<table>
<thead>
<tr>
<th>Contents</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Editorial</strong></td>
</tr>
<tr>
<td>63</td>
</tr>
<tr>
<td>W K M G Amarawardena, S Siyambalapitiya, C J Subasinghe</td>
</tr>
</tbody>
</table>

**Original papers**

| 65 | Reliability of ankle-brachial pressure index measured by pulse palpation method in diagnosing peripheral arterial disease among patients with diabetes mellitus |
| L D Ranasinghe, N P Somasundaram, S W A D A Wickramasinghe, N Ranawake, K R C Jayasena |

| 69 | Success rate of treating acromegaly at national hospital of Sri Lanka |
| S Pathmanathan, M Saranapala, N P Somasundaram |

| 75 | Metabolic risk factors detected among the attendees to free health camps conducted in Western province of Sri Lanka |
| S A S P Subasinghe, C W Jayesundere, Kanthi Piyaseeli, P A Epa, Nirmanee Gamage, Priyanga Senanayaka, R P Palitha Karunapema |

| 79 | Prevalence of the metabolic syndrome among patients with type 2 diabetes |
| S A Abhayaratna, N P Somaundaram, H Rajapakse |

**Clinical update**

| 85 | Insulin technique |
| Sanjay Kalra, Yashdeep Gupta |

**Case reports**

| 91 | Mineral and bone disorders secondary to chronic kidney disease (renal osteodystrophy) |
| Alphansus N. Onyiriuka, Olubunmi B. Fakeye-Udeogu, Mohammad Abdullahi, Chiedozie J. Achonwa, Isaac O. Oluwayemi, Moustafa Kouyate, Abiola O. Oduwole, Elizabeth E. Oyenusi |

(Continued)
95  Challenges in the diagnosis and management of Cushing’s syndrome due to ectopic ACTH from bronchial carcinoid
   M S A Cooray, N P Somasundaram, Janakie Fernando, A H N Fernando, R M De Silva, D Rasnayake

100  Erectile dysfunction with elevated serum testosterone
   L D Ranasinghe, K D Liyanarachchi, N P Somasundaram

103  Successful twin pregnancy in panhypopituitarism
   R D Jeewantha, M R L Perera, C N Wijeyaratne, L D Ranasinghe

Images in endocrinology  107  Acromegaly with normal pituitary MRI
   L D Ranasinghe, K D Liyanarachchi, N P Somasundaram

Supplement
Clinical guidelines  S1  Cardiovascular risk reduction in diabetes mellitus

S16  “SAFE & SMART” Use of sulfonylureas in the management of type 2 diabetes mellitus in South Asia – A consensus statement

Endocrine Abstracts
Cardiovascular disease: the leading cause of diabetes related mortality

W K M G Amarawardena, S Siyambalapitiya, C J Subasinghe

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Diabetes is an independent risk factor for cardiovascular disease (CVD) including coronary arterial disease, stroke, peripheral arterial disease, cardiomyopathy and congestive heart failure in both men and women. Women seem to have an inherent protection against CVD and they seem to loose most of that natural protection, once they develop diabetes. Compared to the patients without diabetes, the patients with diabetes sustain a poorer prognosis with CVD, accounting for two thirds of deaths in diabetes. In Sri Lanka deaths due to cardiovascular diseases are found to be higher than that in most developed countries (1).

The diabetes pandemic is underway and the Asia is at its epicenter. Despite its initial association with the affluent societies, diabetes mellitus is fast becoming a disease of the masses. Global burden of diabetes is rising dramatically, where it is estimated that the prevalence of 387 million in 2013 will grow up to 592 million by year 2035 (2). The Sri Lankan population has not been spared from this malaise and a similar upward trend in prevalence has been observed in local studies. The dramatic rise seen in the prevalence in urban areas deserves special attention and currently stands at a staggering 26.92%. It was noted to increase with age and reached up to 40% in those older than 60 years (3). The prevalence of pre-diabetes was also very high with this study with a figure of 32.34% (3).

Due to the common genetic and patho-physiological background, multiple metabolic and other cardiovascular risk factors get clustered together with diabetes, multiplying the cardiovascular risk in these patients. Paralleling the explosion of diabetes, these coexistent cardiovascular risk factors including hypertension, obesity, physical inactivity and smoking also have reached epidemic proportions. Approximately one fifth of Sri Lankan adults are suffering from hypertension and metabolic syndrome, while same proportion reported to be smokers (3). The guideline on cardiovascular disease in diabetes by Endocrine society of Sri Lanka (ESSL) emphasizes the importance of cardiovascular risk assessment at the time of diagnosis of diabetes and active risk modification from there. Coronary artery disease (CAD) is the leading killer among all cardiovascular complications, as well, is known to be a silent killer in most instances. Active recognition of CAD and secondary prevention is a major step towards reducing CVD related mortality.

Undoubtedly, it has being proven that the multiple intervention approach to be the best to combat the cardiovascular disease related morbidity and mortality in diabetes. STENO-2 trial, despite its limitations including the smaller sample size, holds the land mark of this aspect (4). Lifestyle modifications stand as the foundation of overall better metabolic and cardiovascular outcome, which includes medical nutritional therapy, increased physical activity, weight loss, and smoking cessation.

There is no controversy regarding the impact of blood pressure control on significantly better macrovascular outcome throughout almost all major clinical trials up to date (5-9).

United Kingdom Prospective Diabetes Study (UKPDS) signifies the importance of early aggressive blood sugar control in type 2 diabetes as a fruitful way forward to future cardiovascular risk reduction (10,11). Encouraging evidence for benefits of glycaemic control in cardiovascular benefits among type 1 diabetes comes from the Diabetes Control and Complication Trial (DCCT) (12). However, a non lenient approach to the glycaemic goals may take off the expected cardiovascular benefits of glycaemic control. Therefore, ESSL recommends more individualized glycaemic targets considering the age, life expectancy, co morbidities and complications.

ESSL recommendations on aggressive statin therapy, despite direct primary cost, would be more cost effective for a developing nation, when the long term benefits are taken into consideration. Although the benefit of aspirin in primary prevention of cardiovascular disease in the patients with diabetes without cardiovascular disease is

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Editorial

controversial, the place for secondary prevention has been strongly established for decades. Together with the evidence from Anti Thrombotic Trialist (ATT), American Diabetes Association (ADA), the American Heart Association (AHA) and the American College of Cardiology Foundation (ACCF) recommend that low-dose (75-162mg/day) aspirin for primary prevention is reasonable for adults with diabetes with increased CVD risk (10-year risk of CVD events over 10%) and who are not at increased risk for bleeding. Though we have clearly recognized the disproportionately greater cardiovascular risk among Asians, we still struggle for a better unique CVD risk calculator, where more research work is essential as a way forward.

References
Reliability of ankle-brachial pressure index measured by pulse palpation method in diagnosing peripheral arterial disease among patients with diabetes mellitus

L D Ranasinghe¹, N P Somasundaram¹, S W A D A Wickramasinghe¹, N Ranawake¹, K R C Jayasena¹


Abstract

Introduction: Ankle brachial pressure index (ABI) is a useful screening test to detect peripheral arterial disease (PAD). However, the limitation for the widespread use of this test is the lack of doppler devices in most of the resource poor settings. In contrast, the pulse palpation method requires only a blood pressure apparatus with a suitable cuff and is a cheaper and readily available alternative.

Materials and methods: The objective of this study is to evaluate the accuracy and reproducibility of ABI measured by pulse palpation method and to study the correlation between the pulse palpation and doppler method. Population of 193 patients with diabetes were examined by two trained medical officers and ABI was measured by each examiner using pulse palpation method (pABI) and doppler method (dABI).

Results: There was a statistically significant difference between the values obtained by the two observers for both dABI and pABI. There was a significant difference between dABI and pABI measurements (p<0.01). The pABI was lower than the dABI, but there was a significant positive correlation between dABI and pABI in both lower limbs (p<0.01).

Conclusion: According to our study, pABI had a sensitivity of 62% and a specificity of 90% in diagnosing PAD. Even though the doppler method cannot be replaced by pulse palpation method, there was a significant positive correlation between the two methods indicating that the pABI can be utilized to predict the pABI in resource poor setting.

Key words: ankle brachial pressure index, doppler device, peripheral arterial disease, resource poor setting, palpation method.

Introduction

PAD is common among patient with diabetes with a prevalence of 20% to 30% (4). It is also an important prognostic marker of cardiovascular disease related morbidity and mortality (1, 2, 3). Functional disability associated with PAD also leads to poor quality of life. PAD is usually severe and the outcome is poorer in patients with diabetes compared to patients without diabetes (5). Hence early detection and proper treatment of PAD in diabetic patients is of paramount importance in order to reduce the risk of cardiovascular events and longterm disability. Unfortunately, PAD is mostly silent and diagnosis is made at late stages.

ABI is a simple, non-invasive screening test, which can be used to diagnose as well as to assess the severity ofPAD. The lower ABI values are associated with greater risk of cardiovascular events and the patients with the lowest ABI values have an annual mortality rate of about 25 percent (6, 7).

Due to the high prevalence of PAD in patients with diabetes, a screening ABI is recommended for all the patients with diabetes above the age of 50 years. When the PAD risk is high (when there are other PAD risk factors such as smoking, hypertension, hyperlipidemia or duration of diabetes >10 years) ABP is recommended even for the patients age less than 50 years (8). However, due to the unavailability of doppler devices and the lack of technical skills especially in resource poor setting, ABP is not frequently used in primary care setting for the screening ofPAD.

ABI has a sensitivity of 90% and a specificity of 98% in detecting an angiographically defined stenosis of ≥ 50% (9). ABI values determined by simple pocket doppler devices can give similar results to that measured by automatic vascular laboratory equipment (10). ABI could also measured easily by pulse palpation method in primary care settings. However, previous studies done on accuracy of ABI measured by pulse palpation have not shown impressive results (11, 12).

¹National Hospital of Sri Lanka.
The objective of this study was to evaluate the accuracy and reproducibility of ABI measured by pulse palpation method in diagnosing PAD among patients with diabetes. Furthermore, we aimed to study the correlation between the pulse palpation and doppler method.

Methods

A cross sectional study was conducted at diabetes clinic in national hospital of Sri Lanka over a period of two months. Ethical clearance for this study was obtained from the ethical review committee of the national hospital of Sri Lanka.

Patients attending foot care clinic were included in the study after obtaining informed voluntary verbal consent. Patients who were having active ulceration or pain in legs which makes it difficult to measure ankle pressure and patients with past history of lower limb amputations were excluded. Those who did not consent were also excluded. Eligible patients were examined by two trained medical officers separately initially by palpation method followed by doppler method using hand held doppler device. Following a 10 minute resting period in supine position, systolic blood pressures (SBP) in the brachial, dorsal pedal and posterior tibial arteries were obtained by pulse palpation method and doppler method with a sphygmomanometer cuff placed 2cm proximal to the malleoli or elbows. The first palpable or doppler impulse was used to identify the SBP at each location.

In doppler method, the pulses were located by palpation and the tip of the doppler probe was placed until an audible pulse signal is obtained. Then the pressure cuff was inflated 20mmHg above the point where the pulse is no longer audible. The cuff was slowly deflated at a rate of 2mmHg per second, noting the manometer reading at which the first pulse signal is heard and that was recorded as SBP. In pulse palpation method, pulse palpation was used instead of doppler signal to obtain SBP using the same technique. The ABI was calculated by dividing the highest systolic ankle pressure (either posterior tibial or dorsal pedal) in each leg by the highest systolic brachial pressure.

Data was analyzed using SPSS 17 software. Differences between measurements were assessed using one-sample Student’s t-test. Multivariate linear regression analysis was used to assess the dependency of the observed difference between the two methods (correlation).

Results

We studied 193 patients. The means of the values obtained by observer A were; dABI left 1.08 (SD=0.17), dABI right 1.07 (SD=0.15), pABI left 1.01 (SD=0.14), pABI right 1.03 (SD=0.13) whereas the means of the values obtained by observer B were; dABI left 1.11 (SD=0.18), dABI right 1.07 (SD=0.15), pABI left 1.03 (SD=0.15), pABI right 1.03 (SD=0.16).

There was a statistically significant difference between the values obtained by observer A and B for both dABI and pABI of left lower limb (p<0.01), indicating that there is a significant observer difference in obtaining the pulse and doppler values. Statistically significant differences were also observed between dABI and pABI (p<0.01) in both the observers A and B for both left and right lower limbs and ABI obtained from pulse palpation and Doppler method (palpation gave a lower value than that from doppler method).

Statistically significant correlations were observed between dABI and pABI in both the left and right lower limbs in A and B (figure 1) indicating that dABI can be predicted by pABI. Pulse palpation method had a sensitivity of 62% and a specificity of 90%. The positive predictive value was 39% and the negative predictive value was 96%.

In summary, there was a statistically significant difference between the values obtained by the two observers for both dABI and pABI (p<0.01). There was a significant difference between dABI and pABI (p<0.01) and pABI was lower than the dABI. Interestingly, there was a significant positive correlation between dABI and pABI in both lower limbs (p<0.01). However, the sensitivity of pABI was only 62%.

Discussion

The accuracy and reproducibility of the ABI can vary, according to the population studied, the cut-off threshold and the technique used to detect the blood flow in the arteries. According to available evidence, doppler method appears to be the most reliable method to determine the ABI. However, a recent meta-analysis of 8 studies of different populations, including patients with diabetes, showed a reasonably high specificity (83%-99%) but a lower sensitivity (69%-79%) in detecting peripheral arterial disease (13). Several studies have reported even lower sensitivities (53%-70%) in diabetic patients (14). Our study has showed that a simple technique such as pulse palpation for ABP estimation can also have almost similar predictive values (specificity of 90% with a sensitivity of 62%)

Studies on intra observer and inter observer reproducibility of the dABI have shown varying results with intra observer coefficient of variation (CoV) ranging from 4.7% to 13.0% (15, 16). Our study also showed poor reproducibility of dABI among the observers. Hence, ABI appears to be highly operator dependent. Therefore,
Reliability of ankle-brachial pressure index measured by pulse palpation method in diagnosing clinical judgment is important when interpreting the ABI results in patients at high risk of PAD. When clinical decisions are made, the possibility of falsely elevated ABI, especially in patients with diabetes and operator dependent variation of the results should be taken into consideration. ABI immediately after treadmill exercise has shown to be more sensitive than resting ABI, especially useful in patients who are on maintenance haemodialysis (17, 18) and it could be a worthy experiment to replicate this finding using palpation method.

Former studies have shown that pulse palpation method is inferior (sensitivity of 88% and a specificity ranging from 75% to 82%) to the doppler method in detecting peripheral arterial disease (12, 19). However, our study showed different results with a sensitivity of 62% and a specificity of 90%. Interestingly our study showed a significant positive correlation between dABI and pABI in both lower limbs (p<0.01) suggesting that this could be utilized as a useful alternative to doppler method in assessing peripheral arterial disease in resource poor setting.

**Conclusion**

ABI is a simple non-invasive measurement to detect PAD. Our study showed that both dABI and pABI are highly operator dependent. Therefore, ABI should be interpreted carefully in a given clinical context. Even though doppler method cannot be replaced by pulse palpation method, we noted a significant positive correlation between the two methods. This may indicate that the dABI can be predicted by pABI and pABI may be helpful in screening for PAD especially in resource poor setting.

**References**


Abstract

Introduction: Pituitary surgery, radiotherapy and medical therapy with dopamine agonists (DA), somatostatin analogues (SA) and growth hormone receptor agonists (GHRA) are the main treatment modalities that are recommended for treating acromegaly. Most of these treatment modalities are too expensive or not available in most of the resource settings like ours. The objectives of this study were to describe the demographic factors, presentation and comorbidities in acromegaly patients and to analyze the outcome of the treatment modalities used in our clinical setting, which include remission, recurrence and mortality among patients with acromegaly.

Materials and methods: This was a descriptive cross sectional study conducted among 72 acromegaly patients attending endocrinology and pituitary clinics at national hospital of Sri Lanka between January 2012 and June 2013. Pituitary adenomas were classified based on Hardy’s classification. A remission criteria of nadir growth hormone level <1 mu/l after oral glucose tolerance test (OGTT) or less than 5 mu/l in a five point growth hormone (GH) day curve was used.

Results: 54.1% of the patients were females. The mean age of the patients at the time of presentation was 39.52 (SD± 12.8) years and the mean duration of symptoms on presentation was 3.28 years (SD± 2.7). The commonest presentations were the changes in facial appearances and the increase in shoes and ring sizes (88%). 81.8% had tumour grade II and above. 14.2% had prolactin co-secretion with GH. 86.1% underwent transsphenoidal surgery (TSS). 37.5% of patients with grade I tumour and 33.3% of patients with grade II tumour achieved remission following TSS. None of the patients with tumour grade III or above achieved remission following (TSS). In our series, overall remission was 22.5%. External beam radiotherapy (EBRT) was effective in 20% in achieving remission. Medical therapy (either cabergoline or bromocriptine) as bridging/primary therapy achieved remission in only 20.8%. Irrespective of the mode of treatment, no recurrence was noted in the patients who achieved remission. The mortality in this case series was 2.7%.

Conclusions: Although the grade III and IV tumours has limited success, TSS remains the treatment of choice in acromegaly. EBRT and medical therapy with dopamine agonist have limited efficacy. Most of the other recommended options are very costly or unavailable in Sri Lanka. This study further highlights the importance of establishing specialist pituitary surgery services and introducing modern medical therapy to improve patient outcome.

Key words: acromegaly, dopamine agonists, radiotherapy, transsphenoidal surgery

Introduction

Acromegaly is characterized by increased and unregulated growth hormone (GH) production usually caused by a GH-secreting pituitary tumor. It’s a rare, insidious and potentially life-threatening condition. However, effective control of acromegaly has been shown to improve mortality and morbidity in patients (1, 2). Studies on acromegaly estimate an all-cause mortality rate of at least twice that of the normal population. The major sequelae of acromegaly include cardiorespiratory and cerebrovascular diseases, diabetes and neoplasia; particularly colon cancer (2). Although this an important clinical entity that needs proper interventions, there are no published data on management of acromegaly in Sri Lankan patients.

Treatment of acromegaly is complex and is expensive. Biochemical cure or adequate control is defined as a glucose-suppressed GH concentration of less than 2ng/ml by radioimmunoassay (1mcg/l by IRMA) and normalization of the serum IGF-I concentration (3, 4). No
single modality of treatment has consistently achieved the above levels (4). A multimodality approach is usually required, surgery as the first line of treatment followed by medical therapy, for residual disease. Radiation treatment is generally reserved for refractory cases.

TSS is the preferred treatment of choice. SA and DA and GHRA are the mainstays of medical treatment and are generally used if primary surgery alone does not result in complete remission. SAS and GHRA’s are currently not used in resource limited health care settings because of their cost, instead DA, which have limited effectiveness are the mainstay in the medical management. Bromocriptine can reduce the circulating GH level to less than 5ng/ml in only 20% of patients and can normalize the IGF-I concentration in 10% of patients. Shrinkage in tumor size is also observed in fewer than 20% of patients. Cabergoline, another DA, has fared somewhat better with response rates of upto 46% (4).

Radiation treatment takes time to reduce or normalize GH/IGF-1 levels. About 60% of patients have a GH concentration of less than 5ng/mL 10 years after radiotherapy. Panhypopituitarism develop in a similar percentage as a result of treatment is the main drawback of this treatment modality. Because of the disappointing results and adverse effects, radiotherapy is used as an adjuvant for large invasive tumors and when surgery is contraindicated (4).

Methods

This retrospective descriptive study was conducted among 72 patients diagnosed with GH excess (acromegaly and gigantism) attending the endocrine and pituitary clinic at national hospital of Sri Lanka. The old patients who were already been followed up in these clinics as well as the new patients who were enrolled during the study period were included for the study. Informed written consent was obtained from all patients. Study was carried out between January 2012 and June 2013.

Management protocol adopted

GH excess was diagnosed when there was failure of suppression of GH (<1mU/L) following a 75g glucose load. Serum insulin like growth factor-1 IGF-1 concentration was performed when patients were able to afford the out of pocket cost of test. All the patients underwent pretreatment lab assessment of 9am cortisol, free T4, prolactin, Luteinizing hormone (LH) and follicle stimulating hormone (FSH). Details of these associated pituitary hormones were recorded to identify associated hormonal abnormalities. If serum prolactin value were above 3000 mu/L, diagnosis of prolactin co-secretion with GH was made and further dilution studies were performed. All the patients underwent magnetic resonance imaging (MRI) scan of the pituitary as the primary mode of imaging. Pituitary adenomas were classified based on Hardy’s classifications (Table 1). Grade I tumours are also called as microadenomas (size <10mm) while tumours, which are grade II and above, are classified as macro-adenomas (size10mm and above). In patients with normal MRI on diagnosis additional imaging of the chest and abdomen were performed to look for extra pituitary source.

Table 1. Neuro-anatomical classification of pituitary adenomas (based on Hardy, 1969)

<table>
<thead>
<tr>
<th>Grade</th>
<th>Size</th>
<th>Location</th>
<th>Bony changes</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>&lt;10mm</td>
<td>Intrapituitary</td>
<td>None</td>
</tr>
<tr>
<td>II</td>
<td>&gt;10mm</td>
<td>Intrasellar or suprasellar expansion, no invasion</td>
<td>Sellar expansion</td>
</tr>
<tr>
<td>III</td>
<td>Any</td>
<td>Intrasellar or suprasellar expansion, local invasion</td>
<td>Sellar erosion</td>
</tr>
<tr>
<td>IV</td>
<td>&gt;10mm</td>
<td>Suprasellar expansion, invasion of extrasellar structures</td>
<td>Bone invasion</td>
</tr>
</tbody>
</table>

All patients who were diagnosed of having pituitary adenomas were referred for surgery except the patients who refused surgical intervention and the patients who were not fit to undergo surgery. Where surgery was not possible, external beam radiotherapy (EBRT) and/or medical therapy was considered. Patients who were diagnosed to have extra pituitary source of GH excess were managed with medical therapy.

Five point growth hormone day curve and pituitary functions were repeated post-surgery and after EBRT. Cure or adequate control was defined, as a mean GH concentration less than 5mu/l in a five point GH Day curve. Repeat imaging was done at 3 months and 1 year post operatively and frequency of further imaging was decided on the findings of these post-operative images. Patients who had significant operable residual lesion in the MRI scan done 3 months postoperatively were referred for repeat surgery followed by EBRT. In cases where repeat surgery was not possible, the patients were referred for EBRT. In patients needing medical therapy, cabergoline or bromocriptine was used as the bridging therapy until adequate control was achieved.

Patients who were above 40 years of age were referred for colonoscopy to exclude colonic polys. Echocardiogram
was performed in these patients in order to look for associated cardiac conditions and in patients who were on cabergoline to exclude associated valvular lesions.

Data was collected from case notes and by interviewing the patients. Data included symptoms and signs, imaging and laboratory results, operative findings, clinical outcome, GH values following OGTT and IGF-1 levels. It also included details of radiotherapy and medical therapy given. Data on cure, remission, recurrence and mortality was also collected for analysis.

Results

Among the 72 patients with GH excess, 38 (54.1%) were females. The mean age of patients was 46 (SD±12.6) years while the mean age of the patients at the time of presentation was 39.52 (SD± 12.8) years. The mean duration of symptoms on presentation was 3.28 years (SD± 2.7). The mean follow-up was 5.2 (SD± 4.9) years.

Increased sweating, headache, change in facial appearance and increasing shoes and ring sizes were the commonest symptoms on presentation (Table 2).

The basal mean plasma GH was 62.1mU/L (SD± 55.9) and mean IGF-1 was 605.8 (SD±238).

Table 2. Frequencies of symptoms on presentation

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>No of patients diagnosed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change in facial appearance</td>
<td>64 (88%)</td>
</tr>
<tr>
<td>Change in ring and shoe sizes</td>
<td>64 (88%)</td>
</tr>
<tr>
<td>Increased sweating</td>
<td>59 (81.9%)</td>
</tr>
<tr>
<td>Headache</td>
<td>49 (68.1%)</td>
</tr>
<tr>
<td>Visual field involvement</td>
<td>31 (43.1%)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>28 (38.8%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>22 (30.5%)</td>
</tr>
<tr>
<td>Hypopituitarism</td>
<td>16 (22.2%)</td>
</tr>
<tr>
<td>Delayed puberty</td>
<td>4 (5.5%)</td>
</tr>
<tr>
<td>Kyphosis</td>
<td>3 (4.1%)</td>
</tr>
<tr>
<td>Pituitary apoplexy</td>
<td>1 (1.3%)</td>
</tr>
<tr>
<td>Bony lumps (Associated with Mccune Albright Syndrome)</td>
<td>1 (1.3%)</td>
</tr>
<tr>
<td>Symptoms suggestive of pheochromocytoma (Adrenal lesion producing catecholamines / GH)</td>
<td>1 (1.3%)</td>
</tr>
</tbody>
</table>

Pituitary imaging was available for 55 patients. Out of these 55 patients, 8 patients (14.5%) had Grade I tumour (microadenomas), while 45 patients (81.8%) were diagnosed with a grade II and above (macroadenomas). In this series, two patients (3.6%) had normal pituitary MRI (Table 3).

Table 3. Neuroanatomical classifications of pituitary adenomas (based on Hardy, 1969)

<table>
<thead>
<tr>
<th>Size</th>
<th>Grade</th>
<th>No of patients (n=53)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Microadenoma</td>
<td>I</td>
<td>08 (15%)</td>
</tr>
<tr>
<td>Macroadenoma</td>
<td>II</td>
<td>16 (30.1%)</td>
</tr>
<tr>
<td></td>
<td>III</td>
<td>27 (50.9%)</td>
</tr>
<tr>
<td></td>
<td>IV</td>
<td>02 (3.77%)</td>
</tr>
</tbody>
</table>

In our series, 85% had macroadenomas and 14.2% had prolactin co-secretion with GH.

Outcome of management of acromegaly patients

TSS was performed in 62 patients while 3 patients underwent craniotomy. Two patients were lost for follow-up while awaiting surgery. One patient refused surgery and was started on medical treatment. One patient who was diagnosed as Mccune Albright syndrome did not undergo surgery and was started on medical therapy. One patient had an adrenal lesion, which was co-secreting catecholamines and GH. This patient was diagnosed to have a growth hormone releasing hormone (GHRH) producing adrenal tumour and underwent right sided adrenelectomy, which resulted in cure of acromegaly. Two patients who did not have tumours in pituitary imaging did not undergo surgery. These two patients underwent further imaging for the source of GH. As all the images were negative they were started on medical treatment. In total, surgery could not be done in six patients (8.3%) either as the tumour was not located or due to patient refusal.

Outcome of TSS

Sixty two patients (86.1%) underwent TSS. Twenty six patients had tumour grade III and above (macroadenomas with suprasellar extension), while 15 patients had grade II tumours (macroadenomas without suprasellar extension) and 8 patients had grade I tumour (microadenomas). Thirteen patients did not have details about the tumour grade preoperatively. Remission was achieved in 37.5% of patients with grade I tumour and 33.3% of patients with grade II tumour. No recurrence was noted in these patients. None of the patients with tumour grade III or above achieved remission following TSS. The remission rate in patients with macroadenomas (grade II and above) was 12.1%. In our series, overall remission
rate was 22.5%. Five patients who did not achieve remission had no demonstrable residual tumour on post-surgery MRI and received EBRT. Add on medical therapy with DA was initiated in 49 patients who failed to go into remission after surgery. Out of these 49 patients, 9 patients underwent repeat surgery as there was significant residual tumour found in the three months post-surgery MRI. Currently, 4 patients are awaiting repeat surgery while 4 patients who refused repeat surgery are awaiting radiotherapy. In our study population 28 patients received EBRT while, 4 patients who have undergone TSS are currently awaiting 3 months post-surgery assessment to define cure.

**Outcome of trans-cranial surgery**

In our series, three patients (4.1%) underwent trans-cranial surgery due to the tumour size, extent and preference of the neurosurgeon. These three patients were not cured following surgery and were started on medical therapy and underwent EBRT.

**Outcome of EBRT**

In our study, 30 patients received EBRT either as primary therapy or as adjuvant therapy following surgery while 4 patients are currently awaiting EBRT. 6 patients who refused EBRT were started on medical therapy. Out of the 6 (20%) patients who were not cured previously had normalization their GH levels following EBRT. However, EBRT was ineffective in 24 (80%) patients in achieving remission in five years.

**Outcome of medical therapy (cabergoline/bromocriptine)**

Medical therapy was started as primary therapy (cabergoline/bromocriptine) in 4 patients (1 patient who refused either surgery or EBRT, 2 patients who did have a tumour on imaging and 1 patients who was diagnosed as having McCune Albright syndrome). Out of these 4 patients, 3 of them did not achieve remission with medical therapy. 43 patients were started on medical therapy as a bridging therapy. Clinical cure was achieved in 9 patients. Thus medical therapy, as bridging or primary therapy, achieved remission in only 20.8% of the patients. GH reduction was more with cabergoline and better tolerated than with bromocriptine.

**Mortality**

The mortality in this case series was two out of 72 (2.7%). Both died due to cardiac failure.

**Discussion**

The outcome of patients with acromegaly is determined not only by the efficacy of individual treatment options but also depends on the availability of the treatment options. In resource constrained health systems, the expertise available and the scarcity of the treatment modalities could significantly affect the final outcome. Our study population showed a female predominance, which was consistent with other studies from rest of the world (5,7). Our patients were younger (41-50 years) (39.52, SD± 12.8) compared to those reported in previous series from other countries (5-8) and the duration of symptoms were shorter (3.28 years, SD± 2.7) compared to 5-8 years (6, 8) in the patient populations described in most of the studies.

Acromegaly is well-known for its long delay from onset of symptoms to diagnosis (9,11). It has a slowly progressive nature, which goes un-noticed until patient visits the doctor for other illnesses or for co-morbidities associated with acromegaly. Therefore, most of these patients have visible facial and extremities changes by the time of their diagnosis. 88% of our study population had facial and acral changes at the time of diagnosis. Reid et al (11), in their study noticed that the clinical characteristics at diagnosis of patients with acromegaly has not changed from 1981-2006 suggesting that clinical recognition of acromegaly has not significantly improved over the last 25 years.

In our study population, 81.8% was diagnosed with grade II tumour and above (macro adenomas), which was in concordance with the size of the pituitary tumour reported in most series (6,10,16,18). TSS is the treatment of choice in acromegaly and in our series 86.1% underwent TSS. Overall remission rate after TSS was 22.5% and this is well below the rates reported in other series (42%-75%) (Table 4). In our study, group of 37.5% patients with grade I tumour (microadenoma) and 33.3% of patients with grade II tumour achieved remission while none of the patients with tumour grade III or above achieved remission following TSS. The remission rate in patients with macroadenomas (grade II and above) was 12.1%. Compared to prestigious neurological centres in the developed world, the availability of expertise and limited resources seem to have influenced the outcomes of acromegaly in our series. Publications on outcome studies from countries with limited facilities are not widely available for comparison.

Wang et al. (19) observed that remission rates for acromegaly surgery improved following establishment of a specialist surgical service, with a reduction in surgeon numbers. According to their study, the overall surgical remission rate in 1998 was 27%, which improved to 67% in 2012 after establishing a specialist pituitary surgery service with reduced surgeon numbers. There is also an operative learning curve for the surgeons and there has been an improvement in outcome after performing about 50 TSS (14). This further highlights the benefits of establishing specialist pituitary surgery services in resource poor settings.
Radiotherapy (RT) is an effective, low-cost and reasonably safe mean of controlling the disease activity in acromegaly. Conventional RT is an additional treatment option for patients who have persistent disease activity despite pituitary surgery. It is particularly useful in resource poor settings where newer medical options like SA and GHRA are not readily available. The effect of radiotherapy is delayed and normalization of IGF1 has been reported, in up to 60-90% of patients, 10-15 years after conventional fractionated radiotherapy (26-29). In our study, 20% of the patients who received EBRT normalized their GH levels after a median follow-up period of 5.2 years. This response rate is lower than those reported from other large cohorts with similar observation periods (27), but similar to the response rates of Minniti et al (29) and Gutt et al (28). However, normalization of elevated hormone levels may take up to 15 years (4,5) long follow-up periods are required to assess the outcome of pituitary radiotherapy.

Although DA are widely used, SA are considered as the first-line of treatment in the medical management of acromegaly. DA, cabergoline has greater efficacy and tolerability compared to bromocriptine that has shown to normalize GH/IGF-I levels in only around 10% of cases (1,2,4,5) whereas cabergoline has better response rates of 46% (4). In our study, medical therapy with DA either as primary or bridging therapy achieved remission in only 20.8% of patients. However, in those whom there is response to therapy, DA become a cheaper alternative. In a study by Moyes et al (30), cabergoline demonstrated complete biochemical remission in 27%. Similarly a study from India reports a 25% efficacy of cabergoline (alone/ add-on) in achieving remission (31). GH reduction and tolerability was better in patients who were on cabergoline than the patients who were on bromocriptine (31), which was similar to results published elsewhere.

Conclusion
TSS remains the treatment of choice in acromegaly, though in grade III and IV tumours the success was limited. As most of the recommended options are very costly or unavailable in Sri Lanka, alternative treatment options generally used are EBRT or medical therapy (cabergoline/ bromocriptine) which have limited efficacy. Optimal treatment needs to be individualized depending on the efficacy, availability and affordability of treatment modalities. This study also highlights the importance of establishing specialist pituitary surgery services to improve outcomes.

References


Metabolic risk factors detected among the attendees to free health camps conducted in Western province of Sri Lanka

S A S P Subasinghe¹, C W Jayesundere¹, Kanthi Piyaseeli¹, P A Epa¹, Nirmanee Gamage¹, Priyanga Senanayaka¹, R P Palitha Karunapema²

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Abstract

Introduction: Non communicable diseases, mainly cardiovascular diseases and diabetes have a large but unappreciated negative impact on individuals, families and countries and as such a major barrier to human development. Early diagnosis of these hidden illnesses and achievement of treatment goals are essential in order to prevent complications.

Materials and methods: Population of 495 people above the age of 18 years who attended free health camps in Western province of Sri Lanka were screened for overweight, obesity, pre-diabetes, diabetes, hypertension and hyperlipidemia. Prevalence of above conditions was estimated. Treatment target achievement was assessed among patients with hypertension, diabetes mellitus and hyperlipidemia.

Results: The mean BMI was 23.41 (SD 3.96) in men. It was lower than that in women, 24.45 (SD 4.34). Prevalence of obesity was 35.3% in men and 43.7% in women and prevalence of overweight was 13.7% in men and 18.5% in women. The prevalence of diabetes was 28.0% for men and 13.5% for women and 16.5% of new patients with diabetes were identified by this screening. The prevalence of pre-diabetes was 51.3% for men and 44.2% for women. The prevalence of hypertension was 42.3% and out of that 37.9% were newly diagnosed by screening. Prevalence of hyperlipidemia was 52.2% and 48.5% of them were diagnosed by the screening. Treatment targets were achieved by only 15% of diabetics and 55% of patients with hypertension. Only 38% of previously diagnosed patients with hyperlipidemia achieved total cholesterol (TC) target and only 16.5% achieved low density lipoproteins (LDL) target.

Conclusion: The prevalence of major metabolic risk factors is high in the studied population and is higher than the previously reported prevalence. There is also a reasonably high percentage of undiagnosed patients with cardio-metabolic risk factors. Many patients with CVD risk factors are treated but remained inadequately controlled.

Introduction

Non communicable diseases (NCD) kill 38 million people worldwide each year (1). Almost three quarters of NCD deaths occur in low and middle income countries (1, 2, 3 and 4). Cardiovascular diseases (CVD) account for most NCD deaths (1). Raised blood pressure (BP), increased blood glucose, elevated blood lipids and obesity are the major risk factors which can lead to CVD.

Evidence shows that both the incidence and prevalence of type 2 diabetes mellitus has been rising in adults, children and adolescents in the developed countries such as United Kingdom (5). There is evidence showing both the incidence and prevalence of non-communicable diseases are on the rise in Sri Lankan population as well (6, 7).

The rapid rise in NCD is predicted to impede poverty reduction initiatives in low income countries. To lessen the impact on individuals, families and the society, a comprehensive approach is needed to manage these NCDs. It is necessary to work together to diagnose these NCDs early and to treat properly in order to reduce the associated CVD risks as well as to promote the interventions to prevent these NCDs in the community. We believe that our study will fulfill this task to some extent. The objectives of our study were to determine the prevalence of metabolic risk factors; obesity, overweight, diabetes, pre-diabetes, hypertension and hyperlipidemia among people attended free health camps in the western province of Sri Lanka, to identify the percentage of these risk factors detected by screening and to assess the adequacy of the control of diabetes, hypertension and hyperlipidemia in treated patients.

Method

This is a cross sectional descriptive study done with the patients participated in free health camps that we conducted in three districts of Western province in Sri Lanka.
Measurements

Height and weight were measured and BMI were calculated. Over weight (BMI 23-24.9) and obesity (BMI 25 or more) were determined. Blood pressure was measured. FBS, PPBS and lipid profile were done. Treatment goals were evaluated in accordance with the 2007 European guidelines on CVD prevention (8). Hypertension (systolic blood pressure 140 mmHg or more and/or diastolic blood pressure 90 mmHg or more and/or use of antihypertensive medications) diabetes mellitus (FBS 126mg/dl or more, PPBS200mg/dl or more) and pre-diabetes (FBS 100 mg/dl-125mg/dl, PPBS 140mg/dl-199mg/dl), hyperlipidemia (TC more than 200mg/dl, LDL 160 mg/dl or more and TG 150 mg/dl or more) were determined.

All data collectors underwent training for the specific tasks required for this study. They were trained to ensure standardization of measurement techniques, interviewing, sample collection and labeling.

The data were collected using pre-tested questionnaire, which consisted of four sections. First section included demographic data. Section two included previous diagnoses and risk factor analysis for non-communicable diseases. The third section was to document height, weight, BMI, blood pressure and biochemical results. The fourth section was to document the follow up plan for new diagnoses detected.

Anthropometry

Height was measured using a stadiometer and recorded to the nearest 10th of the centimeter with the subject looking straight ahead and with the back against the vertical support of the instrument. Weight was measured without shoes or slippers on a digital scale.

Blood pressure

Blood pressure was measured in the seated position after the participants had rested for at least 5 minutes. The measurement was taken using the supported left arm at the heart level, using mercury column sphygmomanometer, whose measuring accuracy had been validated and it met the criteria of the British Hypertension Society. Two recordings were taken and the mean was used for analysis. In the event of variation of over 20 mmHg between recordings, a third reading was done and the mean of the last two recordings was used.

Collection of blood samples

From individuals, after 12 hours of fast, 5ml of venous blood was drawn and collected to a sugar bottle for FBS estimation (2ml) and a plain bottle for lipid profile estimation (3ml). Thereafter, they were given a standard Sri Lankan breakfast and 2ml of venous blood was drawn after 2 hours to a sugar bottle for PPBS estimation. Qualified government medical laboratory technicians carried out biochemical analysis at the site. Results were delivered the same day and patients were then seen by medical officers.

Patient education and referral for follow up

All the participants were educated by using audiovisual presentations with regards to life style modification, including healthy eating, exercise and stress reduction, while they were waiting for blood results. Newly diagnosed patients were referred to the dietician who attended the health camps. Referral letters were given to attend local clinics for regular follow up. Trained nurses educated the patients with overweight and obesity to reduce their weight. They were educated about the ideal body weight that they should achieve and maintain verbally as well as with written information leaflets.

Patients with pre-diabetes were advised about intensive life style modification with the aim of prevention or delaying the development of diabetes among them. They were advised regarding the need for yearly screening. People with more than 2 risk factors for developing diabetes were also advised about life style modification and they were advised to have 3 yearly screening as per guidelines.

Results

There were 102 men and 393 women in the sample and the male to female ratio was 1: 3.8. The mean age of men was 53.7 years (SD 14.3) and that of women was 52.9 years. (SD 12.5). The mean BMI was 23.41 kg/m^2 (SD 3.96) in men. It was lower than that in women, 24.45 kg/m^2 (SD 4.34). Prevalence of obesity was 35.3% in men and 43.7% in women and prevalence of overweight was 13.7% in men and 18.5% in women.

The prevalence of diabetes was 28.0% for men and 13.5% for women, and 16.5% of diabetic patients were identified by screening. The prevalence of pre-diabetes was 51.3% for men and 44.2% for women. Out of that 16.4% had both impaired fasting glucose (IFG) and impaired glucose tolerance (IGT) (Table 2). The prevalence

Lanka, namely Colombo, Gampaha and Kalutara. The Study was conducted following the approval obtained from the ethical committee of the Sri Jayewardenepura general hospital. Health camps were conducted in temples and government schools after obtaining permission from relevant authorities. People were informed by distributing leaflets and on some occasions by announcing by loudspeakers. They were asked to come early morning after 12 hours of fast. All the participants of these health camps were recruited for the study. Pregnant women and individuals with physical and mental disabilities were excluded. A total number of 495 people attended free health camps in years 2013 and 2014 were analyzed.
of hypertension was 42.3% and out of that 37.9% were newly diagnosed by screening (Table 2). Prevalence of hyperlipidaemia was 52.2% and 48.5% was diagnosed by screening. Out of which 18.7% had combined hyperlipidaemia and 55.2% had isolated LDL elevation and 26.5% had isolated hypertriglyceridaemia.

Treatment target were achieved by only 15% of the patients with diabetes and 55% of patients with hypertension. Only 38% of previously diagnosed patients with hyperlipidaemia achieved TC target and only 16.5% achieved LDL target.

The prevalence of obesity, diabetes and hypertension among both males and females has increased compared to 2005 data (13). A study done in 1997 has shown that the mean BMI of men were 20.5kg/m² and 20.9kg/m² for woman among 30-65 year old healthy adults (14). The mean BMI was 21.5kg/m² for men and 23.3kg/m² for women according to the study done in 2005 (13). Our study showed mean BMI of 23.41 and 24.45 for men and women respectively. Prevalence of obesity and overweight were 35.3% and 13.7% for men and 43.7% and 18.9% for women respectively. A comprehensive assessment of trends in BMI in 199 countries showed mean BMI and prevalence of overweight has increased since 1980 (15) and our data also shows the same trend.

Studies conducted among general population of Sri Lanka in the past has shown a low prevalence of hypertension and the prevalence of hypertension among adults of 25-64 years in the Matale district was found to be about 8% (16). A study done in four provinces of Sri Lanka in the age group of 30-65 years showed a hypertension prevalence of 18.8% for men and 19.3% for women (13). This study showed a moderately high overall prevalence of hypertension of 42.3% as defined by either systolic blood pressure more than 140mmHg or diastolic blood pressure more than 90mmHg.

Treatment target were achieved by only 15% of the patients with diabetes and 55% of patients with hypertension. Only 38% of previously diagnosed patients with hyperlipidaemia achieved TC target and only 16.5% achieved LDL target.

Data for the prevalence of pre-diabetes is limited. A cross sectional study done in 288 young Mexican adults (18-30 years) in 2005 showed 14.6% of prevalence of pre-diabetes (17). A study done in 2006 has shown an overall prevalence of pre-diabetes as 11.5 (10.5-12.5%) among the Sri Lankan adult population (18). Our study showed 51.3% prevalence in men and 44.2% in women.

Control of diabetes, hypertension and hyperlipidemia among patients diagnosed in the past was highly unsatisfactory. A study done in US population among known diabetics above the age of 20 years showed only 37% had HbA1c less than 7.0, only 35.8% had blood pressure less than 130/80mmHg, only 50% had total cholesterol less than 200mg/dl (19). Another study done in Italy from June to December in 2000 showed that 48% of patients with diabetes had HbA1c level of 7.5 or more, and 77% had blood pressure above target values (that is above 140/90 mmHg in non-diabetics and above 130/80mmHg in diabetics) and 85% had total cholesterol level above 190mg/dl (20). Another study done in Italy from June to December in 2000 showed that 48% of patients with diabetes had HbA1c level of 7.5 or more, and 77% had blood pressure above target values (that is above 140/90 mmHg in non-diabetics and above 130/80mmHg in diabetics) and 85% had total cholesterol level above 190mg/dl (20). According to a study in 12 European countries in 2009 among patient with diabetes aged 50 years and more, only 36.7% has achieved the less than 6.5% HbA1c target. Only 38.8% has achieved the blood pressure target of less than 140/90mmHg. Only 41.2% has

**Table 1. Mean values of BMI, FBS, PPBS, blood pressure and lipid profile**

<table>
<thead>
<tr>
<th>Mean values</th>
<th>Total</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI (Kg/m²)</td>
<td></td>
<td>23.4</td>
<td>24.4</td>
</tr>
<tr>
<td>FBS (mg/dl)</td>
<td></td>
<td>109.5</td>
<td>108.1</td>
</tr>
<tr>
<td>PPBS (mg/dl)</td>
<td></td>
<td>138.2</td>
<td>130.1</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td></td>
<td>131.8</td>
<td>127.5</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td></td>
<td>82.4</td>
<td>78.3</td>
</tr>
<tr>
<td>TC mg/dl</td>
<td></td>
<td>200.7</td>
<td>215.7</td>
</tr>
<tr>
<td>LDL mg/dl</td>
<td></td>
<td>134.6</td>
<td>150.1</td>
</tr>
<tr>
<td>TG mg/dl</td>
<td></td>
<td>126.2</td>
<td>114.1</td>
</tr>
</tbody>
</table>

**Table 2. Cardiovascular risk factors**

<table>
<thead>
<tr>
<th>Total</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>Underweight</td>
<td>19.8</td>
<td>5.6</td>
</tr>
<tr>
<td>Normal</td>
<td>41.2</td>
<td>31.7</td>
</tr>
<tr>
<td>Overweight</td>
<td>13.7</td>
<td>18.9</td>
</tr>
<tr>
<td>Obesity</td>
<td>35.3</td>
<td>43.7</td>
</tr>
<tr>
<td>Pre-diabetes</td>
<td>51.3</td>
<td>44.2</td>
</tr>
<tr>
<td>Diabetes</td>
<td>36.2</td>
<td>26.2</td>
</tr>
<tr>
<td>Hypertension</td>
<td>44.2</td>
<td>41.8</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>44.7</td>
<td>59.9</td>
</tr>
<tr>
<td>Triglyceride</td>
<td>28.4</td>
<td>19.8</td>
</tr>
<tr>
<td>LDL</td>
<td>25.5</td>
<td>38.7</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>44.2</td>
<td>49.6</td>
</tr>
</tbody>
</table>

**Discussion**

Our health camps were mainly attended by the females and the male representation was comparatively less. Cut off values for overweight and obesity were taken according to Asian classification (9). Diabetes and pre-diabetes were identified according to American Diabetes Association (ADA) guidelines issued in 2014 (10). Hypertension was diagnosed according to JNC 8 (11). Hyperlipidemia was classified according to ATP 111 guidelines (12).
attained both the total and LDL cholesterol target of less than 5mmol/l and less than 3mmol/l (21). In our study, 84.9% of patients with known diabetes had FBS more than 100mg/dl and 74.6% had PPBS more than 140mg/dl. Blood pressure control was satisfactory only in 55.8%. Only 39.8% of the previously diagnosed patients with hyperlipidemia had TC less than 200mg/dl and 73.2% had TG less than 150mg/dl. Only 15.9% had LDL value less than 100mg/dl.

The EUROACTION study has shown that a nurse-led, multi-disciplinary team approach can yield significant lifestyle improvements and risk factor reductions (22). Multifactorial treatment considering lifestyle interventions and pharmacotherapy is the way forward in managing these NCDs.

Conclusions

These data showed that the prevalence of non-communicable diseases is on the rise. A significant percentage of these diseases are undiagnosed. The high prevalence of prediabetes gives us a warning that we should intensify diabetes prevention programs, and this also gives us a prediction of the future of current diabetic epidemic. Achievement of targets among already diagnosed patients with above disease conditions is not satisfactory. Early detection and treatment of these conditions are cost effective and reduce the need for expensive interventions. There is a need for strengthening the primary care structure for early detection and timely treatment of these illnesses.

Acknowledgements

We acknowledge the voluntary contribution made by all the doctors, nurses, dietitian, laboratory technicians and orderly staff who participated in this study.

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Prevalence of the metabolic syndrome among patients with type 2 diabetes

S A Abhayaratna¹, N P Somaundaram¹, H Rajapakse¹


Abstract

Introduction: The metabolic syndrome (MetS) consists of a cluster of risk factors that is responsible for most of the excess cardiovascular morbidity amongst persons with Type 2 diabetes mellitus (T2DM).

This study was conducted to find the prevalence of the MetS among T2DM patients attending the diabetic clinic of the main tertiary care hospital in Sri Lanka.

Materials and methods: A prospective cross sectional study was carried out between May 2012 and December 2012 in the diabetes clinic of the National hospital of Sri Lanka (NHSL). Consecutive patients with T2DM with a duration of diabetes of less than 12 months were enrolled into the study on their first visit.

Results: 391 subjects (109 males, 282 females) were included in the study. The crude prevalence of MetS according to the International Diabetes Federation (IDF) criteria was 63.7%. Significantly higher number of females had MetS when compared to males (72% vs. 42.2%). Abnormal waist circumference was the commonest abnormality and was present in 289 (73.9%), while low high density lipoprotein cholesterol (HDL-C) was present in 206 (52.7%). In males, abnormal waist circumference and high blood pressure were the most prevalent risk factors while abnormal waist circumference and low HDL level were the most prevalent risk factors in females.

Conclusion: The prevalence of MetS and its individual components were high in T2DM patients among this urban population attending the diabetic clinic of NHSL. The prevalence of central obesity was high and it was a common risk factor for MetS among both males and females.

Background

The MetS refers to a clustering of cardiovascular disease (CVD) risk factors where underlying pathophysiology may be related to insulin resistance and resultant increase in body fat content (1). Main components of this syndrome include hypertension, hyperglycaemia, hypertriglyceridaemia, reduced high-density lipoprotein cholesterol (HDL-C) and abdominal obesity (1). Different criteria have been proposed to define the MetS (1).

Individuals with MetS are at increased risk for CVD and T2DM (1). Pooled data form 37 studies have shown that MetS doubled the risk of CV disease (2). Apart from CVD and T2DM, individuals with MetS has been shown to be more susceptible to variety of other medical conditions including polycystic ovary syndrome, fatty liver, cholesterol gallstones, asthma, sleep disturbances and some malignancies (1).

National prevalence of adult diabetes in Sri Lanka was found to be 10.3% and this was as high as 16.7% amongst the urban population during the 2005-2006 period (3). Overall, the prevalence of MetS in general adult population in Sri Lanka has been documented as 27.1% (4). Combination of diabetes and MetS possess a greater risk for the development of CVD than either alone and this knowledge is important for planning effective prevention strategies particularly for this high risk group for CVD. Prevalence of MetS among diabetic patients from other regions were reported to be high as 50-80% (5, 6, 7, 8). Prevalence of MetS among diabetes population in Sri Lanka is not known. This prospective cross sectional study was carried out to determine the prevalence of MetS in a limited, urban, adult type 2 diabetes population and its differences between the two sexes.

Methods

This prospective cross sectional study was carried out in the diabetes clinic of NHSL between May 2012 and December 2012. Consecutive patients attending the diabetes clinic with the diagnosis of diabetes for less than
or equal to 12 months duration were included for the study. Data collection was carried out by a team of medical graduates and nurses who were trained in research methodology prior to commencement of data collection. Seated blood pressure was recorded on two occasions, 5 minutes apart after at least a 15-min rest, using a standard mercury sphygmomanometer. Height was measured using stadiometer, to the nearest 0.1 cm according to standard methods. Body weight was measured in indoor light clothing to the nearest 0.1 kg. Waist circumference was measured at midway between iliac crest and lower rib margin at the end of normal expiration using a plastic flexible tape to the nearest 0.1 cm. Body Mass Index (BMI) was calculated as weight in kilograms divided by height in meters squared (kg/m$^2$). An interviewer-administrated questionnaire was used to obtain socio-demographic details, details of other diagnosis and treatment, duration of diabetes diagnosis and treatment. Blood samples were collected at the central laboratory and blood sample for HbA1c was collected to K$_3$EDTA bottles and blood for lipid profile was collected to plain bottles. Lipid profile was checked using POINTE 180 chemistry analyzer and HbA1c checked by a BIO RAD D-10 machine. Method used to analyze HbA1c was traceable to the diabetes control and complication trial (DCCT) method (9). The study was approved by the ethical review committee (ERC) of the faculty of medicine, university of Colombo, Sri Lanka.

**Definitions**

Diagnosis of diabetes was done according to American Diabetes Association (ADA) criteria (10). MetS was defined according to the International Diabetes Federation (IDF) criteria (Table 1) (11).

1. Raised Triglycerides >150 mg/l (1.7 mmol/l) or specific treatment for hypertriglyceridemia.
2. Low HDL-cholesterol < 40 mg/l (1.03 mmol/l) in males and < 50 mg/l (1.29 mmol/l) in females or specific treatment for low HDL-cholesterol.
3. Raised blood pressure: systolic blood pressure > 130 mmHg or diastolic blood pressure > 85 mmHg or treatment for previously diagnosed hypertension.
4. Dysglycaemia: fasting plasma glucose > 100 mg/l (5.6 mmol/l) and/or 2 h post-oral glucose tolerance test glucose > 7.8 mmol/l or previously diagnosed type-2 diabetes.

Central obesity was classified as waist circumference > 90 cm for males and > 80 cm for females. Since all the subjects recruited for the study were diagnosed patients with diabetes, the presences of central obesity together with any one of the above parameters were classified as having MetS.

**Statistical analyses**

Results were expressed as mean ± SD. The data were analyzed with the help of STATA IC version 12 (Stata Corporation, College Station, TX, USA) using the relevant tests of significance such as unpaired ‘t’ test and Chi-square test. A level of $p<0.05$ was accepted as statistically significant.

**Results and Observations**

Out of 430 patients recruited for the study, 391(90.9%) patients attended blood tests and were included in the final analysis. The basic characteristics are tabulated in the Table 2. The study population was categorised to 4 BMI categories and overweight and obese categories were defined as ≥ 23 kg/m$^2$ and ≥ 25 kg/m$^2$ according to the Asian cutoff points (Table 3). 48% of the subjects had a BMI over 25 kg/m$^2$ and 22% had a BMI between 23-24.9 kg/m$^2$. Mean BMI in this population was 25.2 kg/m$^2$. There were 147(52.1%) female patients with BMI>25 kg/m$^2$, in contrast to the 41(37.6%) male patients ($p<0.05$).

<table>
<thead>
<tr>
<th>Number</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total sample size</strong></td>
<td>391</td>
</tr>
<tr>
<td>1. Male</td>
<td>109</td>
</tr>
<tr>
<td>2. Female</td>
<td>283</td>
</tr>
<tr>
<td><strong>Age Category</strong></td>
<td></td>
</tr>
<tr>
<td>1. &lt; 20 years</td>
<td>01</td>
</tr>
<tr>
<td>2. 21-40 years</td>
<td>83</td>
</tr>
<tr>
<td>3. 41-60 years</td>
<td>255</td>
</tr>
<tr>
<td>4. 61-80 years</td>
<td>52</td>
</tr>
<tr>
<td><strong>Ethnicity</strong></td>
<td></td>
</tr>
<tr>
<td>1. Sinhalese</td>
<td>248</td>
</tr>
<tr>
<td>2. Sri Lankan Tamils</td>
<td>74</td>
</tr>
<tr>
<td>3. Sri Lankan Malay</td>
<td>67</td>
</tr>
<tr>
<td>4. Other</td>
<td>2</td>
</tr>
<tr>
<td><strong>Mean duration of diabetes</strong></td>
<td>3 months ± 2.9</td>
</tr>
</tbody>
</table>

The waist circumference was above the cut-off point in 51.4% males and 81.6% females and was the commonest risk factor of MetS in both sexes. 34.9% of males and 40.8% of females had hypertension, while 31.2% of males and 61% of females had low HDL levels. Raised
triglycerides were present in 31.2% of males and 32.6% of females. Prevalence of abnormal waist circumference and low HDL level were significantly higher in female patients (Figure 1).

The crude prevalence of MetS, defined according to IDF criteria was 63.7% in the study population. 42.2% and 72.0% male and female patients had MetS respectively (p<0.001). All five components of the MetS were present in 24 (6.1%) of the subjects.

The mean age in patients with and without MetS was 50.1 years ±10.2 and 49.3 years ±11.3 respectively. BMI, waist circumference, systolic blood pressure, diastolic blood pressure and serum triglyceride levels of the patients with MetS was significantly higher (P<0.001) compared to patients without MetS (Table 3). No significant difference was observed in duration of diabetes, total cholesterol and HbA1c level between patients with or without MetS (Table 4).

**Discussion**

MetS is a constellation of symptoms consisting of hypertension, hyperglycaemia, hypertriglyceridaemia, reduced (HDL-C) and abdominal obesity (1). The key benefit of diagnosing MetS is to identify patients at risk of CVD early and to institute aggressive lifestyle modifications, in order to reduce the future cardiovascular burden.

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**Table 3. Distribution of BMI categories**

<table>
<thead>
<tr>
<th>BMI Category (kg/m²)</th>
<th>Male (n=109)</th>
<th>Female (n=283)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Underweight (&lt;18.5)</td>
<td>09 (8.2%)</td>
<td>09 (3.2%)</td>
<td>18 (4.6%)</td>
</tr>
<tr>
<td>Normal (18.5-22.9)</td>
<td>32 (29.4%)</td>
<td>67 (23.8%)</td>
<td>99 (25.3%)</td>
</tr>
<tr>
<td>Overweight (23-24.9)</td>
<td>27 (24.8%)</td>
<td>59 (20.9%)</td>
<td>86 (22%)</td>
</tr>
<tr>
<td>Obese (&gt;25)</td>
<td>41 (37.6%)</td>
<td>147 (52.1%)</td>
<td>188 (48.1%)</td>
</tr>
</tbody>
</table>

---

Figure 1. Components of MetS among T2DM patients according to IDF criteria according to sex
The crude prevalence of MetS among T2DM patients in this study was 63.7%, when IDF criteria were used to define MetS. This prevalence is nearly similar to the results of other studies from the South Asian region and other regions, which have used IDF criteria (Table 5). However, a higher prevalence of MetS was reported in some studies where the duration of diabetes is longer and this is expected as the risk factors for MetS accumulate with the duration of diabetes.

Prevalence of MetS depends on the criteria used to define it. In South Asians, central obesity has been identified as a key factor for increase prevalence of diabetes (12). When compared with NCEP-ATP III criteria (13), many studies have found that there is a lower prevalence of MetS with the IDF criteria, in diabetic patients (5, 6, 8, 14). However, some studies have found that in Caucasian diabetic patients, prevalence may be higher with IDF criteria (7). In the IDF definition of MetS, central obesity is an essential criterion in diagnosing MetS leading to lower prevalence with the IDF definition. This is a possible explanation for the difference seen between the two definitions. In this study we primarily used the IDF criteria to calculate the prevalence of MetS. In this study, IDF

<table>
<thead>
<tr>
<th>Study (ref)</th>
<th>Country</th>
<th>Study Type</th>
<th>Study population</th>
<th>Duration of Diabetes</th>
<th>MetS (IDF criteria)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Lu B et al. (13)</td>
<td>China</td>
<td>Cross sectional study</td>
<td>1008 Type 2 DM</td>
<td>Newly diagnosed</td>
</tr>
<tr>
<td>2</td>
<td>Cull CA et al. (5)</td>
<td>UK</td>
<td>Retrospective analysis of UKPDS study</td>
<td>4542 UKPDS Type 2 DM patients</td>
<td>Newly diagnosed</td>
</tr>
<tr>
<td>3</td>
<td>Imam SK et al. (14)</td>
<td>Pakistan</td>
<td>Cross sectional study</td>
<td>233 with Type 2 DM</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>M. Monami et al. (7)</td>
<td>Italy</td>
<td>Observational cohort study</td>
<td>882 Type 2 DM</td>
<td>13.1 ± 10.6 years</td>
</tr>
<tr>
<td>5</td>
<td>Alshkri MM et al. (8)</td>
<td>Libya</td>
<td>Cross sectional study</td>
<td>99 Type 2 DM</td>
<td>9.4 years ± 7.4</td>
</tr>
<tr>
<td>6</td>
<td>Nahar S et al. (6)</td>
<td>Bangladesh</td>
<td>Cross sectional study</td>
<td>200 Type 2 DM</td>
<td>Newly diagnosed</td>
</tr>
<tr>
<td>7</td>
<td>Present Study</td>
<td>Sri Lanka</td>
<td>Cross sectional study</td>
<td>391 Type 2 DM</td>
<td>3 months ±2.9</td>
</tr>
</tbody>
</table>
The prevalence of MetS was found to be significantly higher in females compared to males. The prevalence of central obesity and low HDL was also significantly higher in females and these 2 parameters have mainly contributed to overall higher prevalence of MetS seen in females. Similar findings have been noted in some other studies carried out in this group of patients (6, 16). In our study, females were more likely to have high blood pressure and high triglycerides, even though the difference was not statistically significant. Contrary to our findings, Surana et al in their study found that male patients with diabetes were more likely to have high blood pressure and high triglycerides than females in an urban population of India (16). Surana et al have also reported that the most prevalent risk factors for MetS were hypertension, followed by hypertriglyceridaemia in males and central obesity followed by hypertension, in females (16). However, in our study, high waist circumference and high blood pressure were the most prevalent risk factors in males, while high waist circumference and low HDL cholesterol level were the most prevalent risk factors in females. These differences may be due to the fact that most patients in this Indian study had diabetes for a significant time (mean 8.5 years) compared to our study (mean duration 3 months), which would have affected the MetS risk factors.

In our study, there were no differences between HbA1c level in patient with or without MetS irrespective of significantly higher mean BMI (26.9 kg/m2 with MetS vs. 22.2 kg/m2 without MetS) and mean waist circumference (93.3 cm with MetS vs. 82.8 cm without MetS) in the MetS group. This may be due to the fact that majority of patients in our study were in the early stage of diabetes.

Cardiovascular disease is a well-known complication of T2DM and MetS (1). The presence of MetS, in patients with T2DM, increases the risk of cardiovascular disease by fivefold and this risk is independent of age, sex, smoking status, and glycated hemoglobin level (17). However, it is not clear, whether MetS would confer any additional cardiovascular risk rather than individual risk factors it is formed of. The debate between the CV risks of MetS vs. its individual risk factors is still ongoing. It can be argued that grouping the risk factors under the umbrella of MetS and giving a separate diagnosis, draws more attention when highlighting CV risk reduction for this group of patients. The benefit of such multifactorial approach has been highlighted in the STENO-2 study (18). Therefore, an aggressive approach in managing individual risk factors / MetS is needed in order to prevent CV morbidity and mortality in patients with T2DM.

There were some limitations in this study. Since consecutive patients were included in the study, the sampling bias was not entirely excluded. The study population predominantly comprised of females patients and this may have affected the results of the study. Males are mostly employed and the overlapping of clinic hours with the working hours may have contributed to this difference in accessing health care. The study population was limited to the type 2 diabetic patients attending the diabetes clinic of national hospital and therefore, the results may not be applicable to wider diabetic population. Strengths of this study include being the first study to report MetS in relatively newly diagnosed T2DM patients in Sri Lanka and its prospective nature. In patients with diabetes, the prevalence of MetS is high with central obesity being the most common risk factor of Mets, especially among females. The prevalence of MetS is expected to rise with the duration of diabetes and also the associated CV morbidity and mortality. Therefore, aggressive interventions in lifestyle modification and pharmacological treatment to counter the individual risk factors and hence MetS, should be a priority in the managing this population of patients with diabetes.

**Conclusion**

The prevalence of MetS is high in patients with T2DM among the urban population of Sri Lanka. The prevalence of MetS is significantly higher in female patients with diabetes compared to males in this urban setting. A high prevalence of abnormal waist circumference was noted and it was the common risk factor for MetS among both males and females.

**Acknowledgements**

The study was funded by the Diabetes Trust Fund of the NHSL. This is an independent research grant, funded by Novo Nordisk to improve diabetes research. Authors would also like to thank all the research assistants who participated in data collection, the staff of the National Hospital Diabetes clinic and all the patients who participated in this study.

**References**


Insulin technique

Sanjay Kalra¹, Yashdeep Gupta²


Abstract

Insulin is an important treatment modality of treating diabetes and insulin technique; is a vital component of the insulin prescription and of diabetes care. A thorough knowledge regarding insulin preparations, devices, injecting techniques and the problems encountered with insulin use are essential for both health care providers and the patients using insulin. This review highlights salient features of insulin technique, choice of delivery devices and storage of insulin in resource challenged settings.

Key words: insulin technique, injection site, lipohypertrophy, disposal, bio-psychosocial.

Introduction

An appropriate insulin prescription, including the right choice of insulin preparation, the regime and the dosage, is important for the success of diabetes management; so is the correct insulin injection technique. Inappropriate injection technique has the potential not only to limit the utility of insulin, but also to harm the patient. Similar to the strategy of choosing an insulin prescription for a particular patient, insulin technique should also be decided and explained according to the person’s requirements.

Many factors influence the choice of injection technique in persons with diabetes (Table 1). Injection technique is not limited to the injection itself. It comprises the entire process of pre-injection assessment, counseling and motivation, selection of device and explanation of its use, selection and preparation of the injection site, preparation of the insulin/insulin device, and the actual method of injecting. Injection technique does not end with delivery of insulin into the subcutaneous space and needs attention for trouble shooting, pain minimization, management of needle phobia and local injection site reactions. It also includes tips on insulin storage, travelling with insulin, needles/syringe hygiene and disposal of injection-related accessories. Insulin technique education is not a one-time intervention and it is an on-going process of insulin therapy in diabetes care. The aim of this article is to update the knowledge of health care providers regarding these important pre-requisites for proper injection technique.

Pre injection assessment

A thorough clinical (biopsychosocial) and environ-

Table 1. Factors influencing insulin injection technique

<table>
<thead>
<tr>
<th>Biological factors</th>
<th></th>
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</thead>
<tbody>
<tr>
<td>• Choice of site of injection</td>
<td></td>
</tr>
<tr>
<td>• Depth of subcutaneous tissue</td>
<td></td>
</tr>
<tr>
<td>• Dexterity</td>
<td></td>
</tr>
<tr>
<td>• Visual health</td>
<td></td>
</tr>
<tr>
<td>• Auditory health</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Psychological factors</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Fear of insulin</td>
<td></td>
</tr>
<tr>
<td>• Fear of needles</td>
<td></td>
</tr>
<tr>
<td>• Patient motivation</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Social factors</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Clinician’s knowledge</td>
<td></td>
</tr>
<tr>
<td>• Clinician’s time</td>
<td></td>
</tr>
<tr>
<td>• Patient’s learning skills</td>
<td></td>
</tr>
</tbody>
</table>

mental assessment must be done while suggesting insulin therapy. Biomedical factors such as visual, auditory or upper limb impairment, which may limit ability to self injection, must be considered (1). Psychological barriers to insulin must be explored and addressed and socio-cultural issues respected (2, 3). Availability of facilities for insulin storage and disposal must be assessed and modified if required. Psychological insulin resistance, driven by personal anxiety and fuelled by misinformed

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advice from friends and relatives, is common in South Asia. Such self-erected barriers to insulin therapy must be bridged before insulin technique can be taught successfully (2, 3). This is best done through a process of shared decision making, which promotes patient empowerment. Children, adolescents, antenatal women and the elderly need different counseling strategies from adults and must be approached in a manner, which makes them comfortable (4).

**Insulin storage**

Specific storage guidelines are usually mentioned by manufacturers in pack inserts. Insulin should be stored at 2-8°C in refrigerators, but can be kept at room temperature (15-25°C) for up to a month (4). Various methods of insulin storage have been suggested for resource-constrained settings (Table 2).

**Table 2. Alternative methods of insulin storage**

- **In hot climes**
  - In bowl half filled with water
  - In earthen ware pitcher, half filled with water
  - In a shallow hole, dug in the ground
  - In thermo cool boxes with dry ice

- **In very cold climes**
  - Wrapped in multiple layers of woolen cloth
  - In thermo cool boxes
  - In insulin wallets

**Travel with insulin**

While travelling by surface transport, insulin can be kept in flask with ice or in a hand bag. It should never be kept in the glove compartment of a car or in a locked car during summer. During air travel, insulin should be kept in hand baggage (4).

**Device selection**

Choosing the correct device, appropriate to the person’s needs, is vital for successful insulin therapy. The biopsychosocial model of health, which gives equal importance to biological (biomedical), psychological and social aspects of health, can be used to select an appropriate insulin delivery device. Some of the biopsychosocial factors, which inform choice of delivery device, are listed in Table 3.

**Table 3. Alternative methods of insulin storage**

- **Biological factors**
  - Manual dexterity
  - Visual acuity
  - Auditory acuity
  - Magnitude of insulin dose required
  - Adjustment of insulin dose required

- **Psychological factors**
  - Personal preference of pen vs. vial/syringe

- **Social factors**
  - Financial burden
  - Need for privacy while injecting
  - Need for injection while at work/in school/during travel
  - Lifestyle

- **Product-related factors**
  - Number of units that a pen/syringe can hold
  - Largest dose that can be injected
  - Minimum dose that can be changed (increments of half, one, or two units)
  - Indicators for adequacy of insulin left in pen
  - Scope for corrective measures if wrong dose is dialed

**Pre-injection checklist**

Prior to injecting insulin, one must check the delivery device, the insulin and compatibility of all related accessories.

Insulin vials (U40 or U100) must be compatible with their syringes, which can be recognized by their colors and scales. U100 insulin syringes have an orange cover and black scale markings denoting two units each, while U40 syringes have a red cover and red scale markings of one unit each. In general, thinner 31 gauge needles are preferred. Usually the needle length is 6mm or 8mm and there is no advantage of using longer needles (5).

Insulin pens can be reusable or disposable. One must ensure that cartridges, reusable pens and needles are
Insulin technique

compatible with each other. Pen needles may vary from 4mm to 8mm in length and 30 gauges to 32 gauges in thickness (5).

Needle length in specific patient populations

Modern 4 to 6 mm long needles can be used for nearly everyone. Skin fold should be raised only if longer needles are being used or if the injection is being administered to a very slim person (BMI < 20 kg/m²) or toddlers (4, 5, 6).

However, making a skin fold (raised using the thumb and index finger), apart from avoiding intramuscular injection, is helpful in creating diffuse depot of insulin that facilitate uniform absorption. The skin should not be squeezed so tightly that could cause pain or blanching and should be released only after the drug has been injected and the needle withdrawn (4).Injecting at 45° angle is another option in these cases.

Injection sites

Insulin injections should be administered into the subcutaneous tissue to ensure the most reliable and consistent absorption of insulin. Intramuscular injections speeds up absorption and can lead to unexpected hypoglycemia. On the other hand, intradermal injections are more painful, can lead to leakage of insulin from the puncture site, can lead to sterile abscesses and also enhance immune reactions to insulin due to lymphocyte stimulation and should be avoided. The absorption rates are nearly same from the superficial fat layer as is from deep layers near the muscle fascia (6).

Routinely, the abdomen and anterior thigh are used to inject insulin. The lower abdomen, extending from a line drawn 1 inch above the umbilicus to a line connecting the anterior superior iliac spines, may be used. However, the medial part of this space, extending 2 inches from the umbilicus on both sides, should be avoided. The absorption rates are fastest from abdomen. However, in case of multiple dose injection regimens, thigh is the preferred alternative site for injections. The preferred injection sites over the thigh are in the outer and anterior part of the mid one third of the area between anterior superior iliac spine and the patella. The medial part of the thigh should be avoided (4).

Other sites include the upper arm (the posterior mid-third of the arm between the shoulder and elbow joint) and the buttock (upper outer quadrant). The upper arm is preferred for social and practical reasons, especially when insulin is administered by a medical professional, family member or self-injected in public. The buttocks are used in toddlers and younger children.

Since absorption varies from site to site, an injection at a certain hour should be given in the same anatomical site to enable patients to predict the effect of a given dose (6). However, injection sites must be rotated systematically each day to maintain skin health, to avoid lipo-hypertrophy and to optimize insulin absorption. Injections should be spaced 1-2 cm apart in order to minimize tissue trauma.

Using a syringe: One insulin, one vial

Figure 1. Injection preparation.
Injection site preparation

The chosen injection site may be cleaned with cotton balls dipped in water or with alcohol swabs, prior to injection. If the site is ‘socially clean’, i.e., one is willing to touch the skin, there is no need for extra cleansing (4). Soap-based detergents should be avoided as far as pre-injection cleansing is concerned.

Injection preparation

The insulin device should be checked for expiry date, possible damage, clumping, frosting or precipitation, prior to use (7). It should be brought to room temperature by keeping it outside the refrigerator for 30 minutes (4).

If using a syringe and vial, one must wipe the top of the vial with an alcohol swab, draw air into the syringe and push it in the vial, and then draw the insulin dose required, while holding the bottle upside down. The syringe should be checked for air bubbles prior to injection (8).

If insulin preparations have to be mixed, regular insulin should be filled first, followed by NPH insulin, so that no protamine contaminates the regular insulin vial (7). Glargine cannot be mixed with any other insulin preparations, because of its’ low pH.
Table 4. Good injection practices (GIP) to minimize pain associated with insulin

<table>
<thead>
<tr>
<th>Pre-injection</th>
</tr>
</thead>
<tbody>
<tr>
<td>ü Appropriate messaging: convey the benefits of insulin in a positive manner</td>
</tr>
<tr>
<td>ü Appropriate site selection and preparation</td>
</tr>
<tr>
<td>ü Appropriate device selection</td>
</tr>
<tr>
<td>• Thin gauge needles</td>
</tr>
<tr>
<td>• Short needles</td>
</tr>
<tr>
<td>• Pens requiring less pressure</td>
</tr>
<tr>
<td>• New needle for each injection</td>
</tr>
<tr>
<td>ü Appropriate dose selection:</td>
</tr>
<tr>
<td>• Consider splitting doses in persons with high insulin requirement</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>During injection</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Allow insulin to reach room temperature before injecting</td>
</tr>
<tr>
<td>• Allow alcohol to dry before injecting insulin</td>
</tr>
<tr>
<td>• Do not raise a tight painful or blanched skin fold</td>
</tr>
<tr>
<td>• Inject slowly</td>
</tr>
<tr>
<td>• Avoid injecting at hair roots</td>
</tr>
<tr>
<td>• Avoid intramuscular and intradermal injections</td>
</tr>
<tr>
<td>• Avoid injecting over bruised or traumatized sites</td>
</tr>
<tr>
<td>• Do not move the needle while injecting</td>
</tr>
<tr>
<td>• Follow systematic rotation policy</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Post injection</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Release skin fold(if raised earlier) slowly</td>
</tr>
<tr>
<td>• Do not massage the injection site</td>
</tr>
<tr>
<td>• Feel happy: insulin is a life saver</td>
</tr>
</tbody>
</table>

Minimizing pain

Some patients complain of pain with insulin injections. Unless the needle irritates a nerve ending, true pain is rare and it may be a manifestation of needle phobia, insulin phobia, or negative conditioning due to prior experiences. Good injection practices, which can minimize injection-associated pain, are listed in Table 4.

Trouble shooting

As with any medical intervention, insulin administration may be associated with minor complications. Lipohypertrophy is a localized increase in size of adipocytes, which occurs at sites of repeated insulin injections and reuse of needles may precipitate this.

Though patients tend to reuse lipohypertrophic sites because of lowered sensitivity to pain, they should be avoided as absorption of insulin can be erratic. Systematic rotation policy, avoiding reuse of needles and avoiding injections in hypertrophied sites help to prevent and manage lipohypertrophy (4,7).

Other local site reactions include bleeding and bruising, which are usually self-limiting, and amyloidosis (9).

Needle stick injuries are another complication of injectable therapy, which can be minimized by following basic needle hygiene and injection disposal policies. Injection through clothing must be strongly discouraged, as also the injections over the forearm or calf muscles.

Disposal

Appropriate disposal of insulin injections and related accessories is an important, yet often neglected aspect of insulin technique. Inappropriate disposal may lead to needle stick injuries and spread of blood-borne infections, in people with diabetes their family members, health care professionals, and sanitary workers who collect and recycle trash or garbage (4, 7). Dedicated sharps collection and disposal devices are ideal. A practical and safe method of disposing needles and lancets is to collect them in a large glass container (for example, a used intravenous fluid bottle) and seal the container tightly before disposing it off in non-recyclable trash bins.

Conclusion

Insulin technique is an integral part of diabetes therapy and it is as important as the insulin prescription itself. There is a growing realization that incorrect insulin technique is often the reason for suboptimal response to insulin therapy. Inappropriate technique may cause harm to the patient, in form of unexpected hypoglycemia, uncontrolled hyperglycemia, local site reactions, pain and needle stick injuries. It may also harm other people, if good sharps disposal practices are not followed. Ongoing

While using insulin pens, whether reusable or disposable, the first step is to prime the pen with two units of insulin. The appropriate dose should be dialed prior to injecting and this can be checked on the display window of the device (4).
training, audit and improvement in insulin injection practices are required in order to ensure optimal insulin delivery.

References


Mineral and bone disorders secondary to chronic kidney disease (renal osteodystrophy)

Alphonsus N. Onyiriuka¹, Olubunmi B. Fakeye-Udeogu¹, Mohammad Abdullahi¹, Chiedozie J. Achonwa¹, Isaac O. Oluwayemi¹, Moustafa Kouyate¹, Abiola O. Oduwole², Elizabeth E. Oyenusi²


Abstract

Chronic kidney disease (CKD) in paediatric population gives rise to complex of diseases that is known as chronic kidney disease-mineral and bone disorder (CKD-MBD), which mainly involves the calcium and bone metabolism. Associated rickets and secondary hyperparathyroidism leads to pathological changes in the growing bone causing deformities, pathological fractures and growth retardation leading to poor quality of life. Early recognition and proper management can minimize these effects and this care highlights the importance of early diagnosis of proper treatment of CKD in paediatric population.

Key words: chronic kidney disease, mineral-bone disorders, secondary hyperparathyroidism, pathological fracture, renal osteodystrophy.

Introduction

Metabolic bone diseases are those disorders of the skeleton associated with alteration in calcium and phosphorus homeostasis. It is a common complication of chronic kidney disease (CKD), representing part of a broad spectrum of disorders of mineral metabolism that occurs in this clinical setting (1). Chronic kidney disease-mineral and bone disorder (CKD-MBD) is defined as a systemic disorder of mineral and bone metabolism due to CKD that is manifested by either one or a combination of the following: abnormalities of calcium, phosphorus, parathyroid hormone (PTH) and vitamin D metabolism, abnormalities of bone-turnover, mineralization, volume, linear growth and strength, vascular or soft tissue calcification (2). In contrast, the term “renal osteodystrophy” describes the pathological changes that are seen in bone structure in CKD, but fails to describe adequately the adverse changes in mineral and hormonal metabolism that have grave consequences for patient survival. Renal osteodystrophy currently refers specifically to the different bone lesions defined by bone histomorphometry (3) and is therefore, only one aspect of CKD-MBD (4). Such bone lesions include osteitis fibrosa cystica, osteomalacia, dynamic bone disease, mild hyperparathyroidism related bone disease and mixed uraemic osteodystrophy (5).

The kidney is mainly responsible for synthesizing active vitamin D, 1,25dihydroxycholecalceferol (1, 25 (OH) 2 D3) that is needed for calcium regulation in the body (6). With progressive loss of actual or functional renal tissue, there is a decline in renal 1α-hydroxylase activity, resulting in decreased production of 1, 25 (OH) 2 D3, which in turn leads to impaired intestinal absorption of calcium and hypocalcaemia (5). The resultant hypocalcaemia is a strong stimulus for PTH secretion leading to secondary hyperparathyroidism (1). The progressive renal insufficiency also cause phosphate retention that gives rise to hyperphosphatemia, which further promotes hypocalcaemia and increased PTH secretion leading to a high-turnover bone disease (1, 7). CKD-MBD is a result of secondary hyperparathyroidism that developed in chronic renal disease due to the reduction in 1, 25(OH)2 D3 level and phosphate retention.

The impact of CKD-MBD in children may be immediate and it will manifest as a disequilibrium in calcium, phosphorus, and vitamin D metabolism determinants. It has delayed effects such as growth retardation, deformities, fractures, vascular/tissue calcifications that ultimately leads to increased morbidity and mortality and poor quality of life (3, 7, 8). It is estimated that the incidence of clinical or radiographic manifestation of bone disease in children with CKD range from 41% to 68% (9, 10), depending on the age of onset and the stage of CKD. In a
10 year follow-up of 50 children with chronic renal failure, Hsu et al (10) has reported that 34 (68%) developed radiological evidence of bone disease. In a cohort of 249 young Dutch adults with onset of end stage renal disease before the age of 14 years, 61% had severe growth retardation, 37% severe bone disease and 18% disabilities resulting from bone impairment (11). The evidence suggests that CKD-MBD is a common clinical problem in pediatric practice but is probably under-diagnosed in poor resource settings. The purpose of this case report is to increase the alertness of child health physicians to occurrence of mineral and metabolic bone disease as a complication of CKD in children, thereby encouraging early institution of preventive measures.

Case report

An eight-year old Nigerian boy presented to the Lagos University Teaching Hospital (LUTH) with a history of poor growth, swelling of the wrists and ankles with bone pain for 3 years and inability to walk for 2 weeks. He was the shortest among his classmates and also the shortest in his family. His 4 year old younger brother was taller than him. The swelling of his wrists and ankles had increased in size with time and he had also developed bone pain, which became worse about 4 weeks before presentation. Along with the pain, he had developed inability to walk that his mother had to seek medical advice. His early childhood was unremarkable except for a posterior urethral valve ablation done at the age of 4 months when presented with poor urinary stream.

His height, weight and arm span were 90cm (-6.7 SDS), 13kg (-2.4 SDS) and 100cm. His upper to lower segment ratio was 1.2:1. He had genu valgum deformity with anterior convexity of tibia/fibula (Figure 1). He had widening of the wrists and ankles (Figure 2, 3), Rachitic rosary and bossing of the skull suggesting the clinical possibility of Rickets.

Urinalysis revealed proteinuria and his hemoglobin level was 11.5g/dl (Packed Cell Volume 35%). The micturating cystourethrogram (MCUG) showed moderate dilatation of the posterior urethra and well distended urinary bladder with sacculations on the wall suggestive of posterior urethral valve. His biochemical investigations showed evidence of renal impairment and hypocalcaemia (Table 1). His X-rays of hands and pelvis showed evidence of rickets and pathological fractures in both femurs (Figure 3).

Discussion

A biochemical assessment of disorders of bone and mineral metabolism is the mainstay of diagnosis and treatment of CKD-MBD (12). However, the National Kidney Foundation [Kidney Disease Outcomes Quality

Figure 1. Widening of the wrist.

Figure 2. Widening of the ankles and deformities of the lower limbs.

Figure 3. Cupping and fraying epiphyseal bones.
Table 1. Summary of laboratory findings

<table>
<thead>
<tr>
<th>Laboratory parameter</th>
<th>Results</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum Sodium</td>
<td>130 mmol/L</td>
<td>Mildly low</td>
</tr>
<tr>
<td>Serum potassium</td>
<td>3.7 mmol/L</td>
<td>Normal</td>
</tr>
<tr>
<td>Serum chloride</td>
<td>101 mmol/L</td>
<td>High normal</td>
</tr>
<tr>
<td>Serum bicarbonate</td>
<td>15.0 mmol/L</td>
<td>Very low</td>
</tr>
<tr>
<td>Serum urea</td>
<td>13.3 mmol/L</td>
<td>High</td>
</tr>
<tr>
<td>Serum creatinine</td>
<td>284.5 µmol/L</td>
<td>Very high</td>
</tr>
<tr>
<td>Serum calcium (total)</td>
<td>1.78</td>
<td>Low</td>
</tr>
<tr>
<td>Serum albumin</td>
<td>38 g/dl</td>
<td>Normal</td>
</tr>
<tr>
<td>Serum phosphate</td>
<td>2.1 mmol/L</td>
<td>Upper limit of normal</td>
</tr>
<tr>
<td>Serum alkaline phosphatase</td>
<td>1600 iu/L</td>
<td>Very high</td>
</tr>
<tr>
<td>Serum parathyroid hormone (PTH)</td>
<td>90 pmol/L</td>
<td>Very high</td>
</tr>
<tr>
<td>Urine output</td>
<td>6 ml/kg/hr</td>
<td>Polyuria</td>
</tr>
<tr>
<td>Urine calcium</td>
<td>&lt; 0.5 mmol/L</td>
<td>Low</td>
</tr>
<tr>
<td>Urine creatinine</td>
<td>1.6 mmol/L</td>
<td>High</td>
</tr>
<tr>
<td>Urine calcium:urine creatinine ratio</td>
<td>0.31</td>
<td>Low</td>
</tr>
<tr>
<td>Urine culture</td>
<td>No growth</td>
<td>Sterile</td>
</tr>
<tr>
<td>Egfr</td>
<td>19 ml/min/1.73 m²</td>
<td>Very low</td>
</tr>
</tbody>
</table>

eGFR = Estimated glomerular filtration rate

Initiative (KDOQI) Guidelines] suggests that a bone biopsy should be considered in all patients with CKD who have pathological fractures (13). This is similar to the position statement from Kidney Disease: Improving Global Outcome (KDIGO) foundation (2). Although we could not perform bone biopsy in this patient, there was enough biochemical and radiological evidence to suggest the diagnosis of CKD-MBD with increased bone remodeling in our index patient.

In CKD-MBD, hyperphosphataemia is an expected biochemical abnormality. However, the serum phosphate level was just at the upper limit of normal reference range in our patient. It is well established that serum phosphate tend to fall with increasing serum PTH concentration primarily as a result of increasing renal phosphate wasting (14) and this could be the possible explanation for high normal phosphate levels in our patient.

The index patient had bilateral pathological fractures of the femurs at the time presentation, implying that he had pre-dialysis fracture. This finding strongly challenges the general belief, as documented in the literature, which fractures do not occur until the patient is placed on dialysis (13). A review of the literature indicated that the degree of linear growth retardation varies with the stage of CKD as follows: -1 SDS in mild, -1.5 SDS in moderate and -1.8 SDS in severe CKD (15). Anemia, metabolic acidosis, secondary hyperparathyroidism, water and electrolyte disturbances, uremia and renal osteodystrophy are probable causes for the linear growth retardation in CKD. All these factors may have contributed to the linear growth retardation in our patient.

In the management of CKD-MBD, we mainly focused on 3 areas: (I) to provide an optimal nutritional support to maximize the final height and avoid bone deformities, (ii) to equilibrate calcium/phosphate metabolism; so as to provide acceptable bone quality and cardiovascular status and (iii) to control all metabolic and clinical abnormalities that can worsen bone and (mainly) growth, metabolic acidosis, anemia, malnutrition and 25(OH) vitamin D deficiency (16). Monitoring treatment is also important, as over treatment can leads to dynamic bone disease, growth failure, hypercalcaemia and progression of cardiovascular calcification (16). In this regard, determination of the target PTH level is essential in order to assess the success of the therapy. However, the target PTH level still remains debatable (3). In this context, it is currently recommended to monitor growth and phosphorus/calcium/25(OH) vitamin D levels as primary targets in the management of CKD-MBD in children (3). Newer therapeutic agents such as calcimimetic, phosphate-binding agents (Lanthanum carbonate) and vitamin D analogues may suppress serum PTH levels effectively while limiting intestinal calcium absorption and skeletal fibroblast growth factor 23 (FGF 23) stimulation (16). After correcting all metabolic abnormalities, the use of supraphysiological dose of recombinant human growth hormone (rhGH) has been shown to be safe and effective in increasing growth and final adult height of these patients (17, 18). These strategies represent the future therapeutic alternatives in the management of CKD in paediatric age group.

In conclusion, all children with CKD should be evaluated early in the course of the disease for the presence of a metabolic bone disorder with the aim of putting in place preventive strategies.

References


Challenges in the diagnosis and management of Cushing’s syndrome due to ectopic ACTH from bronchial carcinoid

M S A Cooray¹, N P Somasundaram¹, Janakie Fernando², A H N Fernando¹, R M De Silva², D Rasnayake⁴


Abstract

Despite the advances in biochemical methods and imaging techniques, Cushing’s syndrome (CS) related to ectopic adrenocorticotrophic hormone (ACTH) secretion continues to pose diagnostic and therapeutic challenges to the clinician. The work up involves establishment of endogenous Cushing’s syndrome, diagnosis of ACTH dependency, localization of the source of ACTH secretion and rapid biochemical control of hypercortisolaemia. The diagnostic pathway is made difficult by recurrent sepsis, relative hypoadrenalism, drug side effects as well as unmasked incidental lesions.

We report a patient presenting with Cushing’s syndrome associated with ectopic ACTH secretion from a bronchial carcinoid whose management presented multiple diagnostic and therapeutic challenges.

Key words: Cushing’s syndrome, ectopic adrenocorticotrophic hormone, hypercortisolaemia, hypoadrenalism, incidental lesion, small cell carcinoma of lung.

Introduction

The syndrome of ectopic ACTH secretion is one of the greatest diagnostic challenges in clinical medicine. The first association between cancer and CS was first reported in a patient in 1928 (1). However, it was only in the 1960s that ACTH production was demonstrated in tumours other than pituitary tumours (2). Following this, many malignancies other than small cell carcinoma of the lung (SCCL) were recognized to be causative for CS and in several large series, ectopic ACTH secretion has shown to account for approximately 10% of Cushing’s syndrome (3). The causative malignancies include carcinoid tumours of the lungs, thymus and gastrointestinal tract, islet cell tumours, phaeochromocytomas and medullary thyroid carcinomas (4).

The syndrome requires a complete workup that includes the establishment of endogenous CS, diagnosis of ACTH dependency, localization of the source of ACTH secretion and rapid biochemical control of hypercortisolaemia. The effects of severe hypercortisolaemia make the diagnostic pathway difficult. Here, we describe a patient with ectopic ACTH from a bronchial carcinoid tumour highlighting the unusual presentation and difficulties in management.

Case report

A 50-year-old police woman presented to the medical casualty department with acutely worsening shortness of breath, chills, rigors and general deterioration. She admitted that she was having a 12 month history of facial swelling, weight gain, hair loss, fatigue, dyspnea with poor effort tolerance, depression and generalized ill health. She had also developed diabetes mellitus and hypertension 1 year prior to presentation with no family history of the same and had poor control despite being on treatment. She denied any history of taking exogenous steroids or herbal medicine.

On examination, she was noted to be extremely breathless, pigmented, hypertensive and centrally obese. She had a clinically Cushingoid appearance with central obesity, proximal myopathy, easy bruising, facial puffiness and fat deposition in the dorso-cervical region. She had purple stria over her flanks and thighs as well as facial acne and hyperpigmentation of her extensor surfaces on her upper and lower limbs (figure 1). Thyroid examination was normal.

Preliminary investigations revealed that she was hyperglycaemic and hypokalaemic (potassium 1.7

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mmol/l). Although her inflammatory markers and white cell counts (WCC) were not suggestive of an infection, chest X-ray suggested a bilateral pneumonic state and blood cultures confirmed a growth of *Staphylococcus aureas* and she was treated for staphylococcal sepsis and pneumonia with intravenous antibiotics.

Subsequently, she was evaluated for CS. Her 9 am plasma cortisol was unsuppressed after overnight dexamethasone at 890 nmol/L (reference: <50 nmol/L) and 9 am plasma cortisol after 48 hours of low dose dexamethasone was 792 nmol/L (reference: <50 nmol/L), which confirmed a diagnosis of CS. Her plasma ACTH was 212 pg/ml (reference < 50 pg/mL). Thus an extensive search was planned to establish the source of ACTH. As she was very symptomatic, she was commenced on oral ketoconazole 200mg 12 hourly. MRI of the pituitary region reported a microadenoma, which was 1mm in size, giving rise to the need for an inferior petrosal sinus sampling (IPSS) to localize the source of ACTH (figure 2).

<table>
<thead>
<tr>
<th>Table 1.</th>
<th>ACTH levels (pg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Right</td>
</tr>
<tr>
<td>Inferior petrosal sinus</td>
<td>113.1</td>
</tr>
<tr>
<td>Internal jugular</td>
<td>116.4</td>
</tr>
<tr>
<td>Peripheral</td>
<td>108.2</td>
</tr>
</tbody>
</table>

Central ACTH level / peripheral ACTH level = 1.02 (<1.8 - Cushing’s disease unlikely)

She underwent a bilateral IPSS without corticotrophin releasing hormone (CRH) stimulation. The results of the sampling clearly demonstrated that the source of ACTH was unlikely to be the pituitary as the ratio between central to peripheral ACTH levels was 1.02.

Her clinical status was again compromised following the procedure where she developed a urinary tract infection and an abscess at the femoral puncture site. Her condition got progressed to septic shock and was resuscitated with fluids, inotropes and hydrocortisone therapy.

In the meantime, she had a CT scan of the chest, which revealed bilateral diffuse cavitory lesions with patchy consolidation (figure 2). Interestingly, a single solid lesion in the right lower lobe was reported as a “nodule, which may represent metastatic deposit” and the radiology team suggested a CT guided biopsy. Even after this procedure, the patient became extremely breathless with type 1 respiratory failure. The CT findings were suggestive of early infective process on a background of recent staphylococcal pneumonia. Notably her ESR was 5 mm/1st hour and WCC were normal during this time. However, the clinical state was that of an infection and she was immediately treated with carbepenum as well as a systemic antifungals whilst awaiting cultures. Blood and sputum culture yielded extended-spectrum beta-lactamase (ESBL) organisms. As she was on ketoconazole, her cortisol reserve was insufficient to counteract the stress of severe infection and she received intravenous hydrocortisone with fluid resuscitation. As expected, her random blood cortisol done before steroid administration revealed a very low cortisol level of 151 nmol/L. Therefore, diagnostic tests had to be postponed at this stage as she was not fit enough for invasive investigations.

Following recovery from the infection, the patient underwent another CT scan of the chest to re-evaluate the lung lesions. This revealed resolution of almost all the cavitory lesions and consolidation. Interestingly, the small area of consolidation in the right lower lobe remained the same. CT scan of abdomen and pelvis revealed bilateral nodular hyperplasia of the adrenals as well as a lesion...
in the liver, which avidly enhanced with contrast. This was later confirmed to be a haemangioma by ultrasound assessment. Bronchoscopy did not reveal any endobronchial lesions. Octreotide scintigraphy or FDG-PET scan could not be performed due to non-availability.

A CT guided biopsy of her right lung nodule was performed and the histopathology revealed a tumour composed of nests of small cells with hyperchromatic nuclei having finely stippled chromatin. The mitotic count was low (2 per 10 hpf). Small, eosinophilic nucleoli were present staining strongly for ACTH, CD56, chromogranin and synaptophysin (figure 3).

These histological features are shared by SCLC as well as bronchial carcinoids. Differentiation of these 2 lesions can be done using the Ki-67 proliferation index, which would reveal a very low index for carcinoids whereas it would be a very high index for SCLC (figure 4).

Following the histological diagnosis of bronchial carcinoid, the patient underwent right lower lobectomy and she tolerated the procedure well. The resected specimen contained a 2.2 × 2.2 cm size bronchial carcinoid, which was reconfirmed with histology. Following thoracotomy and resection of her lung lesion, the plasma cortisol decreased significantly (post op 25nmol/L) and she remains well on maintenance dose of steroids. When reviewed in clinic 3 months after surgery, she was symptomatically well, with good lung function.

**Discussion**

Bronchial carcinoid, which is a low to moderate grade malignancy, typically has a long history and slow onset of symptoms (1-84 months, median 23.6). Due to this slow progressive nature of this tumour, the classical Cushingoid features are usually present by the time they present with clinical symptoms attributable to lung disease (3). Our patient had symptoms of cortisol excess for at least 12 months prior to presentation. As in most cases, the tumour by itself did not give rise to respiratory symptoms or signs, but secondary to infections of the lung.

The investigative process and management of a patient with CS is very challenging. The hypercortisolaemia leads to hyperglycemia, fluid retention, hypertension, severe infections, electrolyte abnormalities and many other problems that undoubtedly hinder the investigative process. Additionally, these patients cannot mount an adequate cortisol response (even though they have very high basal levels of cortisol) in the event of stress such as sepsis or surgery. Therefore, these patients are always at risk of adrenal crisis, especially when they are on adrenolytic drugs such as ketoconazole, as in this patient. Adrenal insufficiency occurs insidiously and has very subtle features such as better control of blood sugar and blood pressure in a previously uncontrolled patient or reduction in drug doses to achieve control. Thus, daily bed side assessment for these features is mandatory in addition to testing for cortisol levels to prevent an adrenal crisis. This case also highlights the immunocompromised nature of this disease process and the need for extra vigilance in identifying and treating them with steroids appropriately. Our patient presented with a severe atypical pneumonia and continued to have recurrent infections during the investigative process. She also developed urinary sepsis and infection at the catheter site after IPSS. In all these infections, her CRP and ESR did not increase and if the desired clinical vigilance was not advocated, these infections would have not been picked up until in a very advanced state.

Confirmatory investigations for suspected CS in the presence of severe sepsis and critical illness may lead to falsely elevated cortisol levels. Thus, the workup and evaluation for possible hypercortisolism should not be performed while patients are under stress.

Differentiating Cushing disease from an ectopic source of ACTH can be difficult. Generally, these patients
with ectopic secretion of ACTH have higher ACTH levels. They fail to suppress cortisol secretion for high doses of dexamethasone (8mg) and their pituitary adrenal responses to CRH stimulation is also absent (5, 6). However, 20-40% of patients with ectopic ACTH demonstrate cortisol suppression on high dose dexamethasone and 10-15% responds to CRH stimulation (6). Pituitary imaging may unmask incidental lesions and pose difficulties in the diagnosis. It is reported that, 10-20% of endocrinologically normal people have pituitary lesions of no clinical significance on pituitary imaging (7). Pituitary imaging can also lead to false negative results especially in the case of micro adenomas where dynamic imaging with contrast is not used. Modern MRI scanning has been reported to have only 70-80% sensitivities in the detection of micro adenomas (8).

The most valuable investigation for differentiating between pituitary and ectopic sources is the inferior petrosal venous sinus sampling (IPSS), which is considered as the gold standard. A baseline ACTH gradient between the inferior and the peripheral petrosal sinuses >2, and after stimulation with CRH/desmopressin >3, would indicate a pituitary source of ACTH secretion (9, 10). This is an invasive procedure, which need expert skills and may be difficult in a critically ill patients.

Once it is confirmed that the ACTH is from an ectopic source, the localization of the source of ectopic ACTH can be even more difficult, especially if standard imaging is negative. It is also important to consider the possibility of infections and unrelated benign incidental lesions, which may mislead the clinician if not interpreted in their true context. In our patient, the CT scan of the chest showed bilateral cavitory lesions and the peripheral lung nodule. These findings along with the enhancing lesion in the liver could easily have been misdiagnosed as advanced malignancy. The index lesion in the lung was only made prominent after resolution of the florid inflammatory changes and in this situation, patience was the key to the diagnosis.

Confirmation of ectopic ACTH production requires demonstration of immunostaining positivity for ACTH in the resected tumour. Thereafter, the use of ki-67 marker is the key factor in differentiating SCLC from carcinoid tumour, as both these are entities in a spectrum of neuroendocrine tumours.

Management of patients with ectopic ACTH requires control of the hypercortisolaemia as soon as the diagnosis is established (11). Ketoconazole and metyrapone have reasonable amount of evidence for their efficacy and safety (12, 13). Patients with identifiable sources of ectopic ACTH should have the tumours resected and surgery can offer a cure in more than 80% of bronchial carcinoids (12).

Even with modern techniques, in as many as 12% of patients, the source of ACTH may not be found (11). Such cases with “occult” ACTH-secreting tumours remain a challenge and may need repeated investigations for many years. In such cases, bilateral adrenalectomy is the next best therapeutic option, but with the need for lifelong steroid replacement (14).

Conclusion

Ectopic ACTH secreting tumours present some of the most challenging differential diagnoses in endocrinology and require careful clinical, biochemical, radiological, and pathological investigation. Due vigilance for sepsis, adrenal insufficiency and other complications of high cortisol is needed and close liaison between the endocrinologist, endocrine surgeon, chemical pathologist, and radiologist in the management of these patients is the key for a successful outcome.

References


Erectile dysfunction with elevated serum testosterone

L D Ranasinghe¹, K D Liyanarachchi¹, N P Somasundaram¹


Abstract

Symptoms of testosterone deficiency with elevated testosterone levels are rare and could occur with elevated sex hormone binding globulin (SHBG) levels. Here, we report a 59 year old patient presenting with erectile dysfunction (ED) with diminished libido for 4 months. He developed these symptoms 6 months after starting anti tuberculosis treatment (ATT). He had elevated total testosterone concentration along with raised SHBG. However, his free testosterone was normal. Repeated total testosterone level 2 months after completion of ATT was normal indicating normalization of SHBG levels.

Key words: Erectile Dysfunction, SHBG, ATT.

Introduction

ED is defined as persistent or recurrent inability to achieve and maintain penile erection of sufficient rigidity to permit satisfactory sexual activity for at least 3 months (1). The etiology of erectile dysfunction is multi factorial and infections such as tuberculosis (TB) could also lead to ED due to the hypogonadism with the related involvement of the pituitary and testes. Inspite of having normal genitourinary system, patients with pulmonary TB tend to have deterioration of all components of copulatory act, from sexual desire to orgasm, which improve significantly with effective ATT (2). On the other hand, ATT is also known to cause ED, which could resolve with the discontinuation of treatment (3).

Case report

A 59 year old male who had no relationship problems presented with ED for 4 months. He had decreased libido with absent morning erections. He did not have symptoms of depression though he had psychological distress related to ED. He was diagnosed to have tuberculous meningitis 10 months ago when he presented with loss of consciousness associated with headache and a febrile illness. He was started on ATT and he has been on isoniazid, rifampicin and pyridoxine during the last 10 months. He tolerated anti TB therapy fairly well and there were no episodes of ATT induced hepatitis. He also had hypertension and benign prostatic hyperplasia for which he was on amlodipine and tamsulosin. He was otherwise well. He denied use of steroids except at the initial 2 months of ATT or recreational drugs. He had 3 children and was a nonsmoker and a social drinker. Examination revealed a well virilized male with a normal testicular consistency and size (20ml). Rest of the examination was unremarkable.

Biochemical evaluation revealed repeatedly raised 9am total testosterone levels of 64.3 and 57nmol/l (9.7-38.14). Free testosterone level performed using enzyme linked immunosorbent assay (ELISA) was 15.84pg/ml (5.5 – 42), which was normal. He had a raised SHBG level of 112 nmol/l (13- 71), which probably explaining the reason for raised total testosterone. Follicle stimulating hormone (FSH) was slightly raised (10.5 U/L) while, luteinizing hormone (LH) was normal (6 U/L). Other anterior pituitary hormones including 9am cortisol, thyroid stimulating hormone (TSH), FT₄ and prolactin were normal. His serum albumin was 43g/L and other hematological and biochemical markers including liver profile were normal.

Ultrasound scan of the scrotum showed normal testicular size, echogenicity and vascularity on both sides. There was no testicular calcification. An epididymis cyst was noted on right side (5mm size). Minimal scrotal effusions were also noted bilaterally.

The patient was explained the possible hormone derangement due to ATT. He was reassured and informed the possibility of reversibility of sexual function after discontinuation of ATT once treatment is completed. As expected, his total testosterone level got normalized and came down to 22.09 nmol/l (9.7-38.14) 2 months after stopping ATT, indicating that raised SHBG in this patient is most likely due to anti TB medication.

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Discussion

Certain drugs are known to cause elevation of testosterone levels and rifampicin has been one of those drugs that could increase the level of testosterone (4, 5). Brodie, et al has demonstrated that 2 week rifampicin therapy at a dose of 600mg per day increased the level of testosterone and estradiol in males with testosterone returning to normal range within 2 weeks after stopping treatment (4). SHBG levels were also significantly increased after 2 weeks of rifampicin treatment and then fell down to normal level after discontinuation of drug. However, he could not demonstrate a significant correlation between the changes in testosterone and SHBG levels. Raised levels of total testosterone, (and SHBG) while on isoniazid and rifampicin, came down to normal range after stopping these drugs indicate that either isoniazid or rifampicin was responsible for this hormonal change in our index patient. Similar to the above study, rifampicin induced SHBG over production could have been the most likely explanation for the rise in total testosterone concentration in our patient.

Rifampicin induces cytochrome P450 mediated monooxygenase activity (cholesterol side-chain cleavage and 17 alpha-hydroxylase/C17-20 lyase) is required for testosterone biosynthesis in leydig cells (6). Increased biosynthesis of testosterone may occur in patients on rifampicin due to this cytochrome P450 induction. Due to the associated elevation of SHBG, most of the testosterone produced with the activation of cytochrome P450 will get bound to SHBG leading to reduction in biologically active free testosterone level. This reduction in bioavailable testosterone due to high SHBG leads to clinically significant problems such as erectile dysfunction. Therefore, it is important to check free testosterone level in cases where changes in SHBG are suspected (7).

Most of the freely available assays for free or bioavailable testosterone measurements are not very reliable and should be performed in a reliable reference laboratory (7). Free testosterone level can be measured accurately by equilibrium dialysis or can be calculated using total testosterone, SHBG and albumin (8). The calculated free testosterone concentrations depends on the quality of total testosterone and SHBG assays and differ systematically from those measured by equilibrium dialysis (9). Our patient had symptoms of testosterone deficiency despite high total testosterone levels and normal free testosterone levels. The assay that was used to measure free testosterone was not the ideal and could have given a misleading value.

Anabolic steroids, thyrotoxicosis, HIV infection, malnutrition (low Mg, Zn) and liver disease are known to cause SHBG elevation. Anticonvulsants notably phenytoin and phenobarbitone can also increase SHBG and total testosterone levels (10, 11). As a result, free testosterone may reduce and could be the reason for ED in epileptic patients. Clomiphene citrate causes an increase of SHBG and total testosterone concentration, probably due to the elevation of estradiol levels (12). Total testosterone level can be significantly elevated in patients with thyrotoxicosis and this is also due to excessive production of SHBG. They can develop ED due to low free testosterone, which improves with treatment of thyrotoxicosis. Therefore, specific treatment of ED with selective phosphodiesterase-5 inhibitor should be postponed for at least 6 months after restoration of euthyroidism in these patients (13).

Variety of drugs and medical conditions could alter the levels of SHBG and total testosterone level should be interpreted cautiously in the presence of above conditions. Anti-tuberculosis medication, rifampicin is one of these drugs.

References

Case report


Successful twin pregnancy in panhypopituitarism

R D Jeewantha¹, M R L Perera², C N Wijeyaratne², L D Ranasinghe³


Abstract

Panhypopituitarism is characterized by inadequate or absent production of anterior pituitary hormones. This involves hypofunction of most of the major endocrine functions that affect fertility and reproduction. Deficiency of all six anterior pituitary hormones leads to deficiencies of gonadotrophins (FSH, LH), thyroid axis (TSH), adrenocortical hormones (ACTH), Growth Hormone (GH) and Prolactin (PRL). GH and gonadotrophin deficiency are commoner (1) than TSH and ACTH deficiency (2).

Although pregnancy after complete loss of pituitary function is uncommon, advances in fertility treatment have led to increased pregnancy rates in these women. Problems related to pregnancy include infertility, lactation failure and increased risk of complications such as miscarriage, anaemia, pregnancy-induced hypertension, placental abruption, premature birth, and postpartum hemorrhage (3, 4, 5). Conception in this group of patients usually requires the support of assisted reproductive techniques. Induction of ovulation by means of human or recombinant gonadotrophins is widely used in current practice. Progestrogen support following conception, optimizing other hormonal replacement and careful monitoring throughout pregnancy play a vital role in successful pregnancy outcomes. We report a subject with panhypopituitarism who was managed in our Endocrine Antenatal clinic with successful outcome.

Key words: panhypopituitarism, recombinant, gonadotrophins, antenatal clinic, fertility treatment.

Case

A 35 year old mother of one admitted from our antenatal clinic at 34 weeks of period of gestation for the tertiary care management of a dichorionic diamniotic (DCDA) twin pregnancy.

At the age of 20 years, she was diagnosed to have a Rathke’s pouch cyst, which was surgically drained and followed by radiotherapy. Post-interventional panhypopituitarism was diagnosed and she was on hormone replacement for hypocortisolism, hypothyroidism and hypopogonadotropic hypogonadism; while growth hormone was not replaced due to lack of funding. She was replaced with oral levo-thyroxine, hydrocortisone (20mg daily in split doses) and the combined oral contraceptive pill (OCP). The patient remained symptom-free and returned to full time work. Upon her request, at the age of 28 years as fertility treatment, induction of ovulation with gonadotrophins was done. During the second cycle of treatment with recombinant FSH for follicular development and maturation with subsequent human chorionic gonadotrophin (hCG) for ovulation following ultrasound ovum tracking coupled, with Intrutrine Insemination (IUI) resulted in a singleton intrauterine pregnancy.

Her first pregnancy was otherwise uncomplicated apart from the diagnosis of Gestational Diabetes Mellitus (GDM) at 28 weeks gestation, which was managed only by dietary modifications. She gave birth to a healthy male baby at term weighing 3.6kg (90th centile) by an elective Lower Segment Caesarean Section (LCS) on her request.

At the age of 34 years, she requested fertility treatment for her second pregnancy. After failure of initial ovulation induction by recombinant FSH treatment, which ended up with a blighted ovum, she was commenced on Human Menopausal Gonadotrophins (hMG). Ovulation induction with hMG was initiated at a daily dose of 75 units, which was increased to 150 units daily after 15 days. The increased dose was continued for a further 10 days with a total duration of 25 days. When the dominant follicle was beyond 18mm, hCG 5000 IU was administered intramuscularly. Subsequently, she underwent IUI, which resulted in conception and she was given luteal phase support with vaginal progesterone until 12 weeks of gestation. Assessment of adequacy of hormone replacement was confirmed biochemically with serial cortisol levels as a ‘day curve’ while on oral hydrocortisone, free thyroxine along with glucose, renal, hepatic and electrolyte evaluations. The hydrocortisone dose was

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increased to 25mg per day (10mg mane and 5mg at midday and vesper) from 8 weeks of gestation and maintained up to delivery with repeat ‘day curves’. Thyroxine dose was increased to 125µg daily in the first trimester and later in third trimester to 150µg daily to maintain a high normal free thyroxin concentration (>1.5 ng/dl).

A Dichorionic Diamniotic (DCDA) twin pregnancy was confirmed by the dating ultrasound scan at 8 weeks gestation. Diabetes mellitus was diagnosed at 8 weeks of gestation by a high 2nd hour 75g oral glucose challenge test of 158mg/dl (>140mg/dl) and HbA1C level of 7.4% that raised the possibility of pre-existing diabetes. Therefore, renal, eye and cardiovascular assessments were done in order to screening for end organ damage. Patient was initially management with lifestyle interventions and with metformin 500mg twice daily. Later at 28 weeks gestation, pre-mixed 30/70 Human Insulin 4 IU twice daily was added and continued until delivery to attain good glycaemic control.

Fetal growth was monitored using regular ultrasound scans and showed normal growth without any fetal anomalies. During late third trimester, she presented with persistently low Haemoglobin (9.4g/dl) which was further investigated and confirmed as iron deficiency anaemia. The condition was managed with Ferrous sulphate daily with the target of achieving Hb>10g/dl at the time of delivery.

She gave birth to healthy male twins with birth weights of 2.18kg (10th-50th centile) and 2.65kg (50th-90th centile) respectively in T1 and T2 twins at 36 weeks of GA by elective LSCS under epidural anaesthesia. A single stress-dose of hydrocortisone (100mg) intravenously was administered pre- epidural insertion and tapered to the maintenance level of 50mg three times per day for the first 48 hours. Lactation failure occurred following delivery as expected in a patient with panhypopituitarism, that required artificial milk feeds.

Neonatal adaptation was unremarkable with normal growth parameters. Both babies and mother were discharged on postpartum day 8. The mother discharged on pre-pregnant homone replacement doses.

**Discussion**

The patients with panhypopituitarism should be replaced with deficient anterior pituitary hormones this hormonal substitution should be initiated in an orderly manner, which include glucocorticoid, thyroid hormone, sex hormone, and growth hormone respectively. In general, the thyroid hormone replacement is initiated two weeks after glucocorticoid replacement, commencing at a low dosage in order to prevent an Addisonian crisis (6). However, as thyroxine takes approximately two weeks to show the maximum metabolic benefit, both thyroxin and hydrocortisone can be commenced concurrently under close supervision in patients with hypocortisolism.

Although natural pregnancy is uncommon in such patients, modern advances in assisted reproductive techniques and careful monitoring throughout pregnancy has enabled successful outcomes. Pre pregnancy preparation with appropriate adjustment in hormonal level plays a vital role in achieving this.

Approximately one third of maternal thyroid hormone is delivered to the fetus, which is crucial for fetal neurodevelopment in the first half of pregnancy prior to fetal pituitary-thyroid axis development (1). It has shown that perinatal thyroid dysfunction can lead to a significant reduction in body weight and height, delayed neurodevelopment, high risk of cognitive disorders and depression-like behaviors in infants (7). The evidence suggests an association between gestational hypopituitarism and impaired intellectual and cognitive development in offspring (8) and irreversible damage to the auditory system functions caused by perinatal hypothyroidism in rats (9). Considering this vital role played by maternal thyroid hormones on fetal neurodevelopment, our patient’s first trimester thyroxine dose was increased from 100µg daily pre-conception to 125µg daily and later in the third trimester to 150µg daily to maintain a high normal free thyroxin concentration (>1.5ng/dl).

During pregnancy, both total and free plasma cortisol concentration increases during gestation and upto 2- to 3-fold elevation of plasma cortisol values can occur during the third trimester when compared with non-pregnant controls. In some patients, these values could reach as high as to the values in the range seen in Cushing’s syndrome (10, 11). This may be due to the antiglucocorticoid effects of elevated progesterone levels during pregnancy (12). Placental CRH appears to be the primary stimulus for cortisol production especially during third trimester. However, due to the placental 11β hydroxysteroid dehydrogenase-2, which inactivates active glucocorticoids, the fetus is protected from the effects of maternal hypercortisolism as well as exogenous steroids such as hydrocortisone (13, 14). On the other hand, synthetic long-acting glucocorticoids such as dexamethasone should be avoided in pregnancy as it can cross the placental barrier unaltered.

Because of the gradual increase in free cortisol observed during pregnancy, it may be required to increase the hydrocortisone dose by 50% during the last trimester of pregnancy. Stress doses of hydrocortisone should be given for LSCS, which can be tapered over 48 h to a regular replacement dose (1). Our patient received an increased hydrocortisone dose of 25mg per day (10mg mane and midday, 5mg vesper) from 8 weeks of gestation up to delivery, in comparison with 15mg daily (10mg mane and
preparation for LSCS followed by intravenous.

The evidence suggests that GH treatment reduces the abortion rate in patients with GH deficiency and GH replacement during early pregnancy has shown to be of some benefit (15, 16). However in these patients, isolated GH deficiency is unlikely to be a main contributory factor for poor pregnancy outcomes as placental GH can compensate for its action during gestation. Although our patient was GH deficient, she was never given GH replacement due to fund constraints. Further her first successful pregnancy without replacement supported our care plan of not giving GH for the current pregnancy as well.

PRL deficiency is common in panhypopituitary patients and cause problems due to insufficient breast milk production (18). A retrospective study based on 18 pregnancies in 9 hypopituitary patients has shown that only one patient could breastfeed her baby (19). The same result was observed in our patient who presented with lactation failure due to insufficient breast milk production. Currently, there is no effective medication available to treat prolactin deficiency and generally formula milk is recommended. However, a pilot study has shown that twice daily r-hPRL replacement increases milk volume in mothers with prolactin deficiency and also in preterm mothers with lactation insufficiency (20).

Human gonadotrophins either urinary or recombinant are used for ovulation induction in panhypopituitary patients. In patients with central hypogonadism following hypopituitarism, HMG is preferred over recombinant FSH as it contains both FSH and LH, which is needed in the latter part of follicular phase apart from FSH for the final maturation of follicles (18). In general, these patients need higher doses of gonadotrophins and longer duration of treatment since they are lacking endogenous gonadotrophins (18). Our patient received 150 IU of HMG for 25 days and achieved optimum follicular maturation (>18mm) and a successful pregnancy, after an initial attempt with recombinant FSH which ended up in an early first trimester miscarriage.

It is an established fact that follicular growth and probable pregnancy rate improves when GH and HMG-HCG are combined for ovulation induction in hypogonadotropic patients (21). It also increases the IGF1 and IGF2 activity in the ovary thus enhances follicular stimulation (22). Although our patient wasn’t treated with GH, she received HMG and HCG combination with successful conception.

Following implantation, placenta starts to function as a very efficient endocrine organ and produces a variety of peptide hormones produced by the pituitary-hypothalamus including gonadotrophin releasing hormone (GnRH) and chionic gonadotrophin, which is structurally and functionally similar to LH. It also produces significant quantities of estrogen and progesterone, which are also produced by the ovary. Thus the placenta acts as a transient hypothalamo-pituitary-gonadal axis during pregnancy that efficiently overcomes the endocrine problem at hand (23, 24).

Multiple pregnancies are a known complication of ovulation induction (25). However, when considering high risk pregnancies in patients with hypopituitarism, it has been suggested that fertility treatment must strive for singleton pregnancies with application of particular strict criteria to avoid multiple pregnancies (26). Above all, it can be deduced that women with prolonged central hypogonadism have a greater risk of uterine defects following hormonal deficiency, that can add to the complications of twin pregnancy. An audit carried out in a single center concerning outcomes of 18 pregnancies in 9 women with hypopituitarism who underwent ovulation induction has shown a live birth rate of 61% with no survivors from 4 sets of twins (26). This highlights how rare the occurrence of a successful twin delivery in patients with hypopituitarism.

There seem to be an association between hypothyroidism and iron deficiency anaemia (IDA) and it is thought to be due to deficiency of thyrotropic and adrenocortical hormones (27). Therefore, optimum hormone replacement plays a vital role in preventing IDA and normochromic normocytic anemia in these patients with hypopituitarism, which is essential for a successful pregnancy.

Conclusions

Even though the pregnancy after complete loss of pituitary function is uncommon, modern advances in fertility treatment has led to increased pregnancy rates in women with panhypopituitarism. However, preconceptional restoration of hormones, close careful monitoring and changing medications throughout pregnancy plays a vital role in successful outcomes in view of both fetal and maternal wellbeing.

References


Acromegaly with normal pituitary MRI

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**Abstract**

Acromegaly is commonly caused by a growth hormone (GH) secreting pituitary adenoma, which is often evident on pituitary imaging by the time of presentation. Here we describe 4 patients with acromegaly who had normal MRI of the pituitary at the time of diagnosis. Contrast enhanced computer tomography (CECT) chest and abdomen were also normal. All 4 patients were females and aged 45, 53, 69 and 70 years. They had acromegalogoid features of varying severity and duration. Dynamic magnetic resonance imaging (MRI) was performed in 3 patients, which revealed pituitary microadenomas in all 3 of them. This highlights the heterogenous behavior of GH secreting tumours and the value of dynamic MRI in visualizing microadenomas.

**Key words:** acromegaly, microadenoma, pituitary, contrast enhanced computer tomography.

**Introduction**

Acromegaly is a progressive multi system disease associated with significant morbidity and nearly 2 fold increased mortality (1, 2). Usually, it is caused by a growth hormone (GH) secreting pituitary adenoma. Ectopic source is rare and accounts for < 1% cases (3). Since the diagnosis of acromegaly is often delayed by an average of 4-10 years, pituitary adenomas are often large and visible on MRI. When pituitary imaging is normal, localization of GH source becomes a challenge, especially in resource poor setting where growth hormone releasing hormone (GHRH) assay is not available.

**Case 1**

A 53 year old lady with hypertension and dyslipidaemia presented with symptoms suggestive of hypothyroidism such as lethargy, constipation, weight gain, cold intolerance and deepening of voice over a period of 1 year. She had a past history of bilateral osteoarthritis of knees and left sided carpal tunnel syndrome, which required decompression. She also had features suggestive of obstructive sleep apnea. On examination, she had acromegalogoid features such as coarse facial appearance with prominent supra orbital ridge, enlarged nose, lips and prognathism (Figure 1- No.1). She did not have a goiter. Oral glucose tolerance test (OGTT) showed non suppressed GH, confirming the diagnosis of acromegaly. Conventional MRI pituitary did not reveal any lesions. Therefore, CECT scan of the chest, abdomen and pelvis was performed in order to look for an ectopic source, which is usually a neuroendocrine tumour arising from pancreas or bronchus producing GHRH. CECT was also normal. She had secondary hypothyroidism with normal 9 am cortisol and prolactin (PRL- 131 mU/L). Follicular stimulating hormone (FSH), lutetinizing hormone (LH) were raised as in normal post menopausal women (FSH- 28, LH-53 U/L). Her fasting blood sugar (FBS), hepatic transaminases and electro cardiogram (ECG) were normal.

**Case 2**

A 69 year old lady with past history of ovarian cancer, which was treated with total abdominal hysterectomy and bilateral salpingo-oophorectomy developed persistent low back ache and was referred to our unit for evaluation for osteoporosis. We noted that she had acromegalogoid features such as enlarged lips, nose and prominent supraorbital ridges (Figure 1- No.2). Direct questioning revealed that she experienced excessive sweating and tightening of the wedding ring over the last 5 years. Acromegaly was confirmed by OGTT, which showed non suppressed GH. MRI pituitary was normal. CECT- chest, abdomen, which was done to exclude an ectopic source, did not reveal any abnormality. 24 hour urinary 5 hydroxy indol acitic acid (HIAA), which is usually raised in carcinoind tumours, was normal (2.2 mg /3-17). Rest of the anterior pituitary hormones were normal except FSH and LH, which were elevated due to menopause (LH- 52, FSH-66 U/L). FBS, hepatic transaminases, ECG, colonoscopy were normal. DXA scan revealed osteopenia (T score of -2.4) and FRAX score showed a raised 10 year probability of hip fracture (4.5%).

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Case 3

A 70 year old lady presented with change in facial appearance with acral enlargement over 5 years. She also noted deepening of voice and excessive sweating. She had hypertension and bilateral OA of knees, which required knee replacement. Features of acromegaly such as enlarged lips, nose and prominent supraorbital ridges were quite obvious in this patient (Figure 1 - No.3). OGTT showed non suppressed GH. MRI pituitary, CECT- chest, abdomen, and pelvis were normal. Her other anterior pituitary hormones were normal except the FSH, LH, which were elevated due to menopause (LH-47, FSH- 101 U/L). She had impaired fasting glucose (105mg/dl). Hepatic transaminases and ECG were normal. Colonoscopy revealed 2 large polyps, which were histologically tubular adenomatous polyps with grade 2 dysplasia.

Case 4

A 45 year old lady presented with change in facial appearance and excessive sweating over 1½ years. She also noted deepening of voice. She was amenorrhoeic for the past 10 months. On examination, she had obvious acromegaloid features such as coarse facial appearance with prominent supraorbital ridges, enlarged nose, lips and prognathism (Figure 1- No.4). Her blood pressure was elevated (160/100mmHg). OGTT showed non suppressed GH, confirming the diagnosis of acromegaly. MRI pituitary, CECT of chest, abdomen, and pelvis were normal. FSH was raised (25 U/L) indicating that she is going in to menopause. However, LH response was inadequate (LH -8 U/L {post menopausal: >50}). Rest of the anterior pituitary hormones, FBS and ECG were normal.

All 4 patients described above did not have features of MEN-1, MacCune Albright syndrome, Carneys complex or Carcinoid syndrome. They had different clinical, biochemical and imaging findings (Table 1). Dynamic MRI pituitary was performed in 3 patients. It revealed microadenomas in all 3 of them localizing the source of GH (Figure 2 and 3). One patient (No: 4) is awaiting dynamic MRI scan of the pituitary.

Figure 1. Facial appearances of patients 1-4.

Figure 2. Gadolinium enhanced T1- weighted dynamic MR pituitary coronal image (patient no.1).

A: At 60 sec-shows 4mm hypointense lesion while normal pituitary is enhanced
B: At 240sec: lesion is enhanced, cannot differentiate from normal pituitary.

Figure 3. Gadolinium enhanced T1- weighted dynamic MR pituitary coronal image (patient no.2).

A: At 60sec-shows 5mm hypointense lesion.
B: Lesion is marked on MRI film.
Acromegaly with normal pituitary MRI

Discussion

MRI is the best imaging modality in the evaluation of pituitary tumors. When a pituitary micro adenoma is suspected, dynamic contrast-enhanced techniques, which offer better tumor visualization should be employed (4,5). Dynamic MRI involves obtaining a sequence of T1 weighted images at multiple time points after a bolus injection of intravenous gadolinium. The maximum image contrast between the normal pituitary tissue and microadenomas is attained about 30-60 seconds after the bolus injection of the intravenous contrast (6). Most of the microadenomas initially appear as relatively nonenhancing (dark) lesions within an intensely enhancing pituitary gland (7). The peak enhancement of the pituitary adenomas occurs after the most marked enhancement of the normal pituitary gland, and persists for a longer duration (7). Both spatial and temporal resolution must be sufficiently high in order to visualize a micro adenoma. At our institution, dynamic contrast pituitary captured 10 consecutive sets of images in coronal plane every 20-30 seconds (duration: 240 seconds). The thickness of a MRI slice was 0.9 mm with dynamic MRI, whereas that of a conventional MRI was 3mm. In our series of patients, dynamic MRI detected micro adenomas, which were not visualized with conventional MRI in all 3 patients. A special MRI sequence known as volumetric interpolated breath-hold examination MR imaging (VIBE with 1.2-mm slice thickness) had been shown to be useful in detecting pituitary microadenomas in patients with acromegaly (8). Acromegaly with normal pituitary MRI poses a diagnostic challenge. Possible causes include a pituitary micro adenoma, which is not evident on imaging, MacCune Albright syndrome and ectopic source producing GHRH or very rarely GH. Ectopic GHRH production giving rise to acromegaly is rare (<1%). Sources of GHRH include neuroendocrine tumors arising from the pancreas, bronchi and appendix. According to a French nationwide series of 21 cases, these tumours were usually large (10-80 mm) by the time of the diagnosis and the primary tumor and/or metastases were identified by CECT chest/abdomen in nearly all cases (20 out of 21) (9). In one patient, the tumour was not identified by all imaging modalities used including CT, [18F] fluorodeoxyglucose positron emission tomography scan and octreotide scan. Somatostatin receptor scintigraphy (SRS) using radiolabeled octreotide, performed for 16 patients, showed the primary tumor and/or secondary lesions in 81% of patients. This study showed that CT scan was non inferior to SRS (sensitivity 81 vs. 86%) in detecting ectopic GHRH secreting tumors. Most patients with ectopic GHRH secretion had enlarged pituitary rather than a normal pituitary on imaging. Their MRI may be normal or show either a adenoma or a micro cystic lesion. Therefore, in a patient with acromegaly and normal CECT chest and abdomen the possibility of an ectopic source may be very low. Surgical exploration of

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age</th>
<th>Time to diagnosis from onset of symptoms</th>
<th>IGF-1 (ng/ml)</th>
<th>Nadir GH (mU/L)</th>
<th>Ave.GH on GHDC* (mU/L)</th>
<th>CECT-chest,ab</th>
<th>Conventional MRI-pit.</th>
<th>Dynamic MRI pit. size of lesion</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>53</td>
<td>1 year</td>
<td>701 (238)</td>
<td>4.5</td>
<td>4</td>
<td>Normal</td>
<td>Normal</td>
<td>4mm</td>
</tr>
<tr>
<td>2</td>
<td>69</td>
<td>5 years</td>
<td>645 (200)</td>
<td>17.6</td>
<td>13.98</td>
<td>Normal</td>
<td>Normal</td>
<td>5mm</td>
</tr>
<tr>
<td>3</td>
<td>70</td>
<td>5 years</td>
<td>1153 (200)</td>
<td>10.42</td>
<td>N/A**</td>
<td>Normal</td>
<td>Normal</td>
<td>6mm</td>
</tr>
<tr>
<td>4</td>
<td>45</td>
<td>1 ½ years</td>
<td>656 (267)</td>
<td>49</td>
<td>15</td>
<td>Normal</td>
<td>Normal</td>
<td>Awaiting MRI</td>
</tr>
</tbody>
</table>

* GHDC-Growth hormone day curve
**NA- not available
the pituitary gland in such patients had revealed GH secreting adenomas at surgery and led to the cure of the disease (8).

GH-secreting tumor behavior is heterogeneous. It is interesting to note that some patients who had been symptomatic for many years may harbor small adenomas, which are not evident on imaging, whereas the majority has large invasive macroadenomas at the time of diagnosis. Daniel et al classified an acromegaly patient cohort (292 patients) according to clinical, radiological, histopathological characteristics and outcome (10). Three acromegaly types (1-3) were described, where the aggressiveness of the lesion increased from 1-3. Nonaggressive type 1 microadenomas had the most favorable outcome and occurred mostly in older patients. Histologically, these tumors were densely granulated and expressed immunoreactive p21 and somatostatin receptor 2 in abundance. Since resistance to medical treatment correlates inversely with SSTR2 abundance, these tumors are more treatment responsive (11). Densely granulated GH secreting adenomas were biologically more active and less aggressive than sparsely granulated adenomas, which occurred mostly in type 3 acromegaly patients (12).

In conclusion, localization of GH source may be challenging in a minority of the patients with acromegaly. Pituitary imaging is the first step in localizing the lesion. When the conventional MRI is negative, a dynamic MRI, which has a better spatial and temporal resolution, should be performed to detect a micro adenoma. If pituitary imaging is negative, chest and abdomen should be scanned with CECT to look for an ectopic source. It has been shown that ectopic GHRH secreting tumors are generally more than 1cm in size and can be detected on CT in nearly all patients.

References