

Objectives

This study was undertaken to describe the pattern of CLT in patients who have undergone thyroidectomy at National Hospital of Sri Lanka over the last 5 years (2008 to 2013) and to describe any other associated pathology.

Methods

This was a retrospective review of 3675 consecutive histopathology records of total and subtotal thyroidectomy specimens over a five year period from 1st July 2008 to 30 June 2013. The study was conducted at the department of histopathology, National Hospital of Sri Lanka. Two board certified consultant histopathologists with MD Histopathology were involved in making the histopathological diagnosis.

Results

Out of 3675 thyroidectomy specimens 597 (16.24%) had histological features of CLT. In 252 (6.8%) there were no ancillary diagnosis other than CLT but in 345 specimens an ancillary diagnoses were present. Twenty patients with histologically proven CLT had lymph nodes dissected which were reactive. The associated benign pathologies were as follows; colloid goitre 264 (44.2%), hyperplastic nodules 28 (4.6%), follicular adenoma 13 (2.1%) and hurthle cell adenoma 3 (0.5%). The malignant lesions were as follows; papillary carcinoma 34 (5.6%) of which 23 had focal or multifocal micropapillary carcinoma, Hurthle cell carcinoma 1, lymphoma 1 and poorly differentiated carcinoma 1.

Conclusions

The prevalence of CLT in thyroidectomy specimens was 16.24%. In more than 50% of specimens with CLT colloid nodules or hyperplastic nodule were present. Papillary carcinoma was the commonest tumour type in patients with CLT.

The impact of point of care HbA1C on clinical decision making of doctors

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Introduction

Both international and local guidelines recommend HbA1C for monitoring glycemic control. HbA1C is not freely available in most government hospitals which use monthly FBS and PPBS measurements. Our objective was to find out whether point of care (POC) availability of HbA1C is going to affect the clinical decision making.

Methods

The study included 100 randomly selected patients attending the Diabetic Clinic of the NHSL who were followed up for at least one year. First, the patient was allowed to be seen by doctor as a routine clinic visit. Then POC-HbA1C assessed by finger prick capillary blood using Bio-Rad A1C in-office analyzer. Then the doctor was asked to see the patient again with POC-HbA1C and any changes made to the management were recorded.

Results

The selected 100 patients consisted of 65 females and 35 males with a mean duration of diabetes of 7.8 years. Their treatment regimens were as follows; metformin only 8%, metformin plus other OHG 50%, metformin plus insulin 30%, insulin only 10%, insulin plus other OHG 2%. The group average HbA1C was 9.25% (SD 1.88%) with males 8.19% and females 9.53%. The average FBS was 143.60 mg/dL (n=84) and average PPBS was 182.3 mg/dL (n=61).

In 69/100 consultations the management changed after POC-HbA1C reports leading to increased drug doses (80%), numbers (18%) or both (2%). In the remaining 31/100 consultations; reasons for no change were either poor compliance or that changes had already been made after seeing high FBS/PPBS.

Conclusions

There is a wide discrepancy between FBS/PPBS readings and HbA1C and seemingly “satisfactory control” may mislead clinician and expose patient to risks of chronic hyperglycemia. Availability of POC-HbA1C leads to positive changes in management and avoids treatment errors.

Incidental endocrine tumours and other abnormalities in a Sri Lanka population: methodology and preliminary data

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Introduction

Incidental tumours and other abnormalities are increasingly diagnosed in endocrine organs due to the availability of sophisticated imaging techniques. There is paucity of such data among Sri Lankans. Our aim is to determine the prevalence of these abnormalities for the Sri Lankan population.

Methodology

In this descriptive study 500 consecutive autopsies (250 males and 250 females) will be included at the Judicial Medical Officers (JMO) Office in Colombo. Informed written consent will be obtained from next of kin. Patients with history of endocrine diseases except diabetes will be excluded. A structured case record form is used to get demographic and disease related data. Post-mortem examination and specimen collection will be conducted by JMOs and trained data collectors. Pituitary, thyroid, pancreas, adrenal, liver, ovaries and testes will be macroscopically examined. Representative samples from either macroscopically normal glands or grossly visible lesions are taken to be evaluated histologically via H&E staining by two consultant histopathologists. Data analyzed using SPSS.

Results

Among the 28 cases studied to date all were male (mean age 48.76 +/- 8.6 years).

Among the thyroids, 18 (64.3%) were normal, 4 (14.3%) solitary nodules, 5 (17.8%) multinodular goiters and 2 (7.1%) diffusely enlarged glands were identified.

We found 1 (7.1%) micro-pappilary carcinoma, 1 (7.1%) suspicious of burnout multifocal papillary carcinoma and 1 (7.1%) Hurte cell adenoma in a background of thyroiditis.

Colloid nodules, 7(25%), hyperplastic nodules 4(14.28%), thyroid 4 (14.3%) and toxic goiters 2 (7.1%) were benign lesions. All pituitaries were normal. Mild fat infiltration with or without fibrosis was found in 8 (28.57%) pancreases. Nodular hyperplasia of adrenal was found in 1 (3.33%).

Conclusions

This preliminary study has already show interesting results regarding incidental abnormalities in endocrine organs.

The prevalence of diabetes, pre-diabetes and obesity among adults living in an urban setting in Colombo, Sri Lanka

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Introduction

Sri Lanka has been experiencing rapid urbanization, with approximately 20% of the population residing in urban areas. We report the age and sex-specific prevalence of dysglycaemia and obesity among adults living in an urban setting in Colombo, Sri Lanka.

Methods

Using a stratified random sampling method, 369 subjects (116 men; 253 women) aged 18 years and above, representative of all socio-economic strata, were tested by OGTT and HbA1c. Pre-diabetes defined as either HbA1c 5.7-6.4%, FBS 100-125 mg/dl or OGTT 2hr 140-199 mg/dl; BMI cut-offs for overweight 25 - 29.9 kg/m2, obese ≥ 30 kg/m2. Demographic, anthropometric, educational and social details were recorded using a standard case record form.

Results

The overall prevalence of diabetes was 26.92%. The prevalence increased with age and reached a peak of 40% (95% CI 22.66-31.65) in the above 60 age group. Pre-Diabetes was detected in 32.34% of the population with highest prevalence of 40% (95% CI 33.8-47.19) in the 41-60 year group. The cumulative prevalence of diabetes and pre-diabetes in the population was 59.26%.

The overall prevalence of overweight and obesity was 57.82% (overweight 39.89% and obesity 17.93%). The highest prevalence of obesity 20.94% (95% CI 15.9-27.07) was in the 41-60 year group with females having higher prevalence of 22.06% (95% CI 17.09-27.98) compared to males. 8.95% (95% CI 4.7-16.37) to males.

Conclusions

This study shows a high prevalence of dysglycaemia and
obesity in urban Sri Lankan adults with a high prevalence of pre-diabetes who are at high risk of conversion to diabetes.

8

Cardiovascular risk among adults living in an urban setting in Colombo, Sri Lanka

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Introduction
Cardiovascular (CV) disease has emerged as a major contributor to total global mortality. Life style changes associated with urbanization may contribute to increased CV risk. We report the age and sex-specific prevalence of hypertension, dyslipidaemia, metabolic syndrome and central obesity in an adult population in an urban setting in Colombo, Sri Lanka.

Methods
369 subjects (116 men; 253 women) aged 18 years and above, representative of all socio-economic strata, were stratified using random sampling. Their demographic, anthropometric, educational and socio-economic details were recorded using a standard questionnaire and all underwent a fasting plasma glucose, OGTT and lipid profile. Cut offs for central obesity were male ≥ 90 cm, female ≥ 80 cm.

Results
The overall prevalence of hypertension was 27.26% with the highest prevalence of 40.74% (95% CI 30.91-51.37) seen in the over 60-age group.

High LDL cholesterol (≥ 160 mg/dl) was found in 12.18% with the highest prevalence of 18.85% (95% CI 14.05-24.81) in the 41-60 age group. Total Cholesterol of ≥240 mg/dl was seen in 21.42% with highest prevalence 25.13% (95% CI 19.65-31.53) in the 41-60 age group.

Metabolic syndrome, according to the ATP III criteria, was prevalent in 24.69% of the population. The prevalence increased with age but was equal in both sexes.

The overall prevalence of central obesity was 52.52%, highest 59.16% (95% CI 52.28-65.7) in the middle age group 41-60 years. Central obesity was found in 60.7% (95% CI 54.18-66.98) of the females, and 34.57% (95% CI 25.9-44.4) of males.

Conclusions
More than half the population in the study were centrally obese, particularly the middle-aged subjects and women. Dyslipidaemia was more prevalent in the middle-aged population. Metabolic syndrome; a clustering of cardiovascular risks, was detected in a quarter of the population, indicating a high burden of future cardiovascular disease in urban Sri Lankan adults.

9

Child with benign transient hyperphosphatasia of childhood presenting with mild degree of bow legs – A case report

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Introduction
Hyperphosphatasia is characterized by a marked elevation of the bone isoenzyme of alkaline phosphatase in serum and significant growth failure. Transient hyperphosphatasia occurs between 2 months and 2 years of age, has no associated manifestations other than some mild gastrointestinal symptoms, and is usually detected during routine (screening) laboratory evaluation for some unrelated complaint. Serum alkaline phosphatase values as high as 3,000 to 6,000 IU/L may be encountered. The cause is unknown. Resolution usually occurs within 4 to 6 months.

Case report
We report a 1-year and 8 months old patient with transient hyperphosphatasia presenting with mild degree of bow legs. He presented with a history of bowing of his legs of 6 month duration. Child had started walking at 1 year and 2 months and since then he was having worsening of bowing of his legs. He had an uneventful perinatal period with a birth weight of 3.5kg and had normal growth and development. There was no history of nutritional
inadequacy of vitamin D or calcium and no history suggestive of renal or liver diseases. Patient was investigated and was found to have high (3782 U/L) serum alkaline phosphatase levels with normal serum calcium and phosphate. Serum 25-hydroxy vitamin D level was 72.6 nmol/L (sufficiency >50 nmol/L). X-Rays were normal. Child was followed up monthly without any medication with serial ALP measurements which came down after 3 months (580 U/L). Diagnosis of benign transient hyperphosphatasia of childhood was made.

Thyrotoxicosis with normal TSH levels – A case report

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Introduction
Thyroid hormone resistance is a rare dominantly inherited disorder with variable clinical presentations. Patients could either be asymptomatic or will have features suggestive of hyperthyroidism. These patients have elevated free thyroxin (fT4) level with non-suppressed thyroid stimulating hormone (TSH) level.

Case report
We present a child with thyroid hormone resistance due to heterozygous mutation of thyroid hormone receptor (THRB). A 12 year old girl presented to us with features of thyrotoxicosis with high fT4 and non-suppressed TSH. Her initial presentation was at 7 years. She had a nodular goiter, prominent eyes with total thyroxin of 18ug/dl and TSH of 2.1 miu/L. She was started on carbimazole at the age of 10 years. When she presented to us her goitre had increased in size and fT4 level was 3.5 and TSH was 30miu/L. Her father had a goitre at 4 years of age and underwent subtotal thyroidectomy. He does not recollect any toxic features. He subsequently had surgery for papillary thyroid carcinoma.

Both the father and the patient were found to have a mutation in THRB (G344R), which has previously been described in thyroid hormone resistance. We stopped carbimazole on this child and she is currently on propranolol therapy. She is asymptomatic and the size of the goiter has reduced. This is the first genetically confirmed patient of thyroid hormone resistance from Sri Lanka.

Dercum disease – a rare cause of obesity – A case report

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Introduction
Dercum disease is an autosomal dominant disorder characterized by multiple fatty deposits, generalized obesity, generalized weakness and psychiatric manifestations and commonly present in pre-menopausal women between the ages of 35-50.

Case report
A 50 year-old lady presented with weight gain, generalized body pain, discomfort and multiple lumps on limbs and the trunk. Severity of the pain had not changed with menstrual cycles. She wasn’t able to attend to day-to-day activities. She was diagnosed to have hypertension and hypothyroidism recently and was on antihypertensives and thyroxine. Her food habits had not changed recently. Her weight was 116kg and BMI 42.6kgm−2. There were multiple lipomata on legs and trunk.

Discussion
Dercum disease is classified in to four forms, generalized diffused, generalized nodular, localized nodular and juxta articular. Multiple lipomas are seen in limbs, trunk and buttocks and they are not affected by weight reduction. Patient may have features of carpal tunnel syndrome, generalized weakness, cognitive dysfunction and depression. Investigations should be done to exclude other endocrine abnormalities. Ultrasonography and MRI may aid the diagnosis.

Management of Dercum disease is mainly symptomatic. Dietary and lifestyle modification is useful to reduce overall obesity. Liposuction, local anesthetics, surgical treatment and a course of prednisolone could be used to reduce pain. Psychiatric referral may be necessary. Although case reports suggest that pain might get worse with time, data on longstanding outcome and natural history of Dercum disease is limited.
Carbimazole induced agranulocytosis: a case series

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Abstract

Background

Carbimazole is a widely used antithyroid drug in hyperthyroidism. Agranulocytosis is a rare but serious complication of carbimazole with a high mortality rate.

Methods

We conducted a retrospective study, to assess the clinical presentation of agranulocytosis, routine pre-treatment full blood counts and methods of treatment, by analysing five cases of carbimazole induced agranulocytosis, over a period of 18 months in a tertiary care hospital of Sabaragamuwa province in Sri Lanka. Clinical evaluation of the presentation, analysis of the full blood counts and treatment methods were considered in each patient.

Results

Four out of five cases were in their forties and two were male patients. Fever, arthralgia, sore throat and diarrhoea were common symptoms. Pretreatment full blood counts were either not available or documented in three patients. In all five cases, agranulocytosis occurred within 2 months of commencing carbimazole. Three patients were treated with granulocyte colony stimulating factor for 5 days while four were given prophylactic intravenous antibiotics. All five cases recovered from agranulocytosis.

Following recovery, lithium carbonate was started for hyperthyroidism preceded by treatment with radioactive iodine in four patients.

Conclusion

We concluded that 1) a pre-treatment routine full blood count may be important prior to treatment with carbimazole. 2) Patients and caregivers should be educated on common symptoms of agranulocytosis for an early diagnosis of this rare complication. 3) Treatment with granulocyte colony stimulating factor accelerates the recovery. 4) Radioiodine followed by lithium carbonate is an alternative follow up treatment.

The pattern of endocrine disorders among the elderly: data from a specialist clinic

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Introduction

Age more than 60 years is the cut-off for elderly. Sri Lankan population is aging faster than in most countries. This study describes demographic data and pattern of endocrine disorders of the elderly population attending a general endocrine clinic.

Methods

This descriptive cross-sectional study included all elderly patients attending the general endocrinology clinic of National Hospital Sri Lanka during a period of 12 weeks; patients from diabetes, osteoporosis and pituitary tumor clinics were not included. An interviewer administered data collection form was used.

Results

Total number of elderly patients was 209 (16.8% of all clinic patients, n=1248) with 163 (78%) females and 46 (22%) males. New patients were 9.9% (n=20/209). Most (n=91) belonged to age 60-64 years followed by 65-69 years (n=76). Thyroid disorders were seen in 82% followed by pituitary (8%) and adrenal diseases (4%).

In patients with thyroid diseases 53.5% had hypothyroidism and 36.6% had hyperthyroidism. Thyroidectomy was the cause for hypothyroidism in 25% and 52% had evidence of autoimmune thyroiditis according to positive auto-antibodies or FNAC findings. Toxic nodular goiter (TNGs) was the commonest cause of hyperthyroidism (58.7%) followed by Grave’s disease (25.4%).

Non-functioning pituitary adenomas were the commonest cause of pituitary disease (n=8/17). Interestingly there were 4 patients with Sheehan’s syndrome and 2 patients with idiopathic panhypopituitarism. Primary hypoadrenalism was the commonest cause of adrenal disease (n=6/8).

Conclusions

Thyroid disorders being the commonest endocrine disorder in the elderly population in this clinic. TNGs was the main cause for hyperthyroidism and autoimmune thyroiditis for hypothyroidism.