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Editorial

SJDEM will be the platform for excellence in endocrinology

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The Endocrine Society of Sri Lanka was established in 1979 by a group of enthusiastic and dedicated medical professionals, thus encouraging the establishment of professional societies for the subspecialties of clinical medicine. Since then, the society has grown appreciably with a current membership of nearly 200; encompassing endocrinologists and clinicians with special interest in endocrinology practicing in Sri Lanka.

Our society is indeed proud to launch the first issue of its official journal, Sri Lanka Journal of Diabetes Endocrinology and Metabolism (SJDEM) to provide the first fully open access journal dedicated to the field in Sri Lanka. This is a long awaited necessity for clinical endocrinologists, other clinicians who have a special interest in the field and for the postgraduate trainees to share their clinical experience and research.

SJDEM was launched with the incredible support of the editorial board and sponsors as the leading journal in diabetes and endocrinology in Sri Lanka. My sincere wish is for SJDEM to rapidly evolve with the help of our readers and colleagues.

I take this opportunity to thank all our authors for choosing SJDEM as a platform for presenting their work to the medical fraternity in Sri Lanka.

Excellence, accessibility, expansion, and evolution will be the tenets which will guide SJDEM. To achieve excellence, we will make a special effort to be highly selective in the reports we accept. Our goal is to disseminate novel ideas and views, be they in basic science, translational or clinical investigation. To achieve excellence in publication standards, we will rely on our outstanding Editorial Board of leading experts, who will ensure maintaining high standards.

Accessibility will be achieved through making SJDEM available as a biannual publication with no cost. The editorial board expects to expand SJDEM to link with international reviewers and societies around the globe. Hence, the SJDEM will be the platform for local and international experts in endocrinology to report and disseminate important aspects that require to be addressed in our day to day practice.

It is truly an honour and privilege to be the Editor in this first ever publication of the SJDEM and publish your work and represent our Society. As such, our Editorial Board will continue to strive to make SJDEM your journal, for your individual studies and for the sustenance of our specialty.

May we grow from strength to strength!

Dr. Uditha Bulugahapitiya
Editor
Province and ethnic specific prevalence of diabetes among Sri Lankan adults

P Katulanda¹, D A V Rathnapala², R Sheriff², D R Matthews¹


(Index words: prevalence, diabetes, Sri Lanka, province, obesity)

Abstract

Objective: To determine the province and ethnic specific prevalence and correlates of diabetes mellitus among Sri Lankan adults.

Method: A nationally representative sample of 5000 adults aged ≥18 years was selected by a multi-stage random cluster sampling technique in this cross-sectional study conducted between 2005 and 2006.

Results: Response rate was 91% (n=4532), males were 40%, age 46.1±15.1 years (mean ±SD). The age-sex standardized prevalence (95% CI) of diabetes for Sri Lankans aged ≥ 20 years has been previously published as 10.3% (9.4-11.2%) [males 9.8% (8.4-11.2%), females 10.9% (9.7-12.1%), P=0.129). There was a marked variation in the province specific prevalence of diabetes with the highest (18.6%) in the Western and the lowest (6.8%) in the Uva provinces. The monthly income, BMI, waist circumference and per capita monthly expenditure were highest in the Western and lowest in the Uva. In contrast, the mean physical activity level was lowest in the Western province and highest in the Uva. However, the per capita daily energy consumption was lowest in the Western and highest in the Uva provinces.

The Sri Lankan Tamil ethnicity has the highest (22.1%) diabetes prevalence followed by the Sri Lankan Moor (21.4%). The Indian Tamil ethnic group living in the plantation sector had the lowest prevalence.

Conclusions: The provincial and ethnic distribution of diabetes closely resembled that of obesity (waist circumference more than the BMI) and the income level in the respective provinces and ethnic groups. The physical activity level had an inverse relationship. High level of physical activity had a protective effect from diabetes even when the energy consumption is high.

Introduction

In 2002 World Health Organization (WHO) stated that “in many regions, some of the most formidable enemies of health are joining forces with the allies of poverty to impose a double burden of disease, disability and premature death in many millions of people” (1). This is what is happening in South Asia, where one quarter of the global population lives and about half of it below the poverty line with limited access to health care. Although infectious diseases remain a formidable enemy, the population is ageing and non-communicable diseases are rising. Diabetes has become a major and growing contributor to mortality and disability in South Asia (2).

An understanding of the population at risk of developing the disease is critical when projecting future disease burden. Accumulating research shows that there are number of factors which contribute to a person’s overall likelihood of developing type 2 diabetes and heart disease (3). Several surveys on risk factors conducted across South Asian countries have shown high and rising rates of overweight, central obesity, high blood glucose levels, high blood pressure and dyslipidaemia in urban populations (3). Such trends also exist in rural populations but are lower in magnitude and less steep in the slope of change (4, 5). Although ethnic differences in prevalence of type 2 Diabetes are well documented in European and American communities, there is paucity of data among Asians within a single country.

Sri Lanka is a middle-income country with a population of 20.7 million people (6) and the population comprises of two broadly different socio-demographic groups, namely urban and rural. The urban population has higher income and leads a more westernized lifestyle compared to the rural population, where the majority is engaged in agriculture and related occupations, with lower income levels and a more physically active lifestyle. There are four main ethnic groups, namely Sinhalese, Sri Lankan Tamil, Sri Lankan Moor and the Indian Tamil.

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Tamils, Indian Tamils and Sri Lankan Moors. No
countrywide surveillance system for non-communicable
diseases exist in Sri Lanka and the prevalence of diabetes
has been determined by epidemiological surveys. Studies
in rural areas have shown an increase in the prevalence of
diabetes from 2.5% in 1990 (7) to 8.5% in 2000 (8). In the
suburban populations, the prevalence has been reported
as 5.0% in 1994 (9) and 6.6% in 2002 (10). In a mixed urban
and rural population, the prevalence was reported as 5.8%
in 1994 (11). In 2005, a study carried out in adults between
35 and 65 years of age in four provinces in Sri Lanka
reported diabetes prevalence of 14.2% in men and 13.5%
in women (12). The Sri Lanka Diabetes and Cardiovascular
Study (SLDCS) was carried out in 2005 to bridge the gap
data and we have previously reported the national
prevalence of diabetes mellitus in Sri Lanka as 10.3% (13).

In this paper we present the province and ethnic
specific prevalence of diabetes in the adult population in
Sri Lanka based on SLDCS, these data are important for
public health action.

Patients and methods

The Sri Lanka Diabetes and Cardiovascular Study
(SLDCS) was conducted by the Diabetes Research Unit
of the University of Colombo and the Oxford Centre for
Diabetes Endocrinology and Metabolism, UK. It was a
cross sectional study, approved by the Ethical Review
Committee of the University of Colombo. Data collection
was between August 2005 and September 2006. All
participants provided informed written consent.

Participants

This study was done in seven of the nine provinces
in Sri Lanka. Detail method of sampling and data collection
has been reported previously (13).

Data collection

Data collection was carried out by a team of trained
medical graduates and nurses. The selected subjects were
invited to the temporary established data collection centres
within each cluster. Routine unrestricted diet with usual
physical activities at least 3 days prior to the data collection
was recommended. They were advised to fast 12 hours
from the day prior to data collection. An interviewer-
administered questionnaire was used for data collection.
Anthropometric measurements were performed according
to the standard methods using calibrated equipment (14).
Seated blood pressure was recorded on two occasions
after a 10-min rest using an Omron IA2 digital blood
pressure monitor (Omron Healthcare, Asia-Pacific Region,
Singapore). Fasting venous blood samples were obtained
for glucose and lipid estimation from all participants. Those
not known to have diabetes underwent an oral glucose
tolerance test (OGTT) by taking glucose monohydrate
equivalent to 75 g of anhydrous glucose in 300 ml of water
within a period of 5 min followed by 2 hour blood samples
(n=4084). Details of the storage and analysis of blood
samples were previously reported (13).

Definitions

Subjects were considered to have ‘diagnosed diabetes’ if they had been previously diagnosed at a
government hospital or by a registered medical practitioner. Verification was by review of previous medical records,
laboratory reports or prescriptions. New cases (‘undiagnosed diabetes’) were diagnosed according to the
American Diabetes Association (ADA) and WHO criteria
(15,16). Physical activity was recorded using the short
format of the International Physical Activity Questionnaire (IPAQ) (17). Urban and rural sectors were defined
according to the classification of the Sri Lankan
government (18). Those who were detected to have
diabetes or other medical problems at SLDCS were referred
to the closest government medical centre for necessary
follow-up.

Statistical analysis and projections

Data analysis was done using SPSS version 14 (SPSS
Inc., Chicago, IL, USA) and Stata/SE 10.0 (Stata
Corporation, College Station,TX, USA) statistical software
packages. Point estimates for prevalence were obtained
for diabetes and pre-diabetes using the Stata survey data
analysis adjusted for the stratified cluster sampling model.
Samples were weighted for the differences in house hold
and cluster-level participation. The significance of the
differences between proportions (%) and means were
tested using $\chi^2$-test and Student’s $t$-test or ANOVA
respectively $P$ values <0.05 were considered significant.

Results

4532 participated in the study. The response rate was
91%. Data from 4388 subjects aged ≥ 20 years were used
for prevalence estimation. (47 were excluded due to
incomplete data) The sample consisted of 40% males. 18%
of subjects were from urban areas. The mean age
(± standard deviation) was 46.1±15.1 years (males 46.3 ±
15.8, females 46.0 ±14.6).

As reported previously the overall crude prevalence
of diabetes in the sample was 12.6% (n=536) (13).

Province specific prevalence of diabetes

There was a marked variation in the province specific
prevalence of diabetes with 18.6% in the highest (Western)
and 6.8% in the lowest (Uva) (Figure 1 and Table 1)
provinces. The sample from the Western Province had a
lower mean age compared to all the other provinces except
the North Central Province. The provinces with higher
prevalence of diabetes also had higher mean income, BMI,
waist circumference, total per-capita monthly expenditure and lower levels of activity (Met-minutes) compared to the provinces with lower prevalence of diabetes (p<0.001 for diabetes, income, BMI, waist circumference and physical activity between provinces). The mean per-capita energy consumption was lowest in the Western Province, in spite of having the highest prevalence of diabetes, obesity and income. In contrast, despite having the highest daily energy consumption (according to the data from the Household Income and Expenditure Survey 2006/2007 – (Department of Census and Statistics Sri Lanka, 2008), diabetes prevalence remained lowest in the Uva province which has the highest mean energy expenditure.

Ethnic specific prevalence of diabetes

The weighted prevalence of diabetes and underlying correlates among those belonging to the four main ethnic groups in Sri Lanka are shown in Table 2. The weighted prevalence of diabetes for each ethnic group was calculated according to the self disclosed ethnicity of the study participants using the STATA software (Stata Corp LP, Texas, USA). Accordingly, the Sri Lankan Tamil ethnicity has the highest prevalence of diabetes followed by the Sri Lankan Moor. The Indian Tamil ethnic group has the lowest prevalence of diabetes. Similar to the patterns observed in the different provinces, diabetes was higher in ethnic groups with higher levels of waist circumference, BMI, income and lower levels of physical activity (Figure 2).

<table>
<thead>
<tr>
<th>Province</th>
<th>Prevalence of diabetes*† (95% CI)</th>
<th>Mean age (years)</th>
<th>Mean income (LKR)</th>
<th>Mean activity (Met-minutes)¶</th>
<th>Mean BMI (kg/m²)</th>
<th>Mean waist circumference (cm)</th>
<th>Per-capita total monthly expenditure (LKR)*</th>
<th>Per-capita daily energy consumption (Kcal)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Western</td>
<td>18.6 (15.8 – 21.5)</td>
<td>44.5</td>
<td>13609</td>
<td>2721</td>
<td>23.6</td>
<td>83.3</td>
<td>6935</td>
<td>1977</td>
</tr>
<tr>
<td>Central</td>
<td>12.6 (9.3 – 15.9)</td>
<td>47.5</td>
<td>10459</td>
<td>3848</td>
<td>21.6</td>
<td>78.1</td>
<td>4560</td>
<td>2210</td>
</tr>
<tr>
<td>Southern</td>
<td>12.2 (8.5 – 15.9)</td>
<td>48.8</td>
<td>7978</td>
<td>3528</td>
<td>21.7</td>
<td>78.0</td>
<td>5302</td>
<td>2151</td>
</tr>
<tr>
<td>Sabaragamuwa</td>
<td>11.5 (7.5 – 15.5)</td>
<td>47.1</td>
<td>8193</td>
<td>5984</td>
<td>21.3</td>
<td>73.8</td>
<td>3982</td>
<td>2138</td>
</tr>
<tr>
<td>North-western</td>
<td>10.0 (7.6 – 12.3)</td>
<td>48.2</td>
<td>8573</td>
<td>6231</td>
<td>20.9</td>
<td>75.4</td>
<td>5035</td>
<td>2154</td>
</tr>
<tr>
<td>North-central</td>
<td>9.6 (7.3 – 11.1)</td>
<td>44.3</td>
<td>7522</td>
<td>5168</td>
<td>21.7</td>
<td>75.3</td>
<td>5698</td>
<td>2221</td>
</tr>
<tr>
<td>Uva</td>
<td>6.8 (2.4 – 11.1)</td>
<td>47.0</td>
<td>5992</td>
<td>6296</td>
<td>20.8</td>
<td>72.8</td>
<td>3879</td>
<td>2266</td>
</tr>
<tr>
<td>P value</td>
<td>&lt;0.001†</td>
<td></td>
<td></td>
<td>&lt;0.001†</td>
<td></td>
<td>&lt;0.001†</td>
<td>&lt;0.001†</td>
<td>&lt;0.001†</td>
</tr>
</tbody>
</table>

Figure 2. Prevalence of diabetes and the distribution of risk factors and socio-demographic correlates among different ethnic groups in Sri Lanka

[a – prevalence of diabetes, b – mean BMI, c – mean waist circumference, d – mean energy expenditure activity), e – mean age, f – mean family income]
Conclusions and discussion

In this first report of province and ethnic specific prevalence of diabetes in Sri Lanka, we report a marked variation in the prevalence of diabetes among different provinces in Sri Lanka. The pattern of distribution of diabetes closely resembled that of obesity (waist circumference more than the BMI) and the level of income. Diabetes prevalence in the different provinces had an inverse relationship with the physical activity level. Although the income level was higher in the affluent provinces that had high prevalence of diabetes, the per-capita energy expenditure followed an opposite pattern. Therefore, it is likely that physical inactivity plays a vital role in determining the difference in diabetes in different provinces and ethnic groups, and in fact seems to offer protection from diabetes when the energy consumption is higher. The mean Met-minutes in all provinces except the Western province is above 3000 Met-minutes which is the cut-off level for the ‘Physically active’ category according to the IPAQ guidelines.

In the multiple logistic regression analysis, ethnicity did not remain significantly associated with diabetes when it was examined together with other co-variants (obesity, physical activity, province of residence, income, occupation, family history, hypertension and lipid parameters). This suggests the possibility that the differences in diabetes in many sub ethnic groups within a major ethnic entity would be due to the differences in socioeconomic and lifestyle factors that result in different levels of obesity.

Our data indicate the need for higher levels of energy restriction and much higher levels of physical activity for protection from diabetes for South Asians.

Public health importance of these findings and future research

The province and ethnic specific prevalence of diabetes will be very useful in planning future interventions to control the diabetes epidemic in Sri Lanka and for resource allocation. According to the province specific data, there is an indication for the need for higher levels of physical activity (than the usual five days per week moderate exercise, that is equivalent to 600 Met-minutes) and lower levels of energy consumption to be free from diabetes in South Asians. This needs to be studied using interventional models of diabetes prevention in high risk ethnic groups.

Acknowledgements

The National Science Foundation of the Ministry of Science and Technology of Sri Lanka was the main source of funding for this study. The Oxford Centre for Diabetes Endocrinology and Metabolism provided support for data management. All individuals and organisations that supported the Sri Lanka Diabetes and Cardiovascular Study are acknowledged (www.OCDem.com/SLDCS).

Conflicts of interest: Authors have no conflicts of interest to declare.

References


Table 2. Ethnic specific prevalence of diabetes, underlying risk factors and socio-demographic correlates

<table>
<thead>
<tr>
<th>Ethnicity</th>
<th>Prevalence of diabetes (95% CI)</th>
<th>Number (%)</th>
<th>% Urban</th>
<th>Mean age (years)</th>
<th>Mean waist circumference (cm)</th>
<th>Mean Met-minutes*</th>
<th>Mean family income (LKR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sinhalese</td>
<td>11.9 (10.6 – 13.1)</td>
<td>3877 (86.4)</td>
<td>15.8%</td>
<td>46.9</td>
<td>77.4</td>
<td>4617</td>
<td>9694</td>
</tr>
<tr>
<td>Sri Lankan Tamil</td>
<td>22.1 (15.2 – 29.1)</td>
<td>136 (3.0)</td>
<td>58.8%</td>
<td>43.6</td>
<td>79.0</td>
<td>4629</td>
<td>7378</td>
</tr>
<tr>
<td>Indian Tamil</td>
<td>3.2 (0.3 – 6.1)</td>
<td>163 (3.6)</td>
<td>3.7%</td>
<td>46.5</td>
<td>67.8</td>
<td>7282</td>
<td>4847</td>
</tr>
<tr>
<td>Muslim</td>
<td>21.4 (14.3 – 28.5)</td>
<td>298 (6.6)</td>
<td>28.9%</td>
<td>44.8</td>
<td>83.6</td>
<td>2904</td>
<td>8194</td>
</tr>
</tbody>
</table>

[LKR – Sri Lankan Rupees (1£=200 LKR), 11 subjects were from very minor ethnic groups, *Met-minutes per week]


Diabetes in pregnancy among Sri Lankan women: gestational or pre-gestational?

K G H Jayathilaka¹, S Dahanayake², R Abewardhana², A K P Ranaweera³, M R M Rishard³, C N Wijeyaratne⁴


(Index words: pregnancy, diabetes, gestational, pre-gestational)

Abstract

**Introduction:** There is an exponential rise in the occurrence of diabetes during pregnancy in South Asia. However data is sparse on the actual pre-gestational diabetes mellitus (PGDM) versus gestational diabetes mellitus (GDM) case-mix. The applicability of the WHO gold standard diagnostic tool – 75g oral glucose tolerance test (OGTT) – and its optimal timing between 24-28 weeks gestation in South Asians is unknown.

**Objective:** To assess optimal timing for diagnosis, determine the case-mix of PGDM and GDM and their specific risk profiles, insulin needs and pregnancy outcomes among Sri Lankans.

**Method:** Prospective data was collected from consecutive women diagnosed with diabetes in pregnancy, at the Professorial Unit, De Soysa Hospital, Colombo from 1st January 2010 - 28th Feb 2011. All were screened by an initial 2 hour post prandial (PPBS) at antenatal booking and risk stratified to determine the optimal timing of OGTT.

**Results:** (Total n=140) GDM and PGDM occurred in 82% and 18% of patients respectively.

**GDM** (n=115) Mean age 32.16±5.26; booking POA 13.7±5.8weeks; booking BMI 26±4.9kg/m². Risk factor profile – 1(33%); 2(29.3%); ≥3 (29%); 64% were detected before 24 weeks. Those >30 years were 67% among early diagnosis versus. 36% among those diagnosed between 24-28 weeks (p=0.02). Previous miscarriages were 36% among early diagnosed versus. 18% among those diagnosed late (p=0.145). Pregnancy induced hypertension occurred in 7.8% with similar occurrence in both subgroups.

Pregnancy outcome was similar in the two subgroups (100% live births, mean birth weight 3.127±0.50kg, macrosomia 21%; LSCS 43%, pre-term 6.9%; neonatal hypoglycaemia and jaundice 11%; congenital malformation=1(0.9%).

**Pre-GDM** (n=25) Mean age 32.92±5.9 (2/3 >30 years); booking POA 12.7±6.1weeks; booking BMI 23.49±3.52kg/m², significantly less than GDM group (p=0.03). Risk factor profile – 1(28%); 2(28%); ≥3 (32%). Previous miscarriage had occurred in 24% with more still births than in GDM group (p=0.002). Previous GDM was significantly more (p=0.03). Pregnancy induced hypertension occurred in 8%.

Pregnancy outcome: 100% live births. Mean birth weight 3.014±0.56kg; macrosomia 20%; LSCS 44%; pre-term 16%; neonatal jaundice and hypoglycaemia 20% (significantly more than GDM group, p=0.02); congenital malformation =1(4%).

**Conclusion:** Unequivocal PGDM occurs among 18% of pregnant diabetics, among older multiparous women with previous GDM and still births. GDM was diagnosed before the internationally recommended 24 weeks in 64%, although their insulin requirement was significantly less than those diagnosed after 24 weeks.

**Recommendations:** 1) The current timing in pregnancy for screening by OGTT in Sri Lanka requires review. 2) A comprehensive pre-conception screening programme, particularly for older women with previous GDM and/or previous pregnancy loss, is required.

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Introduction

There is an exponential rise in the prevalence of diabetes throughout the world, with South Asia being its focal point. Its incidence has increased in South Asia by 111% in the past 15 years, when compared to other continents such as North America, Australia and Europe which have less than a 50% rise (1). Hence, Sri Lankans are clearly a high risk population. Gestational diabetes mellitus (GDM) is emerging as a common medical complication of pregnancy (2), with a parallel increase to the pandemic of type 2 diabetes mellitus. Currently GDM affects approximately 7% of all pregnancies and up to 14% of pregnancies in high-risk populations while pregestational diabetes mellitus (PGDM) is estimated to affect about 1.3% (3). The incidence of GDM in South India is reported to be 16.55%, while our own incidence in the community was 10.3% (4, 5).

The American Diabetes Association (ADA) defines GDM as “glucose intolerance of any degree with the onset or first recognition during pregnancy, and irrespective of whether or not insulin is required or the condition persists after pregnancy” (6). Therefore pregnancy can be perceived as a “stress test” for glucose intolerance and a predictor of future diabetes/pre-diabetes in any given population. Diabetes in pregnancy, both GDM and pregestational diabetes mellitus (PGDM), are linked to several maternal and fetal/neonatal complications (7, 8, 9). PGDM carries a greater risk for mother and baby, particularly if poorly controlled prior to a planned pregnancy. There is no reliable data on the actual pre-gestational diabetes mellitus (PGDM) versus gestational diabetes mellitus (GDM) case-mix in Sri Lanka. A formal pre-conception assessment package to screen for diabetes mellitus is yet not in place. Neither is the suitability of the diagnostic tool (the 75g oral glucose tolerance test - OGTT) to be performed in South Asian women at the recommended 24-28 weeks of gestation clearly known.

Objectives

We proceeded to determine the case-mix of PGDM and GDM, specific risk profiles, insulin requirement and pregnancy outcomes and to assess the optimal timing for diagnosis by OGTT in a cohort of pregnant Sri Lankan women with diabetes attending a single tertiary care unit in Colombo, Sri Lanka.

Method

This is a prospective review of 140 diabetic pregnant women attending the antenatal clinic conducted by Professorial Unit of De Soysa Hospital for Women. Consecutive women with abnormal glucose tolerance, who attended the clinic between January 2010 and February 2011, were recruited.

The database was maintained by pre-intern medical graduates, by using a previously validated interviewer-administered questionnaire. The information was gathered during the patients’ antenatal clinic visits and hospital admissions, through a one to one in-depth interview and reliability of clinical information determined by cross checking past medical records of each subject. Ethical approval was granted by the Ethics Review Committee of the Faculty of Medicine, University of Colombo to maintain a database.

We defined pre-gestational diabetes mellitus (PGDM) as abnormal glucose tolerance recognized prior to conception, which the patient was aware of at the time of her antenatal booking visit in the first trimester. We included into the GDM group all patients who revealed no previous history of diabetes mellitus but were diagnosed by the attending physician (CNW) based on WHO criteria for diagnosing abnormal glucose tolerance by a 75g oral glucose tolerance test (OGTT).

This was possible because we adopted an in-house protocol that all women with previously unknown diabetes/pre-diabetes undergo a 2 hour postprandial blood glucose (2hr PPBS) test at antenatal booking in the first trimester. When this value exceeds 120 mg/dl, which is the upper limit of target for normoglycaemia in pregnancy complicated by diabetes, we proceed to performing the OGTT as soon as possible in early pregnancy (well before 24 weeks gestation). If the OGTT is abnormal in early pregnancy and particularly before 24 weeks of period of gestation (POG), we categorize them as with ‘early diagnosed’ GDM. If the OGTT thus performed as soon as the 2hr PPBS shows a result >120 mg/dl proves to be normal, we repeat the OGTT in later pregnancy at the recommended period of gestation (24-28 weeks) and if found to be abnormal categorize them as ‘late diagnosed’ GDM.

We identified the standard risk factors for GDM in all women to risk stratify the pregnant women. These include the booking visit and first trimester BMI ≥25kg/m² recognized as maternal obesity, maternal age ≥35 years, polycystic ovary syndrome (PCOS), family history of diabetes mellitus in first degree relatives, migrant workers, previous fetal macrosomia (>3.5 kg at term pregnancy), previous fetal loss as still birth or late spontaneous miscarriage, recurrent pregnancy induced hypertension particularly of the gestational non proteinuric variety, medications with steroids or anti psychotics and excessive weight gain in the current pregnancy (10). We also adopted a standard clinical approach that despite a “normal” 2hr PPBS value at antenatal booking in very early pregnancy, in the presence of multiple risk factors (≥2) that there is compelling evidence of a higher risk for diabetes and ensured that the OGTT is performed “as early as possible” in the high risk women rather than awaiting the recommended 24-28 weeks of gestation.
All those with abnormal OGTT were initially managed by intensive dietary modifications with blood glucose monitoring, with institution of insulin therapy as deemed appropriate by the glycaemic profile. Blood sugar control was assessed by serial blood sugar series over 24 hours. Adjustment of the dose of insulin was made by the attending physician to achieve target blood glucose values of pre-meal 70-90 mg/dl and 2hr PPBS <120mg/dl as early as possible and aimed at being achieved throughout pregnancy by fortnightly review. All those on insulin therapy and with additional risks were admitted at 38 weeks gestation to plan the mode and timing of delivery, while those on dietary modification alone were assessed individually to deliver before 40 weeks. Demographic data, past obstetrics history, current pregnancy factors and associated complications, risk factors for GDM, serial fetal assessment by ultrasound scan, biochemical testing, insulin dose required, mode and timing of delivery, birth weight, pregnancy outcome in respect of maternal, and perinatal complications were carefully recorded and rechecked.

**Statistical analysis**

Data analysis was performed using SPSS13® software. Mean value and standard deviation was estimated for each continuous variable, such as maternal age, booking BMI, POA of booking visit, birth weight; while proportions by percentages were estimated for categorical variables such as sub groups of early and late diagnosed GDM, dietary modification alone and insulin treated groups, the presence and number of risk factors, mode and timing of delivery, maternal, fetal and neonatal complications.

Chi square value was used to compare frequency and/or proportions while Student’s t test was used to compare continuous variables. P<0.05 was considered as the level of significance.

**Results**

Among a total of 140 women studied during this period, GDM occurred in 115 (82%) with PGDM in 25 (18%).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>GDM N=115</th>
<th>PGDM N=25</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>32.16±5.26</td>
<td>32.92±5.9</td>
<td>NS</td>
</tr>
<tr>
<td>Booking POA weeks</td>
<td>13.7±5.8s</td>
<td>12.7±6.1</td>
<td>NS</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>26±4.9</td>
<td>23.49±3.5</td>
<td>0.034</td>
</tr>
<tr>
<td>Parity</td>
<td>2.4±1.2</td>
<td>3.08±1.4</td>
<td>0.023</td>
</tr>
<tr>
<td>Risk Factor</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI&gt;25kg/m²</td>
<td>55 (47%)</td>
<td>5 (20%)</td>
<td>0.037</td>
</tr>
<tr>
<td>Age&gt;30 yrs</td>
<td>71 (61.7%)</td>
<td>19 (76%)</td>
<td>NS</td>
</tr>
<tr>
<td>Previous birth wt &gt;3.5kg</td>
<td>15 (13.0%)</td>
<td>4 (16%)</td>
<td>NS</td>
</tr>
<tr>
<td>Previous IUD</td>
<td>4 (3.5%)</td>
<td>5 (20%)</td>
<td>0.002</td>
</tr>
<tr>
<td>Previous miscarriage</td>
<td>31 (26.3%)</td>
<td>6 (24%)</td>
<td>NS</td>
</tr>
<tr>
<td>Family T2DM</td>
<td>50 (43.5%)</td>
<td>15 (60%)</td>
<td>NS</td>
</tr>
<tr>
<td>Previous GDM</td>
<td>23 (20%)</td>
<td>10 (40%)</td>
<td>0.033</td>
</tr>
<tr>
<td>PCOS</td>
<td>6 (5.2%)</td>
<td>1 (4%)</td>
<td>NS</td>
</tr>
<tr>
<td>Pregnancy outcome</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Live births</td>
<td>100%</td>
<td>100%</td>
<td>-</td>
</tr>
<tr>
<td>Operative delivery</td>
<td>43%</td>
<td>44%</td>
<td>NS</td>
</tr>
<tr>
<td>Preterm delivery</td>
<td>6.9%</td>
<td>16%</td>
<td>NS</td>
</tr>
<tr>
<td>Neonatal complications</td>
<td>14.7%</td>
<td>40%</td>
<td>0.012</td>
</tr>
<tr>
<td>Maternal sepsis</td>
<td>2.6%</td>
<td>16%</td>
<td>0.005</td>
</tr>
<tr>
<td>PIH detected</td>
<td>7.8%</td>
<td>8%</td>
<td>NS</td>
</tr>
<tr>
<td>Birth weight (kg)</td>
<td>3.127±0.50</td>
<td>3.014±0.56</td>
<td>NS</td>
</tr>
<tr>
<td>Macrosomia</td>
<td>21%</td>
<td>20%</td>
<td>NS</td>
</tr>
<tr>
<td>Congenital anomalies</td>
<td>0.9%</td>
<td>4%</td>
<td></td>
</tr>
<tr>
<td>Neonatal complications</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jaundice</td>
<td>8</td>
<td>6</td>
<td>0.01</td>
</tr>
<tr>
<td>Hypoglycaemia</td>
<td>7</td>
<td>3</td>
<td>0.295</td>
</tr>
<tr>
<td>Low birth weight</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Prematurity</td>
<td>-</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Birth asphyxia</td>
<td>1</td>
<td>-</td>
<td></td>
</tr>
</tbody>
</table>

(NS = not significant, BMI = body mass index, T2Dm = type 2 diabetes mellitus, IUD = intrauterine death, PCOS = polycystic ovary syndrome, GDM = gestational diabetes, PIH = pregnancy induced hypertension)
Table 2. Pregnancy outcomes in early and late diagnosis groups among those with gestational diabetes (GDM)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Early diagnosed GDM</th>
<th>Late diagnosed GDM</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth weight</td>
<td>3.25±0.07kg/m²</td>
<td>2.91±0.11kg/m²</td>
<td>0.012</td>
</tr>
<tr>
<td>Shoulder length</td>
<td>37.3 ± 2.7cm</td>
<td>36.4 ± 2.8cm</td>
<td>NS</td>
</tr>
<tr>
<td>Preterm delivery</td>
<td>15%</td>
<td>9%</td>
<td>NS</td>
</tr>
<tr>
<td>LSCS – Elective</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>30.7%</td>
<td>27.3%</td>
<td>NS</td>
</tr>
<tr>
<td>LSCS – Emergency</td>
<td>10%</td>
<td>9%</td>
<td></td>
</tr>
<tr>
<td>Neonatal, complications</td>
<td>23%</td>
<td>18%</td>
<td>NS</td>
</tr>
<tr>
<td>Maternal complications</td>
<td>5.1%</td>
<td>4.5%</td>
<td>NS</td>
</tr>
<tr>
<td>Congenital abnormality</td>
<td>1</td>
<td>-</td>
<td></td>
</tr>
</tbody>
</table>

Their demographic characteristics, risk factor profiles, pregnancy outcomes are depicted in Table 1. Both groups of women are of similar age and period of gestation at antenatal booking in the first trimester. However the PGDM group had a significantly lower BMI and higher parity. The GDM group when further subdivided into two groups depending on the period of gestation (POG) of diagnosis, as before 24 weeks categorized as ‘early’ diagnosis and after the recommended 24 weeks as ‘late’ diagnosis, show that those diagnosed early comprised 64% of the group. Both these subgroups had a similar parity of 2, while women older than 30 years was significantly more (67%) among those diagnosed ‘early’ (p=0.02). Both groups had similar BMI at antenatal booking 26.10±3.7 versus. 24.97±6.07 kg/m² (p>0.05) (Table 2).

Significant risk factors identified included maternal age >35 years, past history of miscarriage or still births, previous birth weight >3.5kg, family history of diabetes mellitus in first degree relative(s), past history of GDM or PIH, previous features of PCOS and current medication with steroids or antipsychotics. Although at least one risk factor was evident in 62% diagnosed ‘late’ versus 34% in those diagnosed ‘early’, the presence of 2 or more risk factors was significantly greater in those found to have ‘early’ GDM (p=0.04) (2 risk factors 37% vs. 22% and ≥3 risk factors in 29% vs. 17%). Comparison of individual risk factors revealed that a previous history of GDM was significantly more in the ‘early’ GDM group (p=0.03). The only baby born with a congenital abnormality was to a para 2 woman aged 35 years, with a BMI of 32.8 kg/m², who had her ante-natal booking at 18 weeks and categorized as early GDM. She was a diagnosed patient with PCOS and had previous history of GDM. Despite dietary modification and achieving good glycaemic control she gave birth to a term, live baby, weighing 3.654 kg, with phocomelia by caesarean delivery.

Discussion

This tertiary clinic based urban cohort of pregnant diabetics reveals for the first time in Sri Lanka that the ratio of pre-gestational to gestational diabetes is approximately 1:4, which is a remarkably high ratio for women in their early 30s. In view of the mean period of gestation at ante-natal booking of the pre-gestational diabetics being at the completion of the period of organogenesis, and the four-fold greater occurrence of congenital fetal malformations in them, this clinic based data further highlights the deficiencies in the current health care delivery system for diabetes care in women of reproductive age. As suggested by others (11), this study highlights the need for a simple low-cost pre-conception package to be made available for all diabetic women of reproductive age attending primary care and tertiary care services and the need to adopt a comprehensive family planning counselling service in the diabetes care for women.

Although there is a limitation in the selection of this clinic based sample, which is more liable to selection bias, it reveals the actual patient characteristics of a busy urban setting clinical service that also brings into question the applicability of the recommended timing of the OGTT for diagnosing diabetes in pregnancy. There is a high probability that those with ‘early’ GDM we identified were more likely to have had previously undetected pre-gestational abnormal glucose tolerance. The community survey conducted in 2003/4 in a semi-urban Colombo based sample revealed that GDM occurred in 10% of the community (5). In the light of our current findings of the early detection of GDM in this hospital based sample, we need to seriously question the current screening strategy for GDM in the community maternity and child health (MCH) service. Although the ADA recommends any woman with an “average risk” be screened at 24-28 weeks of POA (12), the current data confirms that 66% of the
women diagnosed with GDM before 24 weeks had at least two standard risk factors. This argues for the need for universal screening of Sri Lankan pregnant women irrespective of the number of risk factors, and those without proper pre-conception assessment to be screened in the first trimester. The need to screen early for GDM by the OGTT must be dependent on the presence of a high risk status, absence of pre-conception assessment whilst also taking into account the clear ethnic risk for diabetes in our community (13, 14, and 15). A larger scale case control study is recommended to identify the optimal timing for screening (16). Based on our findings, it can be extrapolated that there is an increase in the prevalence of preexisting diabetes in our population, particularly among younger women early in their reproductive years. These issues require appropriate consideration when planning re-organization of the current health service delivery.

It is noteworthy, that despite no significant difference in the individual risk factors, a past history of GDM was significantly higher among those with early diagnosed GDM. This supports our hypothesis of the high probability for a larger proportion of women in the early diagnosed group of GDM to have had previously undetected chronic diabetes / pre-diabetes as many groups including us have shown that nearly 40-60% of those with previous GDM progress into chronic diabetes and the metabolic syndrome, as early as 3 years post partum (7, 17, 18, 19). It is also interesting that those with clear PGDM in this study had a significantly lower BMI. The absence of data collection of the waist circumference in the 1st trimester affects a clear conclusion or interpreting this finding.

As concluded previously universal screening is the most sensitive strategy in identifying nearly all women with GDM. Because of their high risk of type 2 diabetes later in their life, the opportunity to provide counselling on early lifestyle modification will be missed by not having an effective follow up programme for women with previous GDM. No doubt the accurate and timely diagnosis of GDM will also impact in the short term on pregnancy outcome. The responsibility of long-term follow up for these young women at metabolic risk no doubt falls on our primary care services. This is well supported by the fact that 40% of PGDM women had a past history of GDM. Hence, we recommend that until more reliable evidence is available all women with probable PGDM due to early diagnosis of GDM be encouraged long term follow up to achieve metabolic risk modification and regular screening for metabolic disease (20). This strategy would be in keeping with early initiation of primary prevention of diabetes and its associated medical problems. Furthermore, this will also ensure improved pre-conception assessment and better metabolic status for their future pregnancies.

Our data also confirms that the risk of neonatal as well as maternal complications being significantly more in the pre-gestational diabetic woman; while those with early diagnosis of GDM appear to follow a similar trend. Moreover the significantly greater birth weight in the group with ‘early’ GDM than those diagnosed at the recommended period of gestation supports our hypothesis that the early diagnosed group possibly falls within a more severe category of pre-pregnant metabolic disease. Albeit a small tertiary hospital based sample, this data provides valuable information to encourage a more detailed assessment of previous pregnancy outcomes and in particular birth weight exceeding 3.5 kg (95th centile of mean birth weight for Sri Lanka), intrauterine deaths and mid trimester miscarriages in young women to help risk stratify them into regular screening programmes for Sri Lanka. The fact that both PGDM and GDM groups had similar occurrence of pregnancy induced hypertension also supports the need for a multiple risk factor approach to the problem of chronic non-communicable disease being adopted in our community health programme, which must also include such young high-risk women.

To summarize, the case mix of diabetes in pregnancy in an urban based tertiary clinic in Sri Lanka confirms a gestational to pre-gestational ratio of 1: 4 among women in their early 30s. Their mean period of gestation at antenatal booking was well after the period of organogenesis. Two thirds of the women with GDM were diagnosed before the recommended period of gestation of 24 weeks, where early screening was necessary due to the presence of 2 or more risk factors in addition to their high ethnic risk. Previous GDM was significantly more in those diagnosed early, who also had a significantly higher birth weight in their current pregnancy. Although the majority of women with early GDM required dietary intervention alone with a smaller proportion requiring insulin than those diagnosed after 24 weeks, the birth weight being higher in the early GDM group requires further study. Women with unequivocal pre-gestational diabetes had more severe neonatal complications in the form of hypoglycaemia and jaundice, more congenital anomalies and a greater incidence of maternal sepsis.

**Conclusion**

We conclude that pre-gestational diabetes occurs at least in a fifth of urban based women in Sri Lanka and is associated with higher maternal age, multiparity, previous gestational diabetes and intrauterine deaths with maternal BMI not being an important risk factor. Based on the current data we recommend a more comprehensive pre-conception screening programme for the older women with previous GDM and/or previous pregnancy losses and a robust programme to ensure long term follow up of women with gestational diabetes after delivery, with a view to prevent progression to frank type 2 diabetes mellitus and metabolic disease. The MCH programme also requires exploring the optimum timing for screening for diabetes in pregnancy by OGTT in the current context.
References


Efficacy of generic alendronate and ibandronate in post menopausal osteoporosis

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(Index words: efficacy, generic, alendronate, osteoporosis)

Abstract

Objective: To determine whether generic non innovator once weekly oral alendronate is as effective as the innovator once oral ibandronate.

Method: This was an open label, prospective, randomized control trial conducted at the endocrine unit at the National Hospital of Sri Lanka. Postmenopausal women with a BMD T score of <-1.0 were recruited for the trial after excluding those with secondary causes for osteoporosis. Prior to the start of the study all subjects were given a single injection of Vitamin D₃ 200 000 IU. They were thereafter randomized to the alendronate and ibandronate arms. Alendronate arm received alendronate 70 mg once weekly and the ibandronate arm received ibandronate 150 mg once monthly for 3 months. Serum Beta crosslaps (CTX) was measured before and after bisphosphonate treatment. The treatment outcome was assessed using two parameters; i) percentage reduction of CTX and ii) treatment success, defined as greater than 35% reduction in baseline CTX.

Results: Out of 77 women who entered the study 32 women in the alendronate group and 39 women in the ibandronate group completed treatment with 3 drop outs in each group. Mean ages, age since menopause and pre treatment CTX were similar in both groups.

Percentage reduction in beta cross laps levels showed a marginally significant difference favouring the alendronate group (P<0.05).

Treatment success rates were 93.8 percent in the alendronate group and 89.7 percent in the ibandronate group. The difference was not statistically significant.

Conclusions: Our study shows that the generic preparation of alendronate is effective in the treatment of osteoporosis.

Introduction

Most patients with post menopausal osteoporosis (PMO) live in developing countries and the proportion is expected to reach 75% by the year 2050 (1). Cost of drugs to the patients is an important factor to be considered when managing patients in developing countries.

Bisphosphonates are the mainstay of treatment of PMO with proven efficacy in fracture reduction, safety and tolerability (2-6). Alendronate and ibandronate are the commonly used oral bisphosphonates. Comparison of these two drugs has shown that one is not inferior to the other (7). Unfortunately the innovator preparations of these drugs are expensive and beyond the reach of the patients in developing countries. There are generic preparations of alendronate for a reasonable price where they should be almost as effective as the original product in theory. Unfortunately there is insufficient scientific data on bioavailability and effect of these drugs as most landmark studies have used the expensive innovator preparations. Furthermore this concern is justified as only less than 1% of the oral bisphosphonates is absorbed (8).

Inhibition of bone resorption by bisphosphonates can be used as a surrogate marker of their efficacy. Beta crosslaps (CTX) the C terminal telopeptide of the triple helix arrangement assumed by type 1 collagen in the bone matrix is one such marker. CTX shows a high sensitivity and specificity for monitoring individual response to antiresorptive therapy (9). The serum CTX assay shows greater utility for assessing efficacy of antiresorptive treatment than some previously described markers such as urinary NTX and DPD (10). More than 35 percent decrease in CTX from the baseline has been used as an indicator of therapeutic success (11). The level of reduction too correlated reasonably well with BMD at 2 years (12).

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The objective of our study was to determine whether generic alendronate is as effective as the innovator oral ibandronate; we did this by comparing the efficacy of non innovator once weekly oral generic alendronate with the once monthly innovator oral ibandronate using serum beta cross laps.

**Methodology**

**Study design**

This was an open label, prospective, randomized control trial.

**Setting**

The endocrine unit at the National Hospital of Sri Lanka.

**Study participants**

Postmenopausal women with a BMD T score of < -1.0 measured by a central DXA scanner (Hologic Discovery W, QDR system software version 12.4.) were recruited for the trial after obtaining their informed written consent. Those who had taken a bisphosphonate or hormone replacement therapy irrespective of the dose or duration of treatment and those who had secondary causes for osteoporosis were excluded from the study. Secondary causes were screened for using an interviewer administered questionnaire, physical examination and biochemical tests including complete blood count, erythrocyte sedimentation rate, serum calcium (ionized or total), serum phosphate, alkaline phosphatase, serum creatinine and thyroid stimulating hormone concentration.

**Method**

Prior to the start of the study all subjects were given a single injection of Vitamin D$_3$ 200 000 IU to treat any possible vitamin D deficiency or insufficiency as vitamin D was not measured. They were thereafter randomized to the alendronate and ibandronate arms using computer generated random numbers. One week after the vitamin D injection before the start of bisphosphonates fasting CTX level was measured using (Elesys Beta crosslaps, Roche Germany, Elesys 1010). The alendronate group was given oral generic alendronate (OsteoFos®, Cipla, India) 70 mg weekly. The other group received innovator ibandronate (Bonviva®, Roche, Switzerland) 150 mg monthly.

The subjects were reviewed monthly and one month's supply of drugs prescribed. Compliance was checked by observing the blister pack for any remaining tablets. Both groups also received Calcitriol 0.25 mcg daily and elemental calcium 1500 mg per day irrespective of the dietary intake.

At the end of three months of therapy the CTX was re-measured. The treatment outcome was assessed using two parameters; i) percentage reduction of CTX and ii) treatment success, defined as greater than 35% reduction in baseline CTX (11).

**Statistical analysis**

The per-protocol population was analysed. The percentage reduction of CTX values between the two groups was compared using Mann Whitney U test. The difference in treatment success between the two groups was compared using Fisher's Exact test.

Finally the post treatment CTX between the two groups was compared using ANCOVA test. As the pre treatment BMD was significantly different between the two groups it was taken as a covariate in the ANCOVA analysis. The data were analysed using SPSS 17.

**Results**

77 women who fulfilled the inclusion and exclusion criteria were recruited for the study.

**Profiles of the samples**

There were 32 women in the alendronate group and 39 women in the ibandronate group who completed treatment with 3 drop outs in each group. Mean ages were comparable with alendronate group 60.6 years (SD 5.95) years and ibandronate group 62.1 years (SD 7.05) (t= -0.308, df= 69 p= 0.195). There was no statistically significant difference in the age since menopause in the alendronate group (12.3 years (SD 6.61)) and ibandronate group (15.41 years (SD 8.19)) (t= -1.725, df= 67 p= 0.089). The pretreatment BMD was 0.781 g/cm$^2$ (SD 0.14) in the alendronate group and 0.694 g/cm$^2$ (SD 0.11) in the ibandronate group showing a significant difference (t= 2.845, df= 67 p< 0.01). The levels of pretreatment CTX did not show any significant difference between the two groups. (alendronate 0.706 ng/ml, SD=0.35, ibandronate 0.825 ng/ml, SD=0.35, (t= -1.429, df= 69 p= 0.157).

**Percentage reduction of CTX**

The Mann Whitney U test values for percentage reduction in beta cross laps levels showed a marginally significant difference favouring the alendronate group. (U= 448, Z= -2.03, W= 1228, P=0.042). The mean percentage reduction of CTX was 41.5% for alendronate and 31.49% for ibandronate. The median percentage reduction of CTX was 67% for alendronate and 61% for ibandronate.

Analysis of Co Variance (ANCOVA) was used to compare the two groups in terms of post treatment CTX level. ANCOVA was conducted using Univariate Generalised Linear Model. As the base line analysis showed that the BMD value of ibandronate group (0.694 g/cm$^2$)
was significantly lower than the alendronate group (0.781 g/cm) the pretreatment CTX was adjusted in the ANOVA by considering the pre treatment BMD as a covariate. After the adjustment there was no significance in the reduction of CTX level (P=0.285).

**Treatment success**

The success rates were 93.8 percent (n=30/32) in the alendronate group and 89.7 percent (n=35/39) in the ibandronate group. The difference was not statistically significant. (Fisher’s Exact test p=0.683)

**Discussion**

Our findings show that oral generic alendronate once a week therapy, available at an affordable price is as effective as oral innovator ibandronate once a month therapy in terms of reduction of CTX at 3 months.

The MOTION study which compared once a month oral ibandronate against once a week oral alendronate showed that both drugs were comparable in efficacy (7). The main difference of our study from the MOTION study is that a generic alendronate was used instead of the branded product used in the latter (7).

The reduction of CTX by each drug had been similar to previous trials which did not have a head to head comparison. Reginster JY et al used CTX to compare the efficacy of two doses of ibandronate (100 mg vs 150 mg). Here ibandronate 150 mg showed a reduction on in CTX as 56.7% which is quite similar to the reduction shown in our study (61%). (13) 47.2% to 84.7% reduction of CTX had been noted in trials using Alendronate which is again comparable to our values (70%) (14, 15).

According to MOTION study the reduction in CTX was greater with alendronate at 3 months but at 6 months both drugs had a similar effect (7). Our study was concluded at 3 months. But this does not deny the fact that generic alendronate was non-inferior to ibandronate in our study.

**Significance of the study**

The weakest link in the treatment of osteoporosis is compliance (16) and high cost will add to this effect especially in developing countries where patients often cannot afford expensive drugs. This study proves that the generic preparation of alendronate is equally effective as the innovator ibandronate in reduction of bone resorption markers. This study also provides supportive evidence to physicians in the third world who mainly prescribe the generic products of alendronate which is more affordable.

**Limitations**

This was a 3 month study and used only a surrogate marker of treatment efficacy i.e. CTX. BMD has more evidence as a marker for treatment efficacy than CTX although early changes in CTX has been shown to predict long term effects on BMD (17). The ideal measure would have been long term follow up of these patients for fracture reduction.

Technically this was an open label study but the CTX measurements were done by a lab where the staff had no role in the research and they were blind to the two groups in the study.

**Conclusion**

In conclusion our study shows that the generic preparation of alendronate is effective in the treatment of osteoporosis.

**References**


Postmenopausal osteoporosis: some practical issues

Sarath Lekamwasam


Burden of the disease

Osteoporosis-related fractures are a major economic concern in many developed as well as less developed countries. Osteoporosis affects estimated 75 million people in Japan, Europe and USA (1). Currently, approximately 1.6 million hip fractures occur annually worldwide and this figure is estimated to increase gradually and reach 4.5-6.3 million by 2050 (2, 3). According to the Asian osteoporosis audit published by the International Osteoporosis Foundation, the incidence of hip fractures in Sri Lanka will rise from the 2006 figure of nearly 2700 to 4900 in 2020 and 6900 in 2041. These were based on average population projections and according to the growth rate of elderly sector of the population these figures could become higher (4).

Although a fracture at any site could be attributed to osteoporosis, fractures of hip and vertebrae are the classical fragility fractures. Each fracture type has its own patient characteristics and morbidity and mortality pattern. Hip fracture is the most sinister osteoporosis-related fracture owing to the health care cost involved and associated mortality and morbidity. It is estimated that nearly 20-25% hip fracture survivors die within the first year (5). The increased mortality could persist up to five years after a hip fracture. Hip fracture has profound effects on physical independence. Nearly 40% of hip fracture survivors have walking disability while 60% require assistance to maintain day to day physical activities (6). Furthermore, one third of hip fracture patients are totally physically dependent or require nursing home placement at one year following fracture (7).

Vertebral fracture has its own characteristics yet different from hip fracture. Only one third of vertebral fractures are symptomatic (8). Therefore most of the vertebral fractures are detected as an incidental finding. Vertebral fractures are associated with acute and chronic backache, loss of mobility and functions. Further, vertebral fractures lead to more vertebral fractures and non-vertebral fractures in later years (9, 10).

Although considered an end-result of osteoporosis, forearm fractures behave different to fractures at other sites such as hip and vertebrae. Distal forearm fractures lack the classical exponential rise with advancing age (11) seen with typical osteoporosis-related fractures such as hip and vertebrae. Also they tend to occur in relatively young people (11). Although no increased mortality is seen following distal forearm fractures, increased incidence of pain and numbness of affected hand is reported.

Geographical variation of osteoporosis prevalence and incidence of fractures

Prevalence of osteoporosis and the incidence of related fractures have a marked geographical variation and the reasons for this variation are not well understood (12, 13). In defining osteoporosis in 1994, the WHO working group opted for the T-score cut-off value of -2.5 as it demarcated nearly 30% of women over 50 years as having the disease and this approximated to the proportion of population having lifetime fracture risk (14). Subsequent studies applying this cut-off value, however, demonstrated a wide variation in postmenopausal osteoporosis prevalence. This could partly be due to variations in the composition of study samples, inclusion and exclusion criteria, skeletal sites included in the analysis etc. In 2002, Holt et al demonstrated a substantial difference in the prevalence of osteoporosis between USA and UK women older than 50 years (15). Among Thai postmenopausal women, osteoporosis prevalence varies between women of more than five years since menopause and women of less than five years since menopause (16). Among Chinese women between 20-89 years, the prevalence of osteoporosis varies from 15% to 28% between hip and lumbar spine (17). A previous study in Sri Lanka indicated that nearly 48% of women above 50 years are likely to suffer from osteoporosis. This analysis was based on an extrapolation of a subgroup analysis and used bone mineral density in an appendicular skeleton (18). Further community-based studies are required in Sri Lanka to confirm the finding of this solitary study.

Table. T-score thresholds for categorization of postmenopausal women

<table>
<thead>
<tr>
<th>Category</th>
<th>T-Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>Above -1.0</td>
</tr>
<tr>
<td>Osteopenia</td>
<td>Between -1.0 and -2.5</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>-2.5 or lower</td>
</tr>
<tr>
<td>Established osteoporosis fracture</td>
<td>-2.5 or lower + fragility fracture</td>
</tr>
</tbody>
</table>

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Apart from osteoporosis prevalence, the incidence of fragility fracture also varies. While the highest fracture incidence is reported from Scandinavian countries, a marked variation in hip fracture incidence was seen across Europe (12). Furthermore, there is a difference in the hip fracture incidence between the northern and southern regions of Europe. The incidence of hip fractures reported in Asian countries also varies, widely. Although many previous reports indicated a lower incidence of hip fractures (3, 19), recent studies have shown a clear secular change in the fracture incidence (20). Most of the studies indicate an increasing trend of hip fractures in Asian countries (20). While this could be a real increase due to factors such as rapid urbanization and sedentary life-style of modern city dwellers, improved case reporting and easy access to health care may also have played a role.

Problems faced by clinicians in Sri Lanka

Lack of awareness of the disease is a major problem in certain parts of Sri Lanka. Awareness of osteoporosis is high in urban areas but the accuracy of the information they possess is highly questionable. Many have learned about the disease from printed and electronic media but the information given in these appear to be bias towards certain aspects related to the disease. Regular education programmes are being conducted by Osteoporosis Sri Lanka focusing opinion leaders in the health care system who could take the message to community level.

Limited availability of screening facilities for low bone mass is a major problem worldwide and the situation in Asian countries is worse. According to the recent Asian Osteoporosis Audit compiled by the International Osteoporosis Foundation, the availability of Dual Energy Absorptiometry (DXA) in most of the Asian countries is a major concern (4). The situation cannot be expected to improve in the near future and clinicians will have to find an alternative ways to detect women with osteoporosis.

Local Bone Mineral Density (BMD) reference data is essential for accurate categorization of women into the WHO diagnostic categories (Table). Although NHANES BMD reference data are being used widely in the USA and European countries, the applicability of this reference data to populations outside these two regions is highly questionable. Previous studies have shown a wide variation of osteoporosis prevalence when two reference data sets were used on the same patient population (21, 22). Although it is a daunting task, every country should be encouraged to develop their local BMD reference data.

The use of WHO T-score cut-off values introduced in 1994 to identify women at high risk of fracture has major limitations. Although BMD is the most quantifiable risk factor of future fracture, there are many other clinical risk factors of fractures. Furthermore, according to previous studies most of osteoporosis-related fractures occurred in women with osteopenia. As a solution to this issue, WHO recently introduced the FRAX algorithm to help clinicians in therapeutic decision making. FRAX is a web-based calculator (Figure) which, apart from BMD, accommodates multiple clinical risk factors in estimating fracture risk (http://www.shef.ac.uk/FRAX). The clinical risk factors included in the FRAX model are age, gender, weight, height, past history of fracture, parental history of fracture, use of glucocorticoids, smoking habits, alcohol consumption, secondary causes of bone loss and rheumatoid arthritis. The output displays the probability of major osteoporotic as well as hip fractures during the next 10 years. Since its introduction, FRAX has undergone many alterations and many country-specific FRAX models have been developed.
With the introduction of FRAX, the clinical decision making has undergone major changes. Before the introduction of FRAX, DXA reports mostly indicated the diagnostic category; osteoporosis, osteopenia or normal of the patient with a rough assessment of future fracture risk. With the introduction of FRAX, apart from the diagnostic category, DXA reports now include the FRAX based 10 year fracture probability figures. This would help clinician making treatment decisions.

The fracture probability thresholds that should be adapted to make treatment decisions vary in different populations. This would depend on many factors such as cost of treatment, the willingness to pay, reimbursement policies etc, most are country specific. The National Osteoporosis Foundation in the USA recommends treating all postmenopausal women with T-score less than -2.5 and those with osteopenia and major osteoporotic fracture probability exceeding 20% or hip fracture probability exceeding 3% estimated based on the US Caucasian FRAX model (http://www.nof.org/professionals/clinical-guidelines.) These values, however, would not be valid for a country with lower fracture incidence and where generic bisphosphonates are available to treat high risk women.

Drug treatment

Although many therapeutic options are available to treat women with osteoporosis and a high fracture risk, bisphosphonates are the most used therapeutic agent (23). Apart from their anti-fracture efficacy, these drugs are affordable and relatively safe. While alendronate and risedronate are the main oral bisphosphonates used in Sri Lanka, zoledronic acid is becoming popular. The inconvenience of injections and prohibitive cost make teriparatide a reserve drug to treat osteoporosis.

Unwanted effects and drug compliance are the major practical issues involved with long-term bisphosphonate use. Upper gastro-intestinal adverse events associated with oral bisphosphonates are the most common side effects seen among patients. The concurrent use of NSAIDs enhances the upper GI side effects. Myalgia, bone pain and arthralgia are the other common unwanted effects of oral bisphosphonates. Although they can be treated, adequately, with simple analgesics in most of the cases, symptoms can be severe enough to result in discontinuation of oral bisphosphonates in some people.

Summary

Based on the predictions of future fracture occurrence, health care and social care systems in Sri Lanka will have to face an enormous burden in providing the necessary care for fracture patients. The need of preventive programs which would lessen the future fracture burden is a need. Educational programs targeting opinion leaders in health at community level could be used to raise the awareness of the disease in general. Case finding and adequate treatment are the main responsibilities of clinicians.

References


How reliable are capillary blood glucose measurements?

H N Rajaratnam\(^1\), S Pathmanathan\(^2\)


Capillary blood tests measure whole blood glucose as opposed to venous samples which measure plasma glucose. It is used for the care of people with diabetes, as a monitoring tool, giving a guide to blood glucose levels, at a specific moment in time. Capillary blood glucose monitoring was first established in the 1970s using glucometers. With time, the use of glucometers has become easier and faster, with much smaller blood samples, yielding results in a matter of seconds. Today they are used routinely in health care, for the easier achievement of glycaemic targets and diabetic emergencies. Without such technology, intensive glucose control including insulin pump therapy would not have become a reality. Glucometers have also relieved a great amount of anxiety over the management of hypoglycaemia. Today however, we rely so much on capillary blood glucose measurements forgetting its limitations. This article will discuss the pitfalls and limitations of capillary blood glucose monitoring (1, 2).

Accuracy goals for home glucose monitors

The goals for glucometer accuracy have been quite variable. Clarke et al. proposed an accuracy grid to establish a more expansive set of goals for glucometer usage taking into account clinical accuracy, defined as within 20% of the laboratory glucose (3). For glucose levels above 75 mg/dl, the International Organization for Standardization (ISO) recommends a goal for glucometer error of within 20% when compared with a reference glucose sample, but for glucose levels less than 75 mg/dl, the goal is for 95% of readings to be within 15 mg/dl of the reference. The U.S. Food and Drug Administration goal for glucometers is within 20% of the reference value, when glucose is greater than 100 mg/dl and within 20 mg/dl when glucose is less than 100 mg/dl (4, 5).

Although there is no universally binding standard, guidelines issued by ISO are widely acknowledged. Assuming a meter meets the ISO guideline, then a true glucose level of 55 mg/dl could in fact yield a reading of as low as 40 or as high as 70 mg/dl. It could be particularly hazardous in a patient with hypoglycaemia unawareness who would consider the reading of 70 mg/dl as reassuring for a true value of 55 mg/dl, which needs prompt corrective action. At the other end of the spectrum, a true value of 350 mg/dl might register as low as 280 or as high as 420 mg/dl. This could have some consequences, especially in intensive care situations, where insulin infusion algorithms aim at achieving tight glycaemic control (4).

Multiple variables affecting glucometer values

Preanalytical variables

A number of preanalytical variables can also potentially cause inaccuracy in glucometer measurements. Haematocrit (greater than 55% may lead to inaccurate results when the blood glucose level exceeds 11mmol/l), temperature, hypoxia, humidity, severe hypo- or hyperglycaemia, peripheral circulatory failure, elevated cholesterol (>13mmol/l) and some drugs, such as ascorbic acid are recognized variables.

In patients with peripheral circulatory failure and severe dehydration (eg: diabetic ketoacidosis, hyperosmolar non-ketotic coma), shock and hypotension may occur. In these situations capillary blood glucose readings can be artificially low due to peripheral shut down, leading to increased glucose extraction by the tissues, because of low capillary flow and increased glucose transit time. Similarly capillary blood glucose measurements may not be reliable in patients who have defects in microcirculation, such as, those with Raynaud phenomenon and severe peripheral vascular disease (6).

User error/operator error

The technique of the user or operator of the glucometer usually is responsible for more inaccuracy than the glucometer itself. Applying insufficient blood to the strip, using strips that are out of date or exposed to excess moisture or humidity, and failure to enter the proper code, can compromise accuracy (2, 7).

Several important technologic advances that decrease operator error have been made in the last few years. These include “no wipe” strips, automatic commencement of timing when both the sample and the strip are in the meter, smaller sample volume requirements, an error signal if sample volume is inadequate, “lock out”...
if controls are not assayed, barcode readers, and the ability to store up to several hundred results that can subsequently be downloaded for analysis. Together these improvements have produced superior performance by newer meters (2, 7).

New technologies: alternative site testing

Some glucometers allow testing blood from alternative sites, such as the upper arm, forearm, base of the thumb, and thigh. Sampling blood from alternative sites may be desirable, but has some limitations. Blood in the fingertips show changes in glucose levels more quickly than blood in other parts of the body. This means that alternative site test results will be different, not because of the meter’s inability to test accurately, but because the actual glucose concentrations are different. The FDA believes that further research is needed to better understand these differences in test values, and their possible impact on the health of people with diabetes (8).

Choosing the correct blood sample

There are several aspects concerning the blood sample that needs attention. Although there are different recommendations, the first choice is to wash the hands with soap and water, dry them, and use the first drop of blood for assessment. Erroneous blood glucose levels (pseudo hyperglycaemia) have been recorded when patients did not wash their hands with water after peeling fruits and such false readings were still noted when hand washing was substituted with the use of an alcohol swab. If washing hands is not possible, and they are not visibly soiled or exposed to a sugar-containing product, it is acceptable to use the second drop of blood after wiping away the first drop. Firm squeezing of the finger should be avoided (9, 10).

Analytical variables

Whole blood glucose vs. plasma glucose

Glucose levels in plasma are generally 10-15% higher than glucose measurements in whole blood (and even more after eating). This is important because home blood glucometers measure the glucose in whole blood, while most laboratory tests measure the glucose in plasma. There are many meters on the market now that give results as “plasma equivalent”. This allows patients to easily compare their glucose measurements in a lab test and at home. The meters that give “plasma equivalent” readings have a built in algorithm, that translates the whole blood measurement, to make it seem like the result that would be obtained on a plasma sample. It is important to know whether the particular meter gives its results as “whole blood equivalent” or “plasma equivalent” (8, 9, 10).

Enzymatic measurement of glucose concentration

Clinical laboratories estimate glucose concentration based on enzymatic measurement of hexokinase which is the gold standard, while in test strip systems, glucose concentration is based on enzymatic measurement of glucose oxidase, glucose dehydrogenase nicotinamide adenine dinucleotide (GDH-NAD), GDH flavin adenine dinucleotide (GDH-FAD) and GDH pyrroloquino-linequinone (GDH-PQQ). Sensors based on glucose oxidase are more substrate-specific than those based on GDH. In GDH-based systems, GDH-FAD and GDH-NAD strips do not cross react with sugars other than glucose, whereas GDH-PQQ is non specific. Maltose, galactose and xylose will be misinterpreted as glucose by GDH-PQQ-based sensors (3, 11).

U.S Food and Drug Administration (FDA) has listed any product containing or metabolized into maltose, galactose, or xylose, as potential “interfering products” with GDH-PQQ strips. These include, Extraneal (icodextrin) peritoneal dialysis solution; some immunoglobulins including Octagam 5%, WinRho SDF Liquid, Vaccinia Immune Globulin Intravenous (Human), and HepGamB; Orencia (abatacept); Adent adhesion reduction solution (4% icodextrin); and BEXXAR radioimmunotherapy agent. According to FDA, Accu-Chek and Free Style are two strips which use GDH-PQQ. FDA advices to avoid using GDH-PQQ glucose test strips in health care facilities and cautions that if they are used “NEVER use them on patients who are receiving interfering products’. A possible technical solution to the problem is the use of mutant forms of GDH-PQQ involving amino acid substitution, which have good enzymatic activity for glucose but reduced reactivity for other-sugars (3, 11).

The majority of patients as well as many health care providers are unaware of the magnitude of the potential inaccuracy of glucometer results. None of these errors is reason enough for advising against the use of this technology, but we need to educate patients and health care providers about these limitations.

Summary

Capillary whole blood glucose monitoring has considerably improved the management of diabetes. Nevertheless, there are situations where finger stick glucose measurements are not reliable. Physicians and health care personnel should be aware of “Pseudohypoglycemia” and “Pseudohyperglycemia” where the capillary blood sugars do not correlate with venous plasma glucose. Caution must be exercised in accepting the results as equivalent or using as substitutes for a laboratory blood glucose result. Clinicians should always correlate the blood sugar readings with the clinical findings in taking their management decisions.
References


Effects of amiodarone on thyroid function

Shaminda Kahandawa¹, Noel Somasundaram²


**Introduction**

Amiodarone is an effective drug used in the management of ventricular and resistant supraventricular tachyarrhythmias. But it has multiple effects on the thyroid which include abnormalities of thyroid function tests, hypothyroidism and thyrotoxicosis. In Sri Lanka amiodarone is a widely used antiarrhythmic, in controlling resistant arrhythmias and useful in heart failure. The unavailability of other antiarrhythmics and the high cost of internal cardiac defibrillators (ICD) have favored the use of amiodarone. However, the relationship between amiodarone therapy and thyroid dysfunction is not adequately recognized and evaluated in day to day practice.

**Pharmacology of amiodarone**

The structural formula of amiodarone closely resembles that of thyroid hormones (1). Amiodarone is a benzofuran derivative and iodine is responsible for 37% of its weight. Therefore at a standard dose of 100-600 mg per day, recipients are exposed to 3-21 mg iodine per day, which is over 35-140 times the recommended daily allowance of iodide (recommended dose = 150 µg per day) (2). The average half-life of amiodarone is 40 days, leading to a long period of effect after drug discontinuation (2).

**Clinical use of amiodarone**

Amiodarone is a class III antiarrhythmic, according to the Vaughan-Williams classification. Its mechanism of action is inhibition of myocardial Na⁺K⁺-ATPase activity (1). Amiodarone is indicated for the treatment of life-threatening recurrent ventricular arrhythmias and in controlling resistant supraventricular tachyarrhythmias. The ability to use amiodarone in heart failure is an additional advantage.

**Effects of amiodarone on thyroid function**

Abnormalities of thyroid function tests may occur with amiodarone therapy in otherwise clinically euthyroid patients. In the peripheral tissues, particularly liver, amiodarone inhibits conversion of T₄ to T₃. In addition, the drug inhibits T₃ entry into peripheral tissues (2). Both mechanisms lead to increased serum T₄ and decreased serum T₃ concentrations in euthyroid subjects who are on amiodarone therapy. Also it increases the concentration of reverse T₃. Amiodarone may increase serum TSH concentration during the early months of treatment (2). These changes are believed to be related to decrease in intracellular T₃ entry and inhibition of T₄ to T₃ conversion in the pituitary gland. With long term amiodarone treatment (>3 months) TSH levels will normalize, while free T₄ and reverse T₃ may be slightly elevated.

**Amiodarone-induced hypothyroidism (AIH)**

Most patients treated with amiodarone will remain euthyroid throughout the treatment course. However, 10-20% of patients treated short term will manifest AIH (3), slightly more frequent in females, with a female to male ratio of 1.5:1. This occurs more frequently in iodine-sufficient areas, where AIH usually develops in patients with underlying Hashimoto thyroiditis.

The most likely pathogenic mechanism is that the thyroid gland already damaged by preexisting Hashimoto thyroiditis is unable to escape from the acute Wolff-Chaikoff effect after an iodine load and fails to resume normal thyroid hormone synthesis (2). Alternatively, amiodarone may accelerate the natural course of Hashimoto thyroiditis via iodine-induced damage to the thyroid follicles. The clinical manifestations and findings of thyroid function tests are similar to those of primary hypothyroidism. If hypothyroidism is sustained or severe, AIH may precipitate ventricular arrhythmias such as torsades de pointes (1).

**Treatment:** If amiodarone is needed for the underlying cardiac disorder, it can be continued in association with levothyroxine replacement. Because these patients often have severe underlying cardiac disease, it is advisable to maintain the serum TSH concentration in the upper half of the normal range (2). Since amiodarone inhibits T₄ conversion to T₃, larger doses of levothyroxine may be required. Spontaneous remission of hypothyroidism may occur, particularly in patients without underlying Hashimoto thyroiditis.

**Amiodarone-induced thyrotoxicosis (AIT)**

The incidence of AIT is reported as 5-10% in most studies (1). It is relatively more frequent in iodine-deficient areas and particularly in men (male to female incidence

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ratio is 3:1). AIT may develop early during amiodarone treatment or even several months after drug withdrawal due to its long half-life.

Pathogenesis: Type 1 AIT results from the Jod-Basedow effect and is typically seen in patients with preexisting thyroid gland abnormalities (4). Type 2 AIT results from destructive inflammatory thyroiditis caused by amiodarone itself and its high iodine content. Type 2 AIT occurs in patients with otherwise clinically normal thyroid glands at presentation (1). Recent data show that type 2 AIT is by far the most frequent form (4). However, the two mechanisms may coexist in the same patient (mixed or indefinite AIT).

Clinical manifestations: The reappearance or exacerbation of the underlying cardiac arrhythmia, in a patient with previously stable cardiac status while on amiodarone, should prompt an investigation into thyroid function (2). Hyperthyroidism results in potentiation of warfarin effects by increasing the rate of degradation of clotting factors. Therefore hyperthyroidism should also be suspected in a patient with an unexplained decrement in warfarin dosage (2). Classical symptoms of thyrotoxicosis may be absent, due to the antiadrenergic action of amiodarone and its inhibition of conversion of T\textsubscript{4} to T\textsubscript{3}.

Diagnosis: Decreased serum TSH levels and increased serum T\textsubscript{3} concentration confirm the diagnosis of AIT. Serum concentrations of T\textsubscript{3} may be a less useful indicator of hyperthyroidism than those of T\textsubscript{4}, because transient increase in T\textsubscript{3} concentration often takes place after the initiation of amiodarone treatment without hyperthyroidism being present (5).

Identification of the different subtypes of AIT is crucial because this helps determine the best therapeutic approach. Type 1 AIT is suggested by the presence of thyroid abnormalities, such as goiter and positive thyroid autoantibodies. Although not specific, the levels of interleukin 6 (IL-6) are usually elevated in type 2 AIT. Thyroid ultrasonography with colour Doppler studies is a very important diagnostic tool. Most cases of type 2 AIT are characterized by absent hypervasularity, while type 1 AIT usually shows a normal or increased vascularity.

Thyroidal \textsuperscript{131}I uptake (RAIU) can also be used to differentiate the types of AIT. RAIU is usually very low (<3%) in type 2 AIT and low-normal, normal, or even increased (despite the iodine load) in type 1 AIT (6).

Management: Since AIT is associated with increased mortality, euthyroidism must be achieved as quickly as possible. On the other hand, the diagnostic uncertainties regarding the type of AIT may lead to treatment with both thionamides and steroids. This approach has a higher risk of drug side effects.

Type 1 AIT is best treated with antithyroid drugs. However, an iodine-replete thyroid gland is less responsive to the inhibitory action of thionamides. Thus, higher drug dosages for longer periods are required to achieve euthyroidism (7). Potassium perchlorate (1g/day for 4-6 weeks), which decreases thyroid iodine uptake may be added to increase the responsiveness. Unfortunately, long term use of potassium perchlorate is limited by its toxic effects such as agranulocytosis and aplastic anemia. Radioactive iodine treatment may be indicated, if RAI uptake values are sufficiently high (>10%) after the patient becomes euthyroid (2). Total thyroidectomy is indicated in patients who are resistant to medical therapy and with severe cardiac complications (8).

Type 2 AIT may resolve spontaneously. If indicted, the treatment of choice is steroids. Initial prednisolone dose is about 0.5-0.7 mg/kg/day and the treatment is usually continued for 1 to 3 months (2). Side effects of prednisolone such as fluid retention which can precipitate cardiac failure must be anticipated and treated accordingly. About 50% of patients become euthyroid within 4 weeks of treatment. Periodic assessment of thyroid function is indicated in these patients, because of the occurrence of hypothyroidism (up to 17%) during long-term follow up (4).

The most difficult challenge is mixed/indefinite forms of AIT. Treatment of these forms is based on the concomitant use of thionamides (with or without potassium perchlorate) and glucocorticoids (7).

Withdrawal of amiodarone in AIT

Several facts should be taken into consideration before the withdrawal of amiodarone. The biological effects of amiodarone persist long after cessation of treatment. Therefore drug withdrawal might not influence immediate management. On the other hand, amiodarone may protect the heart from the localized effects of thyrotoxicosis due to its antiadrenergic action and related decreased conversion of T\textsubscript{4} to T\textsubscript{3}. Thus, discontinuation of the drug may actually worsen thyrotoxic effects on the heart (9). Therefore amiodarone withdrawal must be done carefully even if permissible and should be in concurrence with the cardiologist.

Dronedarone

Dronedarone was approved by the FDA in 2009 for the treatment of atrial fibrillation (1). This drug has similar electrophysiologic properties to those of amiodarone (10), but does not contain iodine. The DIONYSOS study demonstrated that there was significantly lower incidence of thyroid dysfunction in patients treated with dronedarone in comparison to the amiodarone group (1). In the future dronedarone may become an attractive and effective alternative to amiodarone.
Summary

Amiodarone is an iodine rich drug commonly used in the treatment of many cardiac tachyarrhythmias. But it has multiple effects on the thyroid which include abnormalities of thyroid function tests, hypothyroidism and thyrotoxicosis. Although the widely used antiarrythmic in Sri Lanka, the clinical impact of these effects are yet to be evaluated. Amiodarone transiently produces alterations in thyroid function tests in euthyroid patients. Understanding these changes is crucial in avoiding unnecessary investigations and treatment. In contrast to amiodarone-induced hypothyroidism, amiodarone-induced thyrotoxicosis is a difficult condition to diagnose and treat. Dronedarone will be the suitable alternative to treat patients with atrial fibrillation who are at risk of developing amiodarone-induced thyroid dysfunction.

References

Management of 21 hydroxylase deficiency salt-wasting form of congenital adrenal hyperplasia

K S H de Silva

Introduction

Congenital adrenal hyperplasia (CAH) is a group of autosomal recessively inherited disorders of impaired adrenal steroid synthesis. Approximately 95% of CAH is due to deficiency of 21-hydroxylase enzyme resulting from mutations in the CYP21A2 gene and is known as classical CAH (1) with a world-wide incidence of 1:10,000 to 1:20,000 births. Aldosterone deficiency in addition to deficiency of cortisol and excess androgens is seen in about 75% of classical CAH and results in the salt-wasting form of 21 hydroxylase deficiency CAH (2, 3).

Cortisol deficiency with excess production of androgens is seen in the simple virilizing form of 21 hydroxylase deficiency CAH. 3β hydroxysteroid dehydrogenase (3β HSD) deficiency will result in varying degrees of deficiency of cortisol and aldosterone and cause ambiguous genitalia in a baby girl due to accumulation of DHEAS and inadequate virilization in a baby boy due to lack of testosterone.

Presentation of the salt-wasting form of CAH

A baby girl with this condition would be virilized with ambiguous genitalia (Table 1) and thus it would be difficult to identify the sex of the baby at birth. There will be progressive pigmentation and evidence of salt loss would manifest after the 1st week of life (4,5). There will be a significant weight loss of >10% of the birth weight with poor feeding, vomiting and dehydration with characteristic biochemical abnormalities. Such a baby would collapse and die unless appropriate treatment is commenced.

In an affected baby boy the diagnosis would be missed at birth as genital ambiguity is not a feature and therefore be made only subsequently when presenting with features of adrenal cortical insufficiency.

<table>
<thead>
<tr>
<th>Table 1. Appearance of the external genitalia in a baby girl with congenital adrenal hyperplasia</th>
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<tbody>
<tr>
<td>Clitoromegaly</td>
</tr>
<tr>
<td>Pigmented, rugose, ‘labioscrotal’ folds</td>
</tr>
<tr>
<td>Posterior labial fusion or total fusion</td>
</tr>
<tr>
<td>One / two perineal openings</td>
</tr>
<tr>
<td>No palpable gonads</td>
</tr>
<tr>
<td>Normal anus</td>
</tr>
</tbody>
</table>

The initial investigations that are indicated and the expected results are summarized in Table 2. Neonatal sepsis being an important differential diagnosis, a blood culture and CRP are indicated.

A buccal smear for Barr bodies is a useful preliminary investigation as the result is available within 24 hours and a tentative answer could be given to the parents' anxious query regarding the possible sex of their baby. Nevertheless a karyotype is mandatory to confirm genetic sex.

<table>
<thead>
<tr>
<th>Table 2. Investigations in salt-wasting congenital adrenal hyperplasia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biochemistry</td>
</tr>
<tr>
<td>Serum electrolytes – hyponatraemia and hyperkalaemia</td>
</tr>
<tr>
<td>Blood glucose – low</td>
</tr>
<tr>
<td>17 hydroxyprogesterone (17 OHP)* – very high</td>
</tr>
<tr>
<td>(* preferably taken at 0800 hrs)</td>
</tr>
<tr>
<td>DHEAS* and Testosterone* – higher than expected for sex and age</td>
</tr>
<tr>
<td>Ultrasonography (in a girl)</td>
</tr>
<tr>
<td>Bilateral adrenal hyperplasia, uterus and ovaries present, kidneys normal</td>
</tr>
</tbody>
</table>

Initial management

Definitive management is with intravenous normal saline and hydrocortisone during the initial 24-48 hours followed by oral hydrocortisone and fludrocortisone with or without oral salt supplementation.

The 17 OHP should be repeated in 2 weeks and thereafter the doses of hydrocortisone and fludrocortisone are calculated for the body surface area. Hydrocortisone is ideally given 3 times a day and fludrocortisone either once or twice a day.

Long term management

Follow up is based on clinical features, anthropometry, biochemistry and radiology. Affected girls will also require surgical intervention.
Clinical features and anthropometry

Meticulous monitoring of length/height, weight and OFC is an essential aspect of follow up. Increase in pigmentation and deviation of the growth centile (length) with an increase in 17 OHP indicate inadequate hydrocortisone replacement whereas cushingoid facies with a suboptimal growth velocity would indicate over treatment (1, 6).

In the absence of easy access to plasma renin activity (PRA), salt preference/craving, inadequate weight gain with electrolyte abnormalities and changes in the blood pressure, are helpful to assess the adequacy of treatment with fludrocortisone (6).

Biochemistry

Regular estimations of 17 OHP and serum electrolytes should be done and are used together with the clinical features and blood pressure to adjust the drug doses.

Radiology

Bone age estimations are useful to monitor skeletal maturation which should ideally be compatible with the chronological age ensuring attainment of a height within the target range for the child. A delayed or advanced bone age would indicate over or under treatment respectively with hydrocortisone when an advanced bone age will compromise the final adult height achieved.

Surgery

Baby girls will need endoscopic evaluations and contrast studies in late infancy followed by feminizing genitoplasty with subsequent vaginal dilatations when necessary (1, 5, 7).

Counseling

The process of counseling can be initiated once the clinical diagnosis is made and the possible sex of the baby is known by the presence of Barr bodies in the buccal smear. Once the condition is confirmed and the karyotype is available, a detailed discussion with the parents regarding all aspects of the disease must be undertaken. The importance of clinic attendance and compliance with the medication that has to be taken lifelong, the necessity to perform regular blood investigations, ‘sick day’ management and the need for surgery should all be discussed at length with the parents and reinforced periodically during clinic visits.

Psychological support for the parents and child is essential and should be made available on a regular basis.

Treatment during adolescence

Once the child attains puberty and growth is completed, the hydrocortisone can be changed to a daily dose of dexamethasone at night. Most patients can manage without fludrocortisone by modifying the dietary intake of salt.

Prenatal treatment of CAH

Virilization of the genitalia of an affected female fetus begins approximately 6 weeks after conception. Therefore if prenatal treatment is considered, dexamethasone should be started as soon as possible and will only be beneficial and minimize virilization if the fetus is an affected female (1).

Future pregnancies

21 hydroxylase deficiency CAH is inherited as an autosomal recessive disorder. Therefore the parents should be counselled that for each pregnancy there is a 25% chance of the baby being affected. They should also be informed that antenatal diagnosis for this condition is not possible in this country and that abortion is not legal.

References


Evaluation and management of short stature in children

Y A A Jayasena¹, K Dharshini², K S H de Silva³

*Sri Lanka Journal of Diabetes Endocrinology and Metabolism* 2011; 1: 30-33

Poor growth leading to short stature causes enormous psychological consequences and social disadvantages to the child and family, irrespective of the cause. Short stature is defined as height more than 2 standard deviations below the population mean (1) and it is a variant of normal growth pattern in most instances; nevertheless a serious organic pathology needs to be excluded. In spite of advancement of preventive care, still malnutrition is the leading cause of growth retardation in the developing world (2, 3).

There is no substitute to a complete clinical history and physical examination in evaluation of a child who is abnormally short. Apart from accurate serial height measurements, growth velocity plays an important role in discriminating from a serious underlying organic cause (4). Further laboratory investigations should only be based on the findings of clinical evaluation.

**Clinical evaluation**

**History**

A thorough history starting from prenatal period including consanguinity and family history, child’s growth and development, i.e. when parents were first concerned about poor growth, questions to assess the significance of the short stature (e.g. shortest in the class, shorter than the younger siblings) and nutritional evaluation should be obtained (3,5) (Table 1).

**Table 1**

<table>
<thead>
<tr>
<th>History</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prenatal period</td>
<td>Intra uterine infections, placental insufficiency (PIH, GDM), maternal nutrition / anemia</td>
</tr>
<tr>
<td>Neonatal period</td>
<td>Prematurity. Hypoglycemia and neonatal jaundice to suggest pituitary insufficiency</td>
</tr>
<tr>
<td>Family history</td>
<td>Consanguinity, heights of parents and siblings and age of puberty</td>
</tr>
<tr>
<td>Nutritional history</td>
<td>24 hour dietary recall, quality and quantity of nutrient intake</td>
</tr>
<tr>
<td>Review of systems</td>
<td>Exclusion of an intra cranial lesion - headache, vomiting, visual changes. Assessment of cardiac, renal, gastro intestinal systems</td>
</tr>
<tr>
<td>Social history and psychological evaluation</td>
<td>Psychological impact on the child and family, stressors in home/ school-bullying</td>
</tr>
</tbody>
</table>

PIH – Pregnancy Induced Hypertension, GDM – Gestational Diabetes

**Measurement of growth and physical examination** (4-6)

- Accurate height measurement using a standard method, ideally by the same evaluator plotted serially in a growth chart is the key to diagnosis of disorders of growth. The preferred tool for older children would be a standard stadiometer while an infantometer is used for children younger than 3 years with the child being properly positioned.

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Management of short stature

- Upper to lower segment ratio should be evaluated. The average ratio is 1.7 at birth and decreases to 1 by 10 years due to growth of limbs. Presence of skeletal disproportion indicates a skeletal cause for short stature such as achondroplasia. A radiological skeletal survey is required to make an accurate diagnosis.

- Accurate weight measurement along with calculation of body mass index, weight for height, weight for age and height for age is equally important to assess nutritional status.

- Child’s adult height potential can be assessed by calculating mid parental height using following formula. This value is plotted in the growth chart corresponding to 20 years.
  
  - Boys: \[ \frac{\text{father’s height in cm} + (\text{mother’s height in cm} + 13 \text{ cm})}{2} \]
  
  - Girls: \[ \frac{(\text{father’s height in cm} - 13 \text{ cm}) + \text{mother’s height in cm}}{2} \]

- Any clinical features including dysmorphism suggestive of any genetic syndrome should be assessed. E.g. Silver-Russel syndrome, Turner syndrome, Noonan syndrome and syndromes associated with obesity such as Prader-Willi syndrome and Down syndrome.

- Physical findings suggestive of important endocrine and systemic causes of short stature and laboratory evaluation of those disorders are illustrated in Table 2.

- Determination of bone age is an important investigation to differentiate endocrine and metabolic causes which manifest as delayed bone age and those that reflect an intrinsic abnormality of the bone where bone age is same as chronological age.

- Any girl with short stature irrespective of the presence or absence of characteristic phenotypic features should have a karyotype to exclude Turner syndrome.

### Table 2

<table>
<thead>
<tr>
<th>Cause</th>
<th>Clinical features</th>
<th>Evaluation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypopituitarism/GH Deficiency</td>
<td>Micropenis, midfacial hypoplasia, midline defects</td>
<td>IGF-I, GH stimulation test, serum cortisol, thyroid functions</td>
</tr>
<tr>
<td>Cushing syndrome</td>
<td>Obesity, moon facies, violaceous striae, and cessation of linear growth</td>
<td>Midnight serum cortisol, 24-hour urinary free cortisol, dexamethasone suppression test</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>Increased BMI, sallow complexion, and delayed relaxation of the deep tendon reflexes</td>
<td>Free thyroxine, thyroid stimulating hormone (TSH)</td>
</tr>
<tr>
<td>Chronic renal failure</td>
<td>Pallor, hypertension and oedema</td>
<td>Urine analysis, creatinine, Hb, electrolytes, bicarbonate</td>
</tr>
<tr>
<td>Rickets</td>
<td>Craniotabes, metaphyseal widening and bowing of legs, Harrison sulcus</td>
<td>Calcium, Phosphate, ALP, 25-hydroxy-vitamin D, PTH, radiography</td>
</tr>
<tr>
<td>Cardiac disease</td>
<td>Murmurs, dysmorphism</td>
<td>Electrocardiogram, echocardiogram</td>
</tr>
<tr>
<td>Malabsorption</td>
<td>Features of nutritional deficiency, pallor, oedema</td>
<td>FBC, stool analysis, celiac antibody panel</td>
</tr>
</tbody>
</table>

IGF-1 – Insulin like Growth Factor-1, GH – Growth Hormone, PTH – Parathyroid Hormone, ALP – Alkaline Phosphatase
BMI – Body Mass Index, FBC – Full Blood Count, Hb – Haemoglobin
Management

Management options for a child with short stature would depend on the underlying cause. Short stature secondary to any systemic illness will not reverse unless the underlying cause is evaluated and treated accordingly.

Since malnutrition is a major cause of short stature in developing countries, optimization of nutritional status with appropriate dietary advice or nutritional therapy should be included in the management.

Diagnosis of diseases with genetic implications such as achondroplasia, Prader-Willi syndrome and Laron syndrome necessitates the need for genetic counseling (4).

Treatment of endocrine abnormalities includes replacement of the deficient hormone, i.e. thyroxin in hypothyroidism and growth hormone (GH) therapy for GH deficiency. However, many short children will belong to the group where no active treatment is possible and long term management includes follow up with serial height measurement, height velocity and repeated clinical assessment as necessary.

Growth hormone therapy

20% of children with GH deficiency have an organic cause such as central nervous system tumours, radiation, infection, and traumatic brain injury. Remaining 80% belong to idiopathic GH deficiency (7). GH therapy should be initiated as soon as the diagnosis is made. However, as GH therapy is expensive, careful judgment of the treatment using cost-benefit analysis and side effects associated with therapy should be taken into consideration before initiation of therapy.

GH therapy is indicated in several other conditions apart from isolated growth hormone deficiency and panhypopituitarism. Turner syndrome, Prader-Willi syndrome, chronic kidney disease, inflammatory bowel disease, persistent postnatal short stature following intrauterine growth retardation and idiopathic short stature (ISS) are some of the other indications for GH therapy (7).

ISS is defined by a height 2.25 or more standard deviations below the mean for age and gender without evidence of underlying disease or GH Deficiency (8). Use of GH for the ISS indication remains controversial at present (8).

Dose calculation and titration

GH is administered daily, in the evening via subcutaneous route. GH is routinely used in the range of 4.5-9.5mg/m²/day. Dosage is periodically adjusted by weight and height and the growth response. Under special circumstances such as Turner syndrome higher doses are required.

Monitoring of therapy and side effects

Follow up of patients should be conducted on a 3-6 month basis for anthropometry, pubertal development and adverse effects (Benign intracranial hypertension, scoliosis, slipped capital femoral epiphyseal) (8). Determination of growth response to GH is by assessment of increase in height and change in height velocity (1). Bone age should be obtained periodically to reassess height prediction and IGF-1 levels may be helpful in GH dose adjustments (8). Patients with proven or suspected multiple pituitary hormone deficiency are managed similarly and correct recognition, treatment and monitoring of additional hormonal deficiencies (T₃, cortisol, sex steroids, anti diuretic hormone) is important (1).

Duration of therapy and cessation of therapy

This is decided by the patient satisfaction with the result of therapy, cost-benefit analysis and side effects. Treatment is stopped when near adult height is achieved, i.e. height velocity <2cm/year and/or bone age >16 year in boys and >14 year in girls (8).

Counseling

Many short children are very conscious of being different, and in some cases this will lead to considerable psychological impact on the child leading to interference with academic performance and personality development. In order to prevent this psychological impact the following options may be attempted and this is very important where no active treatment is possible (4).

1. Informed explanation of the exact cause and prognosis of the condition.
2. Objective reassurance: Child should be seen, three to six monthly and he or she should be shown the progress in growth and puberty.
3. Redirection of activities: Morale of the child can be maintained by directing him or her to access to activities suitable for the stature or to activities where height is unimportant such as non sport activities or indoor games.

Nevertheless the treatment and follow up should focus on managing the whole child and not merely the short stature and continued counseling and psychological support should be available to the child and family.

References


Ectopic pituitary adenoma in the ethmoid sinus

Karuppiah Dharshini1, Noel Somasundaram2, Kamani Samarasinghe3, Chandra Jayasooriya4


Abstract

We describe an unusual case of ectopic pituitary adenoma in the nasal cavity. A 69-year-old man complaining of right side nasal bleeding had a polypoid tumor in the right nasal cavity. Findings of computed tomographic scanning and magnetic resonance imaging (MRI) showed that the tumor originated from the right ethmoidal sinus, occupied the nasal cavity, and extended to the floor of the right cranial fossa and a normal pituitary gland. He had normal hormonal assay. Histology suggested ectopic pituitary adenoma. Immuno histochemical assay was positive for pituitary factors and neuroendocrine markers.

Normal pituitary gland on MRI and the histology helped to establish the diagnosis of the ectopic pituitary adenoma. The patient underwent functional endoscopic sinus surgery (FESS) of the tumor followed by an uneventful recovery. The pathologic findings were comparable to those adenomas arising from the pituitary gland.

Introduction

Ectopic pituitary adenoma is a rare entity. By definition, it is a pituitary mass lesion outside the sella turcica (“ectopic”) with a normal situated pituitary gland without any continuity with sella turcica.

Common age range is between 22-84 years (mean, 52 years), and the usual presentations are airway obstruction, chronic sinusitis, epistaxis, visual field defects, headaches and some times with endocrinopathy: Cushing’s syndrome, acromegaly, etc.

Case report

A sixty nine year old male with hypertension and mitral valve prolapse was admitted to ENT ward with a history of right sided nasal block and nasal discharge of two months duration and one episode of epistaxis.

Examination revealed a right side nasal growth.

Investigations

CT sinuses revealed an opacity of the ethmoidal sinus with associated bony destruction in the floor of the right cranial fossa and ethmoidal bone, suggesting a malignant neoplasm (Figure 1).

MRI brain showed features suggestive of malignant neoplasia in right ethmoid sinus with the rest of the brain including pituitary gland being normal (Figure 2).

Biopsy of the nasal growth revealed sheets and trabeculae of polygonal cells with regular nuclei and abundant granular cytoplasm compatible with a pituitary adenoma arising from an ectopic pituitary tissue in the nasopharynx.
positive for pituitary factors (Growth hormone and prolactin) and neuroendocrine markers (synaptophysin and chromogranin).

**Discussion**

The first case of ectopic pituitary adenoma was described in 1909 by Erdheim (1). The majority of these tumours are located at the level of the sphenoid sinus (approximately 40%) or in the suprasellar region (approximately 33%), other locations being sporadically found in the clivus, cavernous sinus, petrous bone, sphenoid bone, mid-nasal ductus, third ventricle, and left cerebral hemisphere (2-9).

Pituitary adenoma presenting as sinonasal tumor as in our patient is very rare and only three other such cases, involving the sinonasal tract are described (10). In none of the cases was the diagnosis of pituitary adenoma suspected clinically.

Ectopic pituitary adenoma has characteristic light microscopic and immune histochemical findings including neuroendocrine markers (chromogranin, synaptophysin, CD56) and Pituitary markers (Prolactin, ACTH, GH, FSH, LH, TSH).

Around 50% are reactive for 2 or more hormones, 39% for single hormone and 11% are non-reactive (null cell).

Radiologically, ectopic pituitary adenomas may mimic other skull base lesions. Even histological diagnosis may be challenging; the differential diagnosis includes carcinoid, neuroendocrine carcinoma, paraganglioma, and carcinomas of the upper respiratory tract (6). Malignant transformation is exceptional (11). The majority of adenomas arising from ectopic hypophysial tissue are adrenocorticotrophin-secreting.

Adenomas (2,4,5,8). Surgical therapy is the mainstay of treatment and can be associated with postoperative radiotherapy whenever resection is incomplete.

**Conclusion**

This case illustrates a rare cause of sino nasal neoplasm. Pituitary adenomas may cause significant difficulties in histological diagnosis when presenting in unusual sites either as extension from an intrasellar lesion or as ectopic tumor. The clues to diagnosis are an endocrine growth pattern comprising tumor cells arranged in packets, ribbons, or rosettes, with prominent delicate vascularized stroma; a high index of suspicion; and immunohistochemical demonstration of neuroendocrine markers and pituitary hormones in tumor cells. A correct diagnosis is important because in contrast to neuroendocrine carcinoma as a whole or to poorly differentiated carcinoma, pituitary neoplasms have a much more favorable prognosis and a low metastatic potential.

He had normal hormonal assay including 9 AM serum cortisol 10.4 microgram/dl, prolactin 6.15ng/ml, FSH 16.8 mIU/ml and LH 6.15 mIU/ml.

The diagnosis of ectopic pituitary adenoma of the nasal cavity was made.

**Management**

The patient underwent functional endoscopic sinus surgery (FESS) of the tumor under general anesthesia followed by an uneventful recovery.

Histology of excised growth suggested pituitary adenoma probably arising from ectopic pituitary tissue in nasopharynx. The tumor was not invading overlying nasal mucosa and immunohistochemical testing was...
References


Virilization in a postmenopausal woman: ovarian steroid cell tumour

S Pathmanathan¹, Noel P Somasundaram², N Wijewardena³, H R Senevirathne⁴, D Lokuhetty⁵


Abstract

Rapid onset of virilization in a post-menopausal woman is usually the result of androgen secretion from a tumour of adrenal or ovarian origin. Androgen secreting neoplasms of the ovary are rare and usually show autonomous secretion. We describe the case of a 61-year-old woman with high serum testosterone and inappropriate normal estrogen despite menopause. Localization of the tumour was not possible by conventional ultrasound or computerized tomography scanning, and was achieved by venous sampling. Complete cure was achieved by oophorectomy. Histopathological examination confirmed the diagnosis. Postoperatively her testosterone returned to normal. Two months after surgery she showed regression of features of hyperandrogenism.

Introduction

Postmenopausal virilization due to an androgen producing ovarian tumour may be autonomous or gonadotrophin driven. Ovarian tumours showing this characteristic include steroid cell tumours of uncertain origin, Leydig cell tumours, granulosa cell tumours, hilus cell tumours and the rare stromal luteoma (1,2). Steroid cell tumours of the ovary account for less than 0.1% of all ovarian tumours. The subtype, not otherwise specified, is associated with androgenic changes in approximately one half of the patients. Because most of these tumours are diagnosed in an early stage and do not recur or metastasize, little is known about their response to therapies such as chemotherapy or radiation (1,3).

Case report

A 61-year old woman presented with an 8 month history of increasing hair growth affecting the face, hands, abdomen, chest and back and deepening of voice. She attained menarche at 12 years and had normal menstrual cycles until she attained menopause at the age of 36 years. She had a history of diabetes, hypertension and dyslipidemia. Physical examination revealed her to be virilized with clitoromegaly and increased hair growth in face, hands, abdomen, chest and back. (Modified Ferriman and Gallway score 14/22).

Initial investigations showed an elevated total testosterone (total testosterone of 5.80 ng/ml (0.06-0.82)), with normal dihydroepiandrosterone sulphate (DHEAS) (DHEAS 84.6µg/dl (35-430)). FSH, LH and estradiol were not compatible with the postmenopausal state. (FSH 22.6 U/l (post menopause >25U/l), LH 8.38 U/l (post menopause>50/l), Estradiol 32 pg/ml (<20-40)). Low dose dexamethasone suppression test (LDDST), did not suppress the total testosterone. (At 48 hours - 14.21 ng/ml (ND - 0.62)) confirming the non-adrenocorticotropic hormone dependency of the hyperandrogenic state, thus favouring ovary as the possible source. A pelvic and transvaginal ultrasound examination did not show any abnormalities. The ovaries were of normal size and appearance. A CT scan of the pelvis and adrenal gland did not reveal any abnormalities, giving no clue as to the origin of the hyperandrogenism.

Figure 1. Ovarian vein sampling locations.

¹Senior Registrar, Endocrinology, ²Consultant Endocrinologist, ³Consultant Interventional Radiologist, National Hospital of Sri Lanka, ⁴Professor of Obstetrics and Gynaecology, ⁵Professor of Pathology, Faculty of Medicine, University of Colombo, Sri Lanka.
Ovarian vein sampling was performed. Figure 1 shows the sampling locations and the results are summarized in Table 1. There was a right to left gradient of 1.9 times (higher on right) suggesting the right ovary as the source of testosterone and estradiol production.

Table 1. Summary of the results of ovarian vein catheterization

<table>
<thead>
<tr>
<th></th>
<th>Right ovarian vein</th>
<th>Left ovarian vein</th>
<th>Femoral</th>
</tr>
</thead>
<tbody>
<tr>
<td>Testosterone (ng/ml)</td>
<td>18.10</td>
<td>10.6</td>
<td>10.7</td>
</tr>
<tr>
<td>Estradiol (pg/ml)</td>
<td>70.0</td>
<td>59.0</td>
<td>53.0</td>
</tr>
<tr>
<td>Cortisol (µg/dl)</td>
<td>13.7</td>
<td>15.3</td>
<td>12.4</td>
</tr>
<tr>
<td>Testosterone/Cortisol ratio</td>
<td>1.32</td>
<td>0.69</td>
<td></td>
</tr>
<tr>
<td>Testosterone/Estradiol ratio</td>
<td>0.25</td>
<td>0.17</td>
<td></td>
</tr>
</tbody>
</table>

The patient was referred to the gynecological team. Because of the malignant potential of the steroid cell tumours, in women who have completed child bearing total abdominal hysterectomy and bilateral salpingo-oophorectomy and complete surgical staging is the preferred treatment while unilateral salpingo-oophorectomy is reserved for those who desire future fertility (4). Therefore our patient underwent a total abdominal hysterectomy and bilateral salpingo-oophorectomy despite the venous sampling lateralizing right ovary as the possible source.

The right ovary was 25×15×15 mm while the left ovary was 35×30×25 mm. Right ovary showed two small nodules of same size measuring 6×6×6 mm. The cut surface showed a well circumscribed yellowish area in the medulla. Microscopic examination showed a well circumscribed tumour composed of sheets, nests and clusters of round cuboidal cells with mildly pleomorphic central vesicular nuclei. The nuclei showed fine granular chromatin and single prominent nucleoli. Mitotic activity was sparse. Some cells showed intranuclear inclusions. The cytoplasm was scanty and acidophilic in some cells and some cells showed abundant foamy cytoplasm with lipid vacuoles. Reinke crystalloids were not identified. Intracytoplasmic lipofuscin pigments were also noted in some cells. The stroma was dense and fibrotic. Some areas showed foci of lymphocytic infiltration. The nodules seen on the ovarian surface showed broad based papillae with a core of fibro ovarian stroma lined by benign cuboidal epithelium. These features were in keeping with an ovarian steroid cell tumour, not otherwise specified (NOS). The uterus showed non secretory endometrium with cystic atrophy. The left ovary was normal.

Two weeks after surgery her testosterone returned to normal. Two months after surgery she showed regression of excess hair growth, and reduction in clitoromegaly. The patient is being followed up regularly with measurement of testosterone levels as marker of recurrence.

Discussion

Both ovarian and adrenal tumours may cause hyperandrogenism in women. While clinical history and baseline serum androgens (testosterone, androstenedione, and DHEAS) may increase clinical suspicion, the localization of virilizing tumours may require several
diagnostic modalities, including dynamic ovarian and adrenal assessment, and diagnostic imaging. In contrast to ovarian tumours, adrenal tumours are generally identified easily by imaging techniques. As a result, an ovarian source may be suspected when anatomic studies of the adrenal glands are normal. Selective venous catheterization has been employed to aid in the diagnosis and localization of androgen-secreting ovarian and adrenal tumours (1, 2).

We describe a case of a postmenopausal woman with recent onset of rapidly progressive virilization. Her initial investigations confirmed hyperandrogenism. Normal DHEAS levels and non suppressible total testosterone during a low dose dexamethasone suppression test favoured ovary and not adrenals as the possible source. Imaging modalities didn't give a clue regarding the source of hyperandrogenism. Selective venous catheterization of ovarian vessels was arranged and based on findings on selective ovarian vein sampling our patient was diagnosed with an androgen secreting tumor localized to the right ovary. As demonstrated by venous sampling, this tumour not only secreted testosterone but also estradiol. Histology of the tumour was proved to be a steroid cell tumour of the ovary.

The spectrum of ovarian neoplasms covers an extremely wide range of tumours. The best recognized of these are the surface epithelial cell tumours. Amongst the less common variants, lipid or steroid cell tumours comprise an important category, although they account for only 0.1% of all ovarian tumours (2).

The term steroid cell tumours not otherwise specified (NOS) was first described by Scully and signifies that the cell lineage is not defined, and they cannot be categorized as either stromal luteomas or leydig cell tumours. However, the majority of cases fall under this category (3,5).

Steroid cell tumours, NOS are associated with androgenic changes in 50% of the cases, oestrogenic in 6 to 23% cases while few cases have shown progesterational changes. Our patient had an increase in both testosterone and estradiol. About 10 to 15% of the patients are asymptomatic, with tumours detected incidentally during routine pelvic examination or in a surgical intervention.

Interestingly our patient has attained menopause at the age of 36 years but she had developed signs and symptoms of virilization only 25 years later (At the age of 61). We were interested to find out whether there can be any association between the onset of menopause and virilization. Although there are reported cases of premature menopause and virilization we couldn't find cases which had longer interval between the onset of premature menopause and virilization as in our case.

The small size (usually <1cm) accounts for the poor visualization with ultrasound and CT scanning. Selective venous catheterization has been employed to aid in the diagnosis and localization of androgen-producing lesion when the imaging modalities have failed. Based on a series of seven patients, Moltz and colleagues reported that an ovarian gradient of >2.7 correctly identified the location of tumor. It was found that most of the tumours were found on the right side and the venous sampling worked better to identify right sided tumours (3, 5). In line with previous studies, selective venous sampling in our case proved to be highly effective in tumour localization with a marked testosterone gradient (gradient of 1.9) being present in the right ovarian vein. Venous sampling is an invasive procedure which is operator dependent and is also dependent on reliable anatomy because differences in catheterization technique and placement may influence the results (6, 7).

The primary treatment is surgical removal of the primary lesion. In a young patient, unilateral salpingo-oophorectomy is adequate since the frequency of bilaterality is only 6%, but follow-up is essential and should include measurement of hormone levels as a marker for recurrence. In older patients, hysterectomy and bilateral salpingo-oophorectomy with surgical staging and bulk removal of tumor is recommended (4, 5). In our patient too considering the malignant potential favouring procedure was hysterectomy and bilateral salpingo-oophorectomy.

There are no reports of effective radiation or chemotherapy. The main reason for poor understanding of the therapeutic value of chemotherapy and radiotherapy in the treatment of these tumours is due to the rarity of the tumour (4, 8).

The most important factor to be determined in lipid/steroid cell tumours of the ovary is whether the tumour has malignant features or not. In one of the major studies done on lipid cell tumours of the ovary, certain histopathological findings were found to correlate highly with clinically malignant behaviour. These can be summarized as 2 or more mitotic figures per 10 high power fields (92%), necrosis (86%), a diameter ≥7 cms (78%), haemorrhage (77%), and grade 2-3 atypia (64%) (4, 8).

It is interesting to note that in our case, the microscopic appearance did not reveal any prominent findings in favour of malignancy. Mitotic activity was sparse, there was no haemorrhage or necrosis, tumour size was less than 7 cms in all dimensions.

It is also known that pathologically benign steroid cell tumours can behave in a clinically malignant fashion. Therefore, careful follow-up is essential in such cases which do not have clinical or pathological evidence of malignancy. As such, presence of metastasis may be the only definite evidence of malignant behavior (8). Our patient needs regular follow-up to look for recurrence.
Conclusion

The present case demonstrates diagnostic and therapeutic challenge posed by androgen-secreting ovarian tumors. We report this case to highlight how venous sampling helped to resolve the source of androgen production. When diagnostic uncertainty exists, selective venous sampling may be useful to localize a tumour, and thereby help in the definitive management of the patient.

References


Inferior petrosal sinus sampling (IPSS) to localize pituitary tumour in Cushing’s disease: its feasibility in Sri Lanka

S Pathmanathan¹, Noel P Somasundaram², C N Antonypilla³, N Wijewardena⁴, H Kularatne⁵


Abstract

A 27-year-old woman who remained undiagnosed regarding the source of hypercortisolism for four years was referred for further investigations. Initial laboratory results confirmed endogenous hypercortisolism, (elevated 9 a.m cortisol and non suppressible low dose dexa-methasone suppression test) suggesting Cushing’s syndrome. High dose dexamethasone suppression test did not suppress and serum adrenocorticotropic hormone (ACTH) level was elevated. MRI pituitary and CT abdomen, pelvis and chest also did not reveal any clue regarding the source of ACTH. Therefore venous sampling of Inferior-petrosal-sinus and mediastinal vessels was arranged. In the unstimulated inferior- petrosal- sinus- sampling (IPSS), there was a central-to-peripheral ACTH gradient, of 2.6 times (higher in centre) and right to left gradient of 2.1 times (higher on right) were noted suggesting the right pituitary as source of excess ACTH. Repeat MRI pituitary revealed a 0.5cm x 0.3cm poorly enhanced area in the right lobe of suggesting a microadenoma. She underwent Trans Sphenoidal Surgery (TSS) and the histology appearances were compatible with a pituitary adenoma. This case illustrates the feasibility of venous sampling in localizing the source of ACTH secretion where imagings were inconclusive.

Introduction

Endogenous overproduction of corticosteroids causes Cushing’s syndrome. Common etiologies include pituitary-dependent adrenal hyperplasia (Cushing’s disease), adrenal tumor, or a nonpituitary (ACTH)-producing tumor (ectopic Cushing’s). Rarer causes include primary pigmented nodular adrenocortical disease, also called bilateral adrenal micronodular hyperplasia which includes the Carney complex and bilateral ACTH-independent macronodular hyperplasia. The most common of these etiologies is Cushing’s disease (1,2), which causes significant morbidity and mortality that warrants early intervention. Inferior petrosal sinus sampling (IPSS) for ACTH is useful in some with Cushing’s syndrome, that helps to distinguish Cushing’s disease from other causes of Cushing’s syndrome to guide optimal management. Furthermore, localization of an occult ACTH producing pituitary tumor in patients with Cushing’s disease can help to lateralize the tumor and guide pituitary sparing surgery (3).

Case report

A 27-year-old woman, who remained undiagnosed regarding the source of hypercortisolism for four years, was referred to our clinic for further investigations. She had initially presented with difficult to control hypertension and diabetes. On direct questioning she had facial puffiness, weight gain, easy bruising, oligomenorrhea and coarse facial features. In addition, she also experienced generalized weakness, depression, irritability, impaired memory and altered sleep. She had resistant hypertension which was controlled with captopril 50mg tid, hydrochlorothiazide 25 mg qd, atenolol 50 mg bid, prazocin 3g tid and furosemide 40 mg qd and diabetes was controlled with metformin 500 mg bid. Physical findings revealed a body mass index of 25.6 kg/m², a Cushingoid appearance with moon face, buffalo hump, hyperpigmentation, easy bruising, thin skin, proximal muscle weakness and purplish abdominal striae.

Initial laboratory results confirmed hypercortisolism, with an elevated 9 a.m cortisol of 35.7µg/dL (normal 5-25 µg/dL) and non suppressible low dose dexamethasone suppression test suggesting Cushing’s syndrome. i.e following dexamethasone 0.5 mg 6 hourly for 48 hours 9 a.m cortisol was 28.3 µg/dL (normal <1 µg/dL). High dose dexamethasone suppression test did not show suppression i.e, (9 a.m cortisol was 35.7 µg/dL) following dexamethasone 2 mg 6 hourly for 48 hours 9 a.m cortisol...

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was 27.9 µg/dL and elevated 9 a.m serum ACTH of 164 pg/ml (10-40 pg/ml). MRI pituitary and CT abdomen, pelvis and chest also did not reveal a possible source of ACTH. Noninvasive means of localizing the source of ACTH production also include the peripheral ovine corticotropin-releasing hormone (ovine CRH) stimulation test. Ovine CRH stimulation followed by peripheral venous sampling of ACTH is reserved for differentiating difficult cases of Cushing’s disease and ectopic ACTH-secreting tumors. In pituitary Cushing’s disease there is normal or exaggerated response to CRH whereas in ectopic ACTH-producing tumor there is no response to CRH. This test was not performed due to unavailability of ovine CRH.

Venous sampling of Inferior-petrosal-sinus (IPS) and mediastinal vessels was arranged. Mediastinal sampling was done to identify extra pituitary source of ACTH. The commonest sources include bronchial carcinoids bronchial adenoma and thymus. So venous sampling of bronchial veins and thymic veins was arranged. Due to difficulty in cannulating the small veins sampling were done from right and left brachiocephalic veins and superior vena cava. IPS sampling (IPSS) of ACTH after ovine CRH stimulation is an established invasive technique with a sensitivity and specificity of 100% for detection of a pituitary source of ACTH (3, 4). Because of the unavailability of ovine CRH unstimulated IPSS was performed. In the unstimulated IPSS, there was a central-to-peripheral ACTH gradient, of 2.6 times (higher in centre) as well as right to left gradient of 2.1 times (higher on right) was noted suggesting right pituitary as source of ACTH. A repeat MRI of the pituitary revealed a 0.5cm × 0.3cm poorly enhanced area in the right lobe of the pituitary gland suggestive of a microadenoma.

Table 1. Unstimulated petrosal sinus and mediastinal vessels catheterization and sampling demonstrating the ACTH gradient between right and left petrosal sinuses and peripheral venous blood, suggesting right pituitary as the source

<table>
<thead>
<tr>
<th>Sampling sites</th>
<th>Right</th>
<th>Left</th>
</tr>
</thead>
<tbody>
<tr>
<td>Petrosal sinus</td>
<td>434 pg/ml</td>
<td>202 pg/ml</td>
</tr>
<tr>
<td>Inferior jugular vein</td>
<td>380 pg/ml</td>
<td>210 pg/ml</td>
</tr>
<tr>
<td>Brachio cephalic vein</td>
<td>314 pg/ml</td>
<td>210 pg/ml</td>
</tr>
<tr>
<td>Superior vena cava</td>
<td>251 pg/ml</td>
<td></td>
</tr>
<tr>
<td>Peripheral vein</td>
<td>164 pg/ml</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: ACTH, adrenocorticotropic hormone.

Results

R/S petrosal sinus shows 2.6 times higher ACTH than in the peripheral veins.

R/S petrosal sinus shows 2.1 times higher ACTH than in the L/S.
Preoperatively her cortisol level was controlled with Ketaconazole 100 mg bid. She was on Ketaconazole for almost 3 years and the doses were adjusted according to her clinical symptoms and ketaconazole day curve. (The mean cortisol was maintained around 300nmol/L). She underwent trans sphenoidal surgery (TSS) and the histology was compatible with a pituitary adenoma. Immunohistochemistry for ACTH was not performed due to non availability in the government sector. 9 a.m cortisol post-operatively remained elevated at 964 nmol/L, suggesting a biochemical non-cure. (24 hours post operatively 3 doses of hydrocortisone which was given at 6 hourly interval were omitted and 9 a.m cortisol was performed.) She was restarted on Ketaconazole 100 mg bid and now awaits radiotherapy.

**Discussion**

Ascertaining the cause of hypercortisolism in a patient with Cushing’s syndrome can be a perplexing problem for the clinician. Two broad categories of hypercortisolism must be distinguished; those processes that are dependent on ACTH production and those that are not (2,4). Pituitary-dependent hypercortisolism accounts for over 70% of cases of Cushing’s syndrome. The differentiation between pituitary and ectopic ACTH secretion is one of the most complex diagnoses in endocrine practice, and requires the integrated evaluation of biochemical tests and imaging techniques, none of which has a 100% diagnostic accuracy (2,4,5).

Measurement of plasma ACTH concentration before and after ovine corticotropin-releasing hormone (ovine CRH) stimulation reliably distinguishes ACTH-independent Cushing's syndrome (eg, functional adrenal tumors) from ACTH-dependent processes (6). The later comprise ACTH production from pituitary adenomas and from nonpituitary (ectopic) sources. The ideal therapy for ACTH-dependent Cushing’s syndrome entails surgical removal of the ACTH-producing neoplasm. Thus, to guide appropriate intervention, one must accurately determine the source of ACTH production. Clinical history, dynamic biochemical tests (eg, dexamethasone suppression, ovine CRH stimulation), and CT or MR imaging (MRI) of the pituitary gland aid in distinguishing the two possibilities. Not infrequently, however, the clinical, biochemical, and imaging test results are indeterminate, resulting in uncertainty regarding the source of ACTH production. In such cases, inferior petrosal sinus sampling (IPSS) can help to resolve this uncertainty by accurately locating the source of ACTH production (3, 4, 6).

Inferior petrosal sinus (IPS) sampling (IPSS) was devised in an attempt to improve the diagnostic work-up of Cushing’s syndrome. The rationale of this technique is that the pituitary gland drains directly into the IPSs, which is uncontaminated by blood from different sources. Therefore, in Cushing’s disease, the concentration of ACTH is expected to be higher in the inferior petrosal sinus draining the hemi-hypophysis bearing the tumour

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**Figure 2.** A - In low power field and B - In high power field: Demonstrating the tumour cells with round nuclei with finely dispersed chromatin, distinct nucleoli and eosinophilic granular cytoplasm.
than the contralateral vessels. A ratio between inferior petrosal sinus (IPS) and peripheral basal (P) ACTH concentrations (IPS:P ratio) of 2:1 or greater is classically considered indicative of Cushing’s disease. If corticotropin-releasing hormone (CRH) is used to stimulate ACTH secretion during IPSS, an IPS: P ratio of 3:1 or greater is classically considered indicative of Cushing’s disease. In addition, a ratio between the right and left inferior petrosal sinus (IPS) of 1.4 or greater indicates that the adenoma is located on the corresponding side (3, 4, 5).

We report this case to highlight how IPSS helped to resolve the source of ACTH production. This patient first presented in 2007 and although the diagnosis of biochemical Cushing’s syndrome was confirmed, and the cause of Cushing’s syndrome was established as ACTH dependent, the source was not found. A plasma cortisol level higher than 50 nmol/L (2 µg/dL) postoperatively implies that the patient is not cured, indicating incomplete tumor removal (2,7). In optimal centers, cure rates are 80% to 90% for microadenomas and 50% for macroadenomas (2,8). Abnormal venous drainage can also lead to a false-positive gradient during IPSS. Even in cured Cushing’s the risk of recurrence of Cushing’s syndrome requires follow-up in all patients. Rate of recurrence increases with high postoperative cortisol values. Our patient also needs follow-up to decide on definite form of therapy whether resurgery or radiotherapy.

References
A diabetic with high haemoglobin A1c due to persistent haemoglobin F

H N Rajaratnam¹, M I Weerakkody², M Weerasinghe², S Siriwardena⁴


Abstract
Laboratory and patient-related factors can result in false glycated haemoglobin (HbA1c) measurements. Haemoglobin (Hb) variants that interfere with laboratory readings is an important cause. We report a case of hereditary persistence of Fetal Haemoglobin manifesting as a falsely high HbA1c in a 35-year old patient with type 2 diabetes mellitus, whose high HbA1c values persisted despite intensive anti-diabetic treatment. His fasting and postprandial blood glucose values as well as serum fructosamine level was incongruously low compared to HbA1c values. The presence of fetal haemoglobin was confirmed by haemoglobin electrophoresis. This case highlights the importance of being aware of the factors that can influence laboratory HbA1c measurements.

Introduction
Glycated haemoglobin (HbA1c) is a widely used measure of glycaemic control. Haemoglobin (Hb) variants can affect laboratory interpretations of HbA1c, resulting in discordantly high or low values. We present a case of an Hb variant causing aberrantly high HbA1c values in a patient with diabetes, and review some of the factors that affect HbA1c measurements.

Case report
A 35-year old welder was referred to the endocrinologist by a general practitioner for the management and follow up of very poorly controlled diabetes mellitus. He had presented one month ago with a fainting episode elevated capillary blood glucose. He was started on Metformin and Glibenclamide after the confirmation of diabetes and later referred to the endocrinologist as his HbA1c was 70%. He did not have a significant past medical history and had never required blood transfusions. However, he had a strong family history of diabetes, with both his parents and two other siblings affected from their early fifties. On examination he was an averagely built man who was not pale or icteric. He had a 2 cm hepatomegaly and a 4 cm splenomegaly. The rest of the clinical examination was unremarkable with no evidence of diabetic retinopathy or neuropathy.

His fasting blood glucose was 154 mg/dl and the post prandial blood glucose was 224 mg/dl. However, his HbA1c was 70% which was discrepantly high compared to his blood glucose values. The HbA1c test was done by ion exchange high performance liquid chromatography (HPLC) using a Biorad D10 machine. The possibility of an erroneous HbA1c reading was considered. This was supported by a fructosamine level of 294 micmol/l (205-285 micmol/l), which denoted only a slightly impaired glucose control. Since Hb variants are known to cause aberrantly high HbA1c values during laboratory testing, we considered a Hb variant to be a strong possibility in our patient who had hepatosplenomegaly. His Hb count was 15.2 g/dl and the blood picture showed hypochromic microcytic red cells, numerous target cells, irregularly contracted cells and irregularly haemoglobinized cells suggesting a thalassaemia trait. His haemoglobin electrophoresis revealed that his haemoglobin consisted entirely of Hb F (foetal haemoglobin) with no detectable Hb A or HbA2. This was suggestive of hereditary persistence of foetal haemoglobin. Although he was a product of a consanguineous marriage a similar illness had not been diagnosed in any of his family members previously.

Discussion
This is an interesting presentation of an otherwise undetected hereditary persistence of haemoglobin F manifesting solely as a discrepantly high HbA1c value.

In healthy adults haemoglobin comprises 97% of Hb A, 2.5% of HbA2 and 0.5% of HbF. Fractionation of Hb A by chromatography identifies several minor peaks referred to as Hb A1 or fast Hbs which include HbA1a, HbA1b and HbA1c. Glucose binds to haemoglobin in a two step process, and as one is irreversible, once bound
it lasts through the lifespan of the red blood cell, approximately 2 to 3 months. The N terminal valine of beta chains provides the most common site of glycation within the haemoglobin tetramer, accounting for 80% of HbA1c (1).

Hence HbA1c is the most widely used to monitor glycaemic control during a period of approximately 3 months and strongly correlates with the mean blood glucose level. The Diabetes Control and Complications trial (DCCT) and the United Kingdom Prospective Diabetes Study (UKPDS) were large trials that demonstrated that HbA1c levels are directly related to the risk of complications of diabetes, stroke and ischaemic heart disease (2, 3). As HbA1c is also a strong predictor of new onset diabetes mellitus, the American Diabetes Association now recommends this test in the diagnosis of diabetes mellitus and for identifying pre-diabetes (4). The American College of Endocrinology (ACE) and American Association of Clinical Endocrinologists (AACE) perceive that HbA1c should not be the primary criterion for the diagnosis of diabetes mellitus and that it should be used in conjunction with fasting plasma glucose and/or oral glucose tolerance tests (5).

As HbA1c is important as a diagnostic and monitoring tool, it is important to be aware of conditions that can affect laboratory HbA1c values apart from plasma glucose levels. Conditions that cause increased cell turnover and reduced average life span of the red blood cells can lead to lower HbA1c values. These include active bleeding, haemolytic disease, haemoglobinopathies and myelodysplastic disease. A patient with renal failure and uraemia can have high concentrations of carbamylated haemoglobin, resulting in aberrantly high HbA1C. Falsely elevated HbA1c measurements may also be obtained when red blood cell turnover is low, resulting in higher proportions of older red blood cells, such as in iron, B12 or folate deficiencies. Haemoglobinopathies can affect HbA1c values in three ways, they can influence the binding of glucose to haemoglobin, affect the peak measurements on chromatography and increase the risk of haemolysis and hence decrease the lifespan of red blood cells (6).

There are several commonly available methods to calculate HbA1c such as cation exchange chromatography, boronate affinity chromatography and immunoassay methods. Glycation alters the structure of the haemoglobin molecule and decreases its positive charge. Cation exchange chromatography separates haemoglobin species based on charge difference. Hb species are eluted from the cation exchange column at different times with the application of buffers of increasing ionic strength. A spectrophotometer measures the concentration of Hb in each column which is then quantified by calculating the area under each peak. The HbA1c percentage is then determined by an equation which includes HbA and HbA1c values (1). Ion exchange high performance liquid chromatography (HPLC) method, which was the method used for our patient by the Biorad D10 machine uses similar principles.

Carriers of variant Hbs that elute separately from HbA and HbA1c theoretically should have little effect on the HbA1c measurement as they have little effect on the equation. However, several reports have indicated that Hb variants and elevated HbF levels can interfere with some HbA1c assays (1). However, only a few studies are available. One such study showed that ion exchange HPLC methods show only very minimal evidence of interference from elevated HbF levels even when the HbF levels exceed 15% (7). As our patient had 100% of HbF it probably interfered with the spectrophotometry of haemoglobin columns and gave the erroneous HbA1c value. Although it was previously thought that the boronate affinity method was not affected by haemoglobin variants, the previously mentioned study showed that the presence of HbF artificially lowered the HbA1c values by this method as well (7). International Federation of Clinical Chemistry (IFCC) Reference Method (IFCC RM) for HbA1c measures glycated and nonglycated hexapeptides from HbA β chains. Because HbF has no β chains, HbF does not cause interference with the IFCC RM because only the HbA terminal hexapeptides are measured. Therefore this method has minimal interference by HbF and can be used to assess glycaemic control in these patients (8).

When there are inconsistencies between a patient’s home blood glucose monitoring and laboratory measured HbA1c, one should suspect a falsely elevated or lowered HbA1c result. Suspicion should also be raised when HbA1c is more than 15%, or when there is a significant change in a patient’s HbA1c when the laboratory assay method is changed (9). Comparing the patients home blood glucose monitoring values with his venous plasma glucose values would verify the accuracy of the blood glucose readings as opposed to the HbA1c value indicating the need to further evaluate a reason for the discrepancy. High HbA1c values would verify the accuracy of the blood glucose readings as opposed to the HbA1c value indicating the need to further evaluate a reason for the discrepantly high HbA1c value. Serum fructosamine level which reflects the average blood glucose control within the previous 2 to 3 weeks could also be used as a surrogate test. However the correlation between fructosamine and complications of diabetes mellitus has not been robustly evaluated in large randomised trials.

Elevated HbF levels can occur in patients as a result of pathologic conditions (eg, thalassaemia and leukaemia) or hereditary persistence of fetal haemoglobin (1). Approximately 1.5% of the US population has been reported to have elevated HbF levels as defined by an HbF level of more than 2% (10). Patients with the most common form of hereditary persistence of fetal haemoglobin can have HbF levels of up to 30%, and because they are generally asymptomatic, patients and their physicians may be unaware of the existence of this
condition (10). Our patient had 100% of HbF but was otherwise asymptomatic making hereditary persistence of foetal haemoglobin the most likely possibility in our patient.

In summary, this case illustrates the importance of maintaining a high degree of suspicion when the blood glucose values in a diabetic are incongruous with the HbA1c values. It also emphasizes the importance of using other biochemical parameters to diagnose and monitor glycaemic control in patients with haemoglobinopathies and haemoglobin variants.

References

Slipped capital femoral epiphysis in a boy with hypogonadism

Henry N Rajaratnam1, Dharshini Karuppiah2, S Sridaran3


Abstract

The etiology of slipped capital femoral epiphysis (SCFE) remains uncertain. The frequent findings of growth abnormalities in affected patients lead to the hypothesis that various endocrine disorders cause this condition. We encountered a 14-year old boy referred by an orthopedic surgeon with the clinical presentation of lack of age appropriate sexual maturation. He had bilateral slipped capital femoral epiphysis and underwent surgical correction. Further examination and hormonal assessment revealed hypogonadotrophic hypogonadism which persisted over the next six months.

Introduction

Slipped capital femoral epiphysis (SCFE) is unusual in the adolescent hip. Although endocrine, traumatic, mechanical, and toxic causes are all possible, the definitive etiology of this condition is still unknown. SCFE often occurs during the adolescent growth spurt and may be associated with endocrinopathies. We present a young boy with hypogonadism and SCFE. The possible mechanisms, associations and causes of SCFE are reviewed.

Case report

A boy aged 14 years was referred from an orthopedic unit because of lack of secondary sexual characteristics. He was presented to the orthopedic unit with a one-year history of chronic, insidious-onset pain in his hip, poor tolerance of weight bearing and limping of three weeks. The patient denied a history of any major trauma. He was investigated and found to have bilateral SCFE for which he underwent surgical correction.

The patient had a normal birth at term. His growth and development were normal and since 11 years old he rapidly gained weight. There was no history of delayed dental maturation, anosmia, hyposmia or a family history of delayed puberty. His parents noticed he had lack of secondary sexual characteristics compared to his peers. He was studying in grade nine with average academic grades and normal social activity.

On examination, his vital signs were normal. He was 155 cm tall and 61.5 kg weight with a body mass index (BMI) of 25.6 kg m⁻². His arm span was 157 cm and lower body segment (floor to pubis) was 1.5 cm longer than upper body segment (pubis to crown). He had no midline defects. His thyroid was not palpable. He lacked axillary and pubic hair, and the external genitalia showed a micropenis with a phallus length of 2 cm and testicular volume of 3 ml and 4 ml in right and left testes respectively: consistent with a Tanner’s pubertal stage of 1.

Neurologic examination including visual field proved normal.

Laboratory evaluation revealed the following data (normal values in parenthesis): Thyroid stimulating hormone (TSH) 1.55 IU/ml (0.4-4.0 IU/ml), free T4 1.16 ng/dl (0.8-2.0 ng/dl ), prolactin 8.3 ng/ml (2.8-29.2 ng/ml), follicle-stimulating hormone (FSH) 0.473 mIU/ml (4.0-9.0 mIU/ml ), luteinizing hormone (LH) 0.10 mIU/ml (1.6-9.0 mIU/ml ), total testosterone 0.20 ng/ml (1.95-11.05 ng/ml), 9:00 a.m. fasting plasma cortisol 19.7 microgram/dl (5-25 microgram/dl), and Insulin like growth factor 1 (IGF1) 338 ng/ml which was appropriate for his age and sex.

Anteroposterior and lateral radiographs revealed bilateral SCFE (Figure).

Figure

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The bone age was 13 years (with the standard deviation of 11 months) at the chronological age 14 years and 5 months.

He had a normal MRI (magnetic resonance imaging) brain.

The diagnosis of hypogonadotrophic hypogonadism was made.

At six months the levels of FSH, LH, and plasma testosterone were not much changed and were still in the prepubertal level. At this stage it may be contended that this patient had either an isolated hypogonadotrophic hypogonadism or a delayed onset of puberty. But since the hormonal parameters and the testicular volume had not changed in six months, the diagnosis of hypogonadotropic hypogonadism appeared more likely.

Due to the stress caused by the lack of sexual characteristics of patient compared to his peers he was started on testosterone enanthate 50mg deep intra-muscular injection monthly for three consecutive months. He was observed for pubertal signs over a further three months (six months in all) which remained unchanged. The LH, FSH and plasma testosterone levels repeated at six months were also unchanged.

### Discussion

SCFE occurs when shearing forces applied to the femoral head exceed the strength of the capital femoral physis (1, 2). The factors that weaken the physeal plate are not fully clarified, but are thought to include: adolescence growth (3), trauma (4), obesity (5), inflammatory changes, genetic predisposition (6-9), endocrine and metabolic disorders such as hypothyroidism and growth hormone deficiency (10-14), growth hormone therapy (15, 16) and sex hormone deficit (10-14). In many instances a combination of the features may operate to cause SCFE.

In our case the diagnosis could be either delayed onset of puberty or secondary hypogonadism. The distinction between delayed puberty and secondary hypogonadism can only be made over time, by observing whether LH, FSH, plasma testosterone level and clinical features are consistent with the onset of puberty. Since our patient had reached the age of fifteen and he had not demonstrated any pubertal signs and his LH, FSH, plasma testosterone levels had remained in the prepubertal range, it was concluded that he was most likely to be a patient with hypogonadotrophic hypogonadism.

Deficit of sex hormones relative to growth hormones can result in widening of the growth plate and subsequent reduction of the shearing force necessary to displace the epiphysis. Androgens indeed increase the strength of the physeal plate, and low levels of androgens may delay puberty and weaken the physeal plate. Low androgen levels may therefore be a possible etiologic factor for SCFE.

As a mechanical factor, obesity is also a predisposing factor for SCFE. It increases the shear stress placed across the physeal plate. If this stress is combined with a weak and immature physeal plate due to architectural irregularities resulting from endocrine abnormalities such as hypogonadism, slippage of the epiphysis may result.

In both sexes, hypogonadism accelerates the loss of bone and the development of osteoporosis. Sex steroids also influence circulating levels of growth hormone and insulin-like growth factor-1, and the interaction among these hormones is likely to be important in the acquisition and maintenance of normal bone mass. Androgens directly bind to androgen receptors or form aromatic compounds with estrogens and subsequently interact with estrogen receptors. Both pathways are important for skeletal health. The former is especially important in early skeletal development and in the determination of dimorphic sexual traits.

Bone remodeling, which is primarily stimulated by estrogen, is important in maintaining healthy bone throughout life. Some studies found the occurrence of more than one case of SCFE in a particular family.

In our case the contributory factors appeared to be hypogonadism and obesity. These lead to poor development of skeletal muscle, delayed epiphyseal closure and the mechanical factor of obesity.

The complications of SCFE includes osteonecrosis and osteoarthritis, which leads to a poor joint functional outcome.

### Conclusion

Careful clinical examination and hormonal assessment is required for all patients with SCFE to exclude an associated endocrinopathy. Hypothyroidism should be screened first in all such patients as primary hypothyroidism, the commonest endocrine cause may cause retardation of osseous development and delay in epiphyseal plate closure. Pituitary deficiency should be considered in those who have a relatively short stature for their age. Hypogonadism is a specially relevant aetiological factor when sexual development is absent.

### References


Gender assignment: whose decision is it?

Y A Arundathi Jayasena¹, K S H de Silva²


Introduction

Congenital adrenal hyperplasia (CAH) is a group of autosomal recessive disorders which are attributed to be the commonest cause of virilization in a girl (1). 21 – hydroxylase deficiency accounts for approximately 95% of CAH of which about 75% are of the salt losing type or classic CAH (2). Classic CAH patients suffer both aldosterone and cortisol insufficiency and present with salt wasting, failure to thrive and potentially fatal hypovolaemia and shock (3). The appearance of external genitalia in females depends on the degree of hyperandrogenism as well as on the severity of CYP21A2 allelic variation (2). Therefore CAH in a girl results in ambiguous genitalia which could be detected at birth but if complete virilization occurs, male gender assignment could result (4, 5). Male bias in choice of gender in certain populations might result in strong social pressures on families resulting in male gender assignment in extremely virilized girls with congenital adrenal hyperplasia (4). Once the true identity is known, changing the gender of patients is extremely difficult once assigned and is influenced by numerous social, cultural and medical aspects and will then result in immense psychological trauma to the child and family (5).

Case report

A 4-year and 9-month old boy, born to unrelated parents, was referred for further evaluation. He was the third living child of a family of five, where there had been one miscarriage and a death of a child with genital ambiguity whose details were not available.

He was born at term with a birth weight of 2.8kg. Genital ambiguity had been noted at birth with a 2.5cm phallus, fused, rugose labioscrotal folds and no palpable gonads. He had been transferred to Lady Ridgeway Hospital (LRH) on the third day of life for management of possible salt losing congenital adrenal hyperplasia. On day 6 of life, he had developed features of adrenal crisis clinically and biochemically with 17 hydroxy progesterone (17-OHP) 145nmol/l. Initial management of salt losing congenital adrenal hyperplasia with intravenous hydrocortisone and oral fludrocortisone and fluid resuscitation was done and thereafter lifelong replacement of oral hydrocortisone and fludrocortisone commenced. A buccal smear was arranged which suggested XX genotype with subsequent confirmation by karyotype as 46XX. Ultrasonically a uterus and vagina with a common urogenital sinus were seen. He was then referred back to the local hospital for follow up. By the review at 4 months of age, he had already been registered as a male despite counseling on several occasions.

He was re-referred back to Lady Ridgeway Hospital at 4 years and 9 months of age, by which time he was a well adjusted boy, the tallest in his class in nursery with a height of 110cm (75th - 90th centile) and weighed 16kg (25th centile). There was evidence of possible poor treatment or compliance as he was dark in complexion with pigmented palms and buccal mucosa with an advanced bone age of 10 to 11 years at a chronological age of 4 years and 9 months. His repeat 17-OHP was >57.6 nmol/l and serum testosterone was 0.65pg/ml (0.15-0.6). His hydrocortisone and fludrocortisone doses were optimized. Genitourinary endoscopy to assess the anatomy of genitourinary tract showed a uterine cavity, vagina and a urogenital sinus. Systemic examination was normal and blood pressure 100/70mmHg.

Counseling of parents was done regarding the probable future implications of continuing as a male. The fact that fertility was possible only as a female was emphasized by the consultant paediatrician and consultant paediatric surgeon.

Discussion

Genital ambiguity in a genotypic female with features of mineralocorticoid insufficiency during the neonatal period and markedly elevated 17-OHP is suggestive of salt losing/classic CAH due to 21-hydroxylase deficiency (2). Definitive genetic diagnosis was not possible due to limited facilities. The child was reared as a boy for 4 years and 9 months which presented numerous problems in the management. The psychosocial implications of genital ambiguity were documented in literature, and include perceived incongruence between genital appearance and assigned gender by parents and society, conflicting gender typing by family members, increased stigmatization, impaired genital self image and impaired body image by short stature (6).

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Gender reassignment and surgical intervention

This child was managed as classic CAH in a girl which was suspected at birth due to ambiguous genitalia. Despite counseling to delay the birth registration until karyotype was available, the parents registered the child as a boy. At this stage of presentation, reassignment of gender is very likely to result in significant psycho-emotional trauma as well as immense social repercussions to the child and the family. Breast development at puberty with ‘menstruation’ manifesting as bleeding per urethra are to be anticipated if continued to be brought up as a boy (5). Therefore to prevent the resultant psychological damage to some extent, he will need to undergo oophorectomy and hysterectomy which are irreversible surgical procedures. This child will have the possibility to retain fertility only if reared as a girl. If gender reassignment as a girl is done she will invariably need feminizing genitoplasty which involves several stepped surgeries such as clitoral reduction, labioscrotal reduction and vaginoplasty. These surgical interventions can help facilitate heterosexual relationships and conception if desired (2).

Precocious puberty

Inadequately controlled adrenal androgen production associated with poor compliance or under treatment would result in premature activation of the hypothalamo-pituitary-gonadal axis which leads to advanced skeletal age (7). This will give rise to secondary central precocious puberty which then results in breast development and cyclical bleeding (5, 7). Inhibition of the above process is possible to some extent with a gonadotrophin releasing hormone (GnRH) analogue which is a planned option for our patient. Nevertheless suppressing androgen production by treatment with hydrocortisone could also help the innate female characteristics which are disadvantageous if the child continues to be a boy (5).

Short stature

Markedly advanced bone age will compromise final height potential and would be further reduced if precocious puberty was to occur. This will invariably result in the child being a short adult (7). However, suppression of puberty with a GnRH analogue would facilitate gaining more height.

In view of the above problems and decisions regarding gender reassignment the following management plans were agreed to after detailed discussion with the parents.

- Continue to bring up the child as a boy because at present he is a well adjusted boy with a male gender identity which was in keeping with the parents’ wishes.
- Feminizing genitoplasty or the need of uterus and vagina is to be decided, depending on which gender the child identifies with, when he is old enough to understand the future implications and gender identity. Therefore not to perform any irreversible surgical procedures such as oophorectomy or hysterectomy until the patient is old enough to decide.
- At present ‘hypospadias’ is to be corrected as this could still be reversed in case if feminization is required.
- A GnRH analogue to suppress puberty when there is evidence of central precocious puberty until the above decisions are made.
- Testicular prostheses around the time of puberty and treatment with testosterone may have to be considered if he continues as a male.

The goal of gender assignment is to ensure the best possible quality of life for the patient and it is dependent on sexual identity, sexual function and possibility of fertility (8). Furthermore parents’ making this decision has been strongly challenged by some patient advocacy groups and ethicists who believe that responsibility for this decision belongs, as a right, to the affected individual. In their view gender assignment and surgery should be deferred until such an age when the individual can make informed decisions (9).

Thus undoubtedly, there will be many challenges to be faced by the child and family in the future necessitating continued psychological support and counseling.

References

3. NNSIS 2009 National Newborn Screening Information System. Available at http://www2.uthscsa.edu/nnsis


Case report

Camurati-Engelmann disease

S Pathmanathan¹, Noel P Somasundaram², Anil de Silva³, J Jeyakumar⁴, M V Perera⁵, Anandi Samarasekara⁶

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A 59 year-old man presented with left sided lower motor neurone facial nerve palsy and reduced hearing of 5 years duration, and noted recent worsening of symptoms. He had lower limb deformities since childhood but denied recurrent fractures or family history of similar illness. He was initially presumed to have polyostotic Paget’s disease on the basis of his age, the presentation and radiological appearance. However after careful evaluation, Camurati-Engelmann disease (CED) was diagnosed on the basis of radiological appearances and histological examination of bone. CED, also known as progressive diaphyseal dysplasia, is a rare genetic disorder of unknown etiology characterized by progressive expansion and sclerosis predominantly affecting the diaphyses of long bones and associated with cranial sclerosis (1,2,3).

Our patient had striking radiographic changes of skull and long bones. Plain Xray showed expansile sclerotic bone lesions of tubular bones, skull vault and mandible. The long bones showed a remarkably symmetrical involvement mainly of their diaphysis. On comparison, Paget’s disease, shows an asymmetrical involvement of long bones and usually begins at the end of a bone. Pelvis is commonly involved in Paget’s disease (4, 5). In our patient pelvis was relatively spared.

Histology of the left humerus showed mature thick cortical lamellar bone with regular prominent cement lines. Prominent osteoblasts were present on the surface of bone within the haversian canals. There was no osteoclastic activity or significant inflammation seen. In comparison, in the mature lesion of Paget’s disease, there is a mixture of lamellar and woven bone, which transforms the matrix into a chaotic “mosaic” pattern of irregularly juxtaposed pieces of lamellar bone, interspersed with woven bone (4, 5). This was not observed in our patient.

References


Figure 1. Xray skull – lateral.

Figure 2. Histology of the bone biopsy shows mature thick cortical lamellar bone with regular prominent cement lines (thick arrow) with prominent osteoblasts (thin arrow) within the haversian canal.

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Towards a cost-effective delivery of diabetes care in Sri Lanka

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Diabetes mellitus, whilst reaching epidemic proportions in many parts of the world including Sri Lanka, affects in addition to the urban sector, an increasing number of rural communities (1). The rise in the prevalence of diabetes would correspondingly lead to an increase in number of patients seeking treatment in hospitals (2). Sri Lanka being a lower middle income developing country lacks adequate resources, both financial and human, to manage this increased load of diabetic patients. However, the author is of the opinion that cost-effective utilization of existing resources would enable us to face this challenge. The primary healthcare system in Sri Lanka has been a true success story where we have reached a high standard of care despite limited resources. Similarly, in the case of diabetes cost-effective mechanisms should be identified and implemented in screening, education and the delivery of diabetes care and its prevention.

Of the three methods of screening available for diabetes, namely universal, opportunistic and high risk screening, the latter two might be the most practicable in Sri Lanka. In a recent study we carried out in a Teaching Hospital, nearly 22% of patients presenting to a medical ward for illnesses other than diabetes appeared to have raised blood glucose values which however needed reconfirmation (personal communication). Screening for diabetes in selected groups in the community could also be considered a method of opportunistic screening. Compared to an oral glucose tolerance test, the urine dipstick test performed after a standard glucose meal is simple and may be acceptable to patients and might be cost-effective (3). However this should not be advocated for routine use, but reserved as an alternative only in circumstances where resources are not available to carry out blood glucose testing. In a study conducted in India on 63,305 subjects participating in an opportunistic screening programme, a random capillary blood glucose value of 110mg/dl at screening was recommended to refer for definitive testing(4). In another study conducted in Sri Lanka the yield of undiagnosed diabetes in high risk subjects based on a family history was 13% (5). Polycystic ovary syndrome (PCOS) is considered to be a pre-diabetic state and should be sought for particularly among adolescent girls so that appropriate early preventive strategies could be adopted (6). In this respect, in a study conducted in an urban school in Sri Lanka, 13% of adolescent girls were found to have acanthosis nigricans, a possible marker of PCOS (7).

Diabetes education is of paramount importance in its management. There is a severe dearth of trained diabetes educators in Sri Lanka. With the view of overcoming this problem, the Kandy Branch of the Diabetes Association of Sri Lanka, pioneered a project where volunteers from a locality were trained to impart diabetes education to the community. The results achieved were remarkable. Among those patients who present to the hospital in the absence of formally trained educators, the patients depend on busy medical officers for education. In a study conducted in a Diabetic Clinic in Sri Lanka it was found that written instructions on diabetes are equally effective as the more accepted and standard method of providing verbal instructions (8). Other categories that could be used for diabetic education includes the mass media, volunteers, members of non-governmental organizations and enabled patients.

Diabetic care in Sri Lanka is delivered at government and private hospitals and by the general practitioners. In a study conducted at a diabetic clinic at a teaching hospital, we found that the quality of care was less than what was expected due to lack of resources and overcrowding (9). Since this has reached the status of becoming a specialized subject, more diabetic clinics should be opened at least in district general and teaching hospitals as well as in the major private sector hospitals. In a recently opened ‘diabetic clinic’ in the private sector despite limited resources, a significant fall in the blood glucose values and a high patient satisfaction score was observed (personal communication).

In a country such as ours where certain socio-culturally related misconceptions exist among patients that can interfere with diabetic care, it is pertinent to address these issues. One such issue is in relation to the diet; when what is really required is not the reduction of carbohydrate intake but the lowering of total energy intake and reduction of fat consumption. Another issue that affects proper glycaemic control in our patients is the reluctance to accept insulin treatment, although there is convincing evidence that insulin remains the most potent agent to lower the blood glucose and to achieve targets. Early initiation of insulin therapy, followed by oral hypoglycaemic agents later would be beneficial in preventing complications (10). However this is not widely practiced even in the West at present. In the event that

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this strategy becomes standard recommended practice in the future, it might prove to be a cost effective strategy in the control of diabetes. Hence, medical personnel should strive to convince their patients of the need to institute insulin therapy when there is an indication; thereby contributing to more cost effective diabetes care by preventing long term complications.

Although traditional anti-diabetic agents improve hyperglycaemia, this is achieved at a cost, which may also entail hypoglycaemia, increased body weight, exacerbation of dyslipidaemia and hypertension which are components of the metabolic syndrome; thereby potentially increasing the cardiovascular risk. To overcome this some support an early and aggressive polypharmacy addressing the underlying pathophysiology, with medical nutrition therapy, exercise, metformin and other oral hypoglycaemic agents and insulin if glycaemic goal is not achieved within 3 months (11).

Another area where sufficient attention is not paid in delivery of cost effective diabetes care in Sri Lanka is in relation to diabetes care in pregnancy. In a study reported previously, it was shown that only 25% of pregnant mothers attending an antenatal clinic have been screened for diabetes (12). Pregnancy outcome among women with diabetes is significantly poorer than in the background population (13). In this situation too, suitable strategies need implementation for screening for diabetes during pregnancy and for the long term management of such patients.

Cost effective diabetes care consists of preventing as well as treating complications. The complication which accounts for the highest morbidity and mortality in diabetes is cardiovascular disease. Several studies have shown the association of glucometabolic perturbations with higher cardiovascular morbidity and mortality especially in women, and the importance of controlling post-prandial glycaemia to lower the cardiovascular mortality (14). In patients with diabetes and heart failure metformin appears to be associated with more favorable clinical outcomes (15). In the clinical experience of the author, metformin may be an option when patients are unable to use insulin or other oral agents for glycaemic control in chronic stable heart failure. Periodonitis is another condition which is common in Sri Lankans. It is more prevalent and more severe in those with diabetes (16). Periodontal treatment could lead to a significant reduction in HbA1c level (17). Recent work has also demonstrated an important relationship between diabetes and depression. One in eight individuals with diabetes has major depression, and another one fifth may have less severe but clinically significant depressive symptoms. Diabetes patients with comorbid depression can have worse self care and treatment adherence, glycaemic control, increase morbidity and mortality (18). The symptoms of diabetes and depression often intervene in what can be termed “diapression”. Approaching depression in an integrated manner may be a novel approach to improve patient care. Even though there is no data on the prevalence of depression in Sri Lanka, the author is of the opinion that this could be an important factor contributing to inadequate control of diabetes among our patients. Diabetic nephropathy is a common morbid complication of diabetes and is a leading cause of chronic renal disease. Approximately 40% of patients with diabetes develop chronic renal disease (19). An even mild degree of albuminuria such as microalbuminuria is associated with a marked increased risk of cardiovascular disease, death and higher health care costs (20). In relation to painful diabetic nephropathy the most effective agent to lessen the pain and improve quality of life is pregablin (21).

Primary prevention of diabetes would be highly cost-effective in a developing country such as ours where the cost of treating the illness and its complications would be very high. All the land mark diabetes prevention trials such as the Chinese Da Qing study (22), the Finnish Diabetes Prevention Study (23) and the Diabetes Prevention Programme in USA (24) have shown that diabetes could be prevented by as much as by 58% with lifestyle modification and use of drugs such as metformin. The lifestyle measures advocated include physical exercise, prevention of obesity, reduced alcohol consumption, stopping smoking and reduction of mental stress. In a study reported from India, educational intervention was successful in reducing some of the obesity parameters and dietary patterns in individuals with prediabetes and diabetes (25).

All these measures stated by the author based on personal experience as well as based on evidence presented should enable us to deliver a more cost-effective diabetes care thereby leading to substantial reduction of morbidity and mortality due to diabetes in a resource limited setting like in Sri Lanka.

References


Purpose and Scope

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

General Information

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

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Completed Copyright Assignment and Affirmation of Originality form.

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