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Editorial

Managing hyperglycaemia in hospitalized patients


Hyperglycaemia is a common, serious and costly health care problem in hospitalized patients. There is substantial observational evidence linking hyperglycaemia in critically ill patients (with and without diabetes) to higher rates of hospital complications, longer hospital stay, higher health care resource utilization, and greater hospital mortality (1,2). Although several cohort studies as well as early randomized clinical trials (RCTs) suggested that tight glucose control (80 to 110 mg/dL [4.4 to 6.1 mmol/L]) reduced hospital complications and mortality (3,4), this target has been difficult to achieve without increasing the risk for severe hypoglycaemia. In addition, recent RCTs in critically ill patients have failed to show a significant improvement in mortality or have even shown increased mortality risk with intensive glycemic control (5-7).

Managing hyperglycaemia in Intensive Care Settings

In NICE-SUGAR, a multicentre, multinational RCT, tested the effect of tight glycemic control (target 81-108 mg/dl) on outcomes among 6,104 critically ill participants (5). Ninety-day mortality was significantly higher in the intensive vs. the conventional group (target 144-180 mg/dl) (78 more deaths; 27.5% versus 24.9%, P<0.01). There were reductions with basal bolus as compared with sliding scale insulin (SSI) in the composite outcome (24.3% and 27.5%, P=0.02). Severe hypoglycaemia was also more common in the intensively treated group (6.8% vs. 0.5%; P<0.001). This study’s findings do not disprove the notion that glycemic control in the ICU is important; however, it strongly suggests that it is not necessary to target blood glucose values <140 mg/dl, and that a highly stringent target of <110 mg/dl may actually be dangerous.

In a recent meta-analysis of 26 trials (N=13,567), the pooled relative risk (RR) of death with intensive insulin therapy was 0.93 as compared with conventional therapy (95% CI 0.83-1.04) (6). The pooled hypoglycaemia RR with intensive therapy was 6.0 (95% CI 4.5-8.0). The specific ICU setting influenced the findings, with patients in surgical ICUs appearing to benefit from intensive insulin therapy (RR 0.63, 95% CI 0.44-0.91), while those in other critical care settings did not (medical ICU: RR 1.0, 95% CI 0.78-1.28; *mixed*ICU: RR 0.99, 95% CI 0.86-1.12).

Based on recent RCTs, the Endocrine Society and ADA recommended raising glycemic targets in the ICU. For the majority of patients in the ICU setting, using insulin infusion and targeting blood glucose levels between 140 and 180 mg/dL (7.8 and 10.0 mmol/L) is recommended (8). Despite the lack of strong scientific evidence, lower glucose targets between 110 and 140 mg/dL (6.1 and 7.8 mmol/L) may be appropriate in selected ICU patients such as CABG surgical patients and stable glycemic control patients without hypoglycemia. Blood glucose targets >180 mg/dl or <110 mg/dl are not recommended.

Managing hyperglycaemia in inward settings

In general medical and surgical non-ICU patients, observational and RCT have also shown a strong association between hyperglycaemia and poor clinical outcomes, including prolonged hospital stay, infection, and disability after hospital discharge, and death (9,10). In such patients, the presence of hyperglycaemia is associated with prolonged hospital stay, infection, disability after hospital discharge, and death (1,9,11). Hyperglycaemia on admission has also been linked to worse outcomes in patients with community-acquired pneumonia (12).

In a prospective cohort multicentre study of 2,471 patients, those with admission glucose levels of >11 mmol/L (198 mg/dL) had a greater risk of mortality and complications than those with glucose <11 mmol/L. The risk of in-hospital complications increased 3% for each 1 mmol/L increase in admission glucose. In a retrospective study of 348 patients with chronic obstructive pulmonary disease and respiratory tract infection, the relative risk of death was 2.10 in those with a blood glucose of 7-8.9 mmol/L, and 3.42 for those with a blood glucose of >9.0 mmol/L compared to patients with a blood glucose 6.0 mmol/L (13). Each 1 mmol/L (18 mg/dL) increase in blood glucose was associated with a 15% increase in the risk of an adverse clinical outcome, which was defined as death or length of stay of greater than nine days. A recent RCT reported that improving glycemic control with basal-bolus vs. sliding scale insulin (SSI) in patients with type 2 diabetes undergoing general surgery reduced a composite of postoperative complications, including wound infection, pneumonia, bacteremia, respiratory and acute renal failure. In this study, a mean daily glucose concentration after the 1st day of basal-bolus and SSI was 145 ± 32 mg/dl and 172 ± 47 mg/dL, respectively, p<0.01. There were reductions with basal bolus as compared with SSI in the composite outcome (24.3% and 8.6%, OR: 3.39 [95% CI: 1.50-7.65]; p=0.003).
Achieving safe and effective glycaemic targets

Insulin therapy is the preferred method of glycaemic control in the majority of patients in the hospital setting (8). In the ICU, IV infusion is the preferred route of insulin administration. Numerous examples of successful Continuous Insulin Infusion algorithms in achieving glycaemic control are reported in the literature (3,4,14). A computer-based algorithms aiming to direct the medical staff in adjusting insulin infusion rate have become commercially available. All published ICU insulin algorithms appear to be equally effective in controlling blood glucose without major clinical outcome differences, including frequency of severe hypoglycaemic events, length of ICU and hospital stay, or mortality, among different treatment algorithms (1,8). Outside of critical care units, subcutaneous insulin administration is used much more frequently. Oral agents have a limited role, and should be avoided in the inpatient setting. Scheduled subcutaneous insulin is the preferred method for achieving and maintaining glucose control in non-ICU patients with diabetes or stress hyperglycaemia. The recommended components of inpatient subcutaneous insulin regimens include a basal, nutritional and a supplemental (correction) component (1,8). Hospitalized patients often require high insulin doses to achieve target glucose levels due to increased insulin resistance; thus, in addition to basal and nutritional insulin requirements, patients often require supplemental or correction insulin for treatment of hyperglycaemia. Use of repeated doses of short-acting insulin per sliding scale, as a sole form of therapy in hospitalized patients with diabetes, should be avoided because of persistence of hyperglycaemia in type 2 diabetes and risk of ketoacidosis in patients with type 1 diabetes (8). The use of a basal-bolus regimen has been shown to improve glycaemic control with a similar rate of severe hypoglycaemia than SSI alone and to decrease hospital complications in patients undergoing non-cardiac surgery.

Considering above, it could be highlighted that hyperglycaemia is associated with poor outcomes in the hospital not only in patients with diabetes but also without diabetes with hyperglycaemia. It is evident that good metabolic control with target blood sugars are associated with improved hospital outcomes.

– Dr. Uditha Bulugahapitiya
Editor

References
Exercise: an essential component of diabetes management

S Siyambalapitiya¹, G Gunathilake¹, I Perera²


ABSTRACT

Objective: Regular exercise constitutes an essential component of diabetes management. However, the compliance with exercise related advice is poor among patients. Our objectives were to assess the compliance with exercise recommendations and the barriers to exercise among patients with diabetes.

Methods: 253 patients with type 2 diabetes treated in 3 different clinical settings; hospital diabetes clinic, hospital general medical clinics and general practitioners (GPs), were recruited for the study. Data were collected using an interviewer administered questionnaire.

Results: Out of 253 patients, only 45.1% (n=114) were properly educated regarding exercise as part of diabetes management. A higher percentage of patients in diabetes clinics were educated (60.6%, n=63) compared to patients attending medical clinics (26.5%, n=26) and the GPs (49%, n=25) regarding exercise. However, the compliance with exercise recommendations is poor (11.5%) irrespective of the clinical setting. Walking is the commonest mode of exercise (72.4%, n=21) followed by exercise machines (13.8%, n=4) and running (13.8%, n=4). In the non-exercising group, majority (51.6%, n=48) think that the activities of daily living are adequate as daily exercise. 18.3% (n=17) claim that they do not have time to exercise and 14% (n=13) are not really interested.

Conclusions: Adherence to regular exercise as part of diabetes management is poor among patients with diabetes. Current health promotional and health information delivering techniques have also failed to achieve the desired attitude change among patients towards regular exercise. This highlights the need for novel approaches to address this problem.

Introduction

Type 2 diabetes is one of the commonest non communicable diseases and it is associated with significant morbidity and mortality. Current epidemiological data suggest that the prevalence of diabetes is on the rise and its negative economic impact is enormous (1, 2). With the genetic predisposition, unfavourable environmental contributors such as unhealthy dietary patterns and lack of exercise can lead to the development of diabetes in susceptible individuals. Physical inactivity that goes hand in hand with the economic development has been one of the most important reasons for this epidemiological transition. Reduction of insulin sensitivity is one of the main pathological processes of developing type 2 diabetes and lack of physical activity and obesity are the main contributors. Regular exercise improves insulin sensitivity, thereby the glycaemic control in patients with diabetes. Therefore, it is recommended as one of the most important treatment modalities in the management of diabetes.

Health benefits of exercise are enormous. In patients with diabetes, it improves the glycaemic control by increasing insulin sensitivity and glucose utilization and by decreasing the hepatic glucose production (3,4). It can also prevent or delay the onset of diabetes in high risk individuals (5-7). It also helps in reducing weight in obese individuals. It reduces the cardiovascular co-morbidities such as hypertension, dyslipidaemia and improves the quality of life of diabetic patients. In order to get these benefits, it is recommended to carry out at least 150 minutes of exercise per week.

Although there is enough evidence to prove the benefits of exercise, initiating and maintaining regular physical activity remain a difficult challenge (8,9). People in different communities have different individual, socio-cultural and environmental reasons and barriers that hinder the adherence to regular exercise. Level of education and understanding regarding the importance of physical activity are important determinants for compliance with exercise (10,11). Lack of interest (10,12), lack of time (10,13), depressive symptoms (14), physical limitations (11,14), smoking (11), and female sex (14) are important patient factors. Fear of hypoglycaemia is one of the main reasons for not doing exercise among insulin-treated diabetics (15). Lack of social support from family and friends (14) is another important factor especially for elderly patients. Availability and accessibility to a proper place where physical activity can be carried out is another important

¹North Colombo Teaching Hospital, Ragama, ²Community Dental Unit, Dental Institute, Maligawatta, Sri Lanka.
environmental barrier (12,13). Distraction from television is another noteworthy obstacle in some communities (13).

Although the barriers to carry out exercise are many, the factors that influence exercise practices in South Asian communities are largely unknown. The objectives of this study were to assess the knowledge regarding exercise, the degree of compliance to exercise recommendations and to find out reasons for non-adherence to exercise recommendations among Sri Lankan patients with diabetes.

Method

The study was conducted in North Colombo Teaching Hospital, Ragama (a tertiary care hospital). Ethical approval for the study was obtained from Faculty of Medicine, University of Kelaniya. Data collection was also done from 2 community clinics in 2 Medical Office of Health (MOH) areas, Ja-Ela and Katana. In order to obtain a proper cross-section of the diabetes population, we recruited a total number of 253 diabetic patients, 104 and 98 managed in the diabetes clinic and the medical clinics at North Colombo Teaching Hospital respectively, and 51 patients from the community (Katana and Ja-Ela MOH areas) who received treatment from the general practitioners (GPs). Patients from the diabetes clinic and medical clinics were selected randomly using the clinic registration numbers. Two clusters of patients receiving treatment from GPs were randomly selected from the 2 community clinics at Katana and Ja-Ela MOH area. After obtaining informed consent from the recruited patients, demographic data, data related to exercise level and the reasons for not exercising were collected using a pre-tested interviewer administered questionnaire.

Results

Distribution of the patient sample by type of care and socio-demographic characteristics is shown in Table 1. Out of 253 patients, 45.1% of participants were managed in the government tertiary care hospital diabetic clinic, another 41.1% in the government tertiary care hospital medical clinics and the rest (13.8%) by the GPs in the community. Mean age of the participants was 57.03 years (±10.75) and the overwhelming majority (80.3%) consisted of females. 193 (76.3%) of the patients had above primary level (above grade 5) of education. However, only 17% were employed.

Out of 253 patients, only 45.1% (n=114) had received proper education regarding exercise. Patients in the diabetic clinic were better informed (60.6%, n=63) compared to patients attending medical clinics (26.5%, n=26) and those managed by the GPs (49%, n=25) regarding exercise. Irrespective of the clinical setting that they attended for treatment, the compliance with exercise advice has been poor (11.5%) among patients with diabetes (Table 2). Walking is the commonest mode of exercise (72.4%, n=21) followed by work outs in exercise machines (13.8%, n=4) and running (13.8%, n=4). In the non-exercising group, majority of the patients (51.6%, n=48) were under the impression that activities of daily living were adequate as daily exercise and they have not done any changes to improve their level of activity. 18.3% (n=17) claimed that they did not have the time to do exercise and 14% (n=13) were not interested in doing any exercise. The rest (16.1%, n=15) did not carry out exercise due to physical disabilities such as back pain, joint pain, chest pain and age related disability (Table 2).
Discussion

We have evaluated a cross section of patients in the community, who attended different types of clinic settings for diabetes care. Significant proportion of patients had received information regarding the importance of regular exercise as part of diabetes management. However, a very small percentage of patients were actually carrying out regular exercise. As expected, the patients attending the diabetes clinics were better informed than those attending the general medical clinics and the GPs regarding the importance of regular exercise as a part of diabetes management. It was interesting to note that most of the patients in modern society with sedentary lifestyles believed that activities of daily living are more than adequate as exercise. These findings highlight the poor level of understanding regarding exercise and the importance of exercise as part of diabetes management among patients with diabetes. Current diabetes education strategies and techniques have failed to achieve the desired effects among patients in initiating and maintaining regular exercise. This highlights the need of novel approaches to achieve the desired attitude change among patients towards promoting exercise as part of diabetes management.

Despite knowing the importance of regular physical activity in the management of diabetes, most of the medical practitioners have failed to educate and re-enforce the patients to carry out regular physical activities. During busy patient consultations, priority is given to optimize and highlight the importance of drug treatment. However, due prominence is not given to this important management aspect and very limited time is devoted in educating and promoting exercise practices. This probably is one of the main reasons for our observations that need to be addressed properly in order to achieve the expected results.

Our study sample is dominated by elderly housewives (80.2%). It could be speculated that they may be under the impression that engaging in day to day household chores provides adequate physical exercise. Moreover, there could be a plethora of socio-cultural and lifestyle factors especially among low and middle class females that influence their perceptions and attitudes regarding exercise in Sri Lankan context. Therefore, it is important that the health educators take these factors into consideration when delivering information regarding physical activity especially for overweight and obese housewives with diabetes. Walking has been the most accepted mode of exercise among our patients and this probably is the best mode of exercise that we could recommend. However, it is essential that these health care messages are tuned according to the level of health literacy of the individual patient and delivered in a way that are personally, socially and environmentally acceptable.

Although a reasonable proportion of patients received exercise advice as part of diabetes management, the desired outcome was not evident. This highlights the ineffectiveness of health education strategies and currently used health educating techniques such as health education leaflets and mass lectures that are carried out in our health care settings for diabetic patients. One to one advice tailored to individual needs has been the most effective especially for promoting exercise practices among patients (16,17). However, it is time consuming, expensive and difficult to implement even in resource abundant settings. Several studies have shown promising results with the use of cheaper modes of communication such as mobile phones (18), internet (19) and social networking sites (20) in managing chronic diseases that can also be used for educating and promoting regular exercise in patients with diabetes. It is timely to make good use of these technological advances and find better novel cost effective solutions to suite different clinical settings.

Our study has shown that the compliance with exercise advice is poor among our patients despite receiving a reasonable degree of information regarding the importance of regular physical activity. This highlights the deficiencies and failures of current health educating strategies in healthcare settings to achieve the desired objectives. It is time to work out better cost effective ways of imparting this information aimed at attitudinal and behavioural changes in order to achieve better outcomes. Moreover, it is important to create health promoting settings with facilities to engage in exercise, which are easily accessible for the people to make “easy healthy choices”.

References


Prevalence and associations of overweight among adult women in Sri Lanka: a national survey

Renuka Jayatissa¹, S M Moazzem Hossain², Sandya Gunawardana¹, J M Ranbanda¹, Malsha Gunathilaka¹, P C De Silva¹


Abstract
The rates of overweight and obesity are rising to epidemic proportions, especially among women. There are many health risks associated with increased weight. This study aims at providing information on the overweight and obesity and its associated factors among non pregnant and non lactating women aged 15 to 49 years in Sri Lanka. Multistage cluster sampling method was used. A household survey was carried out in nine districts, each randomly selected from all 9 provinces. Thirty Grama Nildhari areas per district were selected, each cluster consisting of 21 randomly selected households. Data collection was by an interviewer administered questionnaire. Weight and height were measured and body mass index (BMI) calculated. International classification was used to identify overweight women. Total of 6071 households were included in the study. Of the 27,862 residents in the selected households, 27.3 percent were women aged between 15 and 49 years. Of them, 18.2% had BMI <18.5 (thin), 52.4% were BMI between 18.5-24.9 (normal), 22.8% were between 25.0 and 29.9 (overweight) and 6.6% were BMI 30.0 or above (obese). When Asian cutoff value is applied 37.8% (BMI 18.5-23.0), 28.7% (BMI 23.01-27.5) and 15.2% (BMI>27.5) were normal, overweight and obese respectively. Higher level of husband’s education and higher wealth quintiles were associated with risk of overweight or obesity. Increasing level of overweight and obesity prevalence among women between 15-49 years indicates the important role of health professionals in promoting preventative measures and encouraging positive lifestyle behaviors of women during health encounters. We recommend counseling women about safe and effective weight loss and weight management programs.

Introduction
Worldwide, at least 2.8 million people die each year as a result of being overweight or obese. Risks of coronary heart disease, ischemic stroke and type 2 diabetes mellitus increase steadily with increasing body mass index (BMI), a measure of weight relative to height. Raised body mass index also increases the risk of cancer of the breast, colon, prostate, endometrium, kidney and gall bladder. Mortality rates increase with increasing degrees of overweight, as measured by BMI. To achieve optimum health, the median BMI for an adult population should be in the range of 21 to 23 kg/m², while the goal for individuals should be to maintain body mass index in the range 18.5 to 24.9 kg/m². There is increased risk of co-morbidities for body mass index 25.0 to 29.9, and moderate to severe risk of co-morbidities for body mass index greater than 30 (1).

The prevalence of overweight and obesity were highest in the WHO Regions of the Americas (62% for overweight in both sexes and 26% for obesity) and lowest in the WHO Region for South East Asia (14% overweight in both sexes and 3% for obesity). In all WHO regions women were more likely to be obese than men. In the WHO regions for Africa, Eastern Mediterranean and South East Asia, women had roughly doubled the obesity prevalence of men (1).

Sri Lanka is not an exception regarding overweight and obesity. Demographic and Health Survey (DHS) in 2000 and 2006/7 found 24% and 31.2% of women were overweight respectively (2,3). Among adults, a study took place at the national level in 2005/6 and found the prevalence of overweight for both genders (n = 4532) was 25.2% (4).

In accordance with the nutrition policy of Sri Lanka, national priorities in research encompassed the identification of the problem of overweight among the Sri Lankan population and its geographical, sex, and socioeconomic distribution (5).

The objective of this study was to (i) estimate the prevalence and distribution of overweight and obesity, in adult females and (ii) to analyze its possible causes.

¹Department of Nutrition, Medical Research Institute, Ministry of Health, Colombo, Sri Lanka. ²UNICEF, Afghanistan.
Materials and methods

Muti-stage cluster sampling method was used to select a representative sample at national level. A cross sectional household survey was carried out in nine districts of Sri Lanka, one district randomly selected from each province. Each district constituted one study area, except the Colombo district which had two study areas: the Colombo Municipal Council area (Colombo MC) and the Colombo Regional Director of Health Services (RDHS) area. The selected study areas were Jaffna, Trincomalee, Colombo MC, Colombo RD, Kurunegala, Anuradhapura, Nuwara Eliya, Badulla, Ratnapura and Hambantota districts.

The probability proportional to size sampling technique was used to identify the clusters which are defined at the Grama Niladhari (GN) division level. The first cluster was identified randomly, followed by identification of a total of 30 clusters per district, using the sampling interval. A systematic random sampling technique was used within each cluster to identify 21 households. Each GN area was divided into several blocks, including 100 households per block. One block was randomly selected to collect the samples. A household was defined as persons routinely sharing food from the same cooking pot and living in the same compound or physical location. The first household was selected randomly and after that every third household was visited. The estimated sample size per district was 617 households totaling to 6170 households in the 10 study areas. Non pregnant and non lactating women between 15-49 years living in the selected households were included. A pregnant woman was defined as any reported pregnancy status of women using anthropometric indicators which was done using standardized procedures for measuring the height and weight (6). Height was recorded to the nearest 0·1 cm, using UNICEF stadiometers. Body weight was measured to the nearest 0·1 kg using a SECA digital UNICEF weighing scales.

Data analysis was conducted in SPSS software packages. Body mass index (BMI) was calculated using weight and height. Four categories of women were identified based on BMI – thin (<18.5), normal (18.5-24.9), overweight (25.0-29.9) and obese (≥30.0) (7). Asian cutoff was also applied to assess the BMI categories as follows; BMI – thin (<18.5), normal (18.5-23.0), overweight (23.01-27.5) and obese (≥27.5) (7). For detail analysis international BMI cutoff values were used for comparative purposes. Multiple logistic regression analysis was used to determine the factors associated with overweight or obesity in women of 15-49 years of age. The magnitude of association was expressed as adjusted Odds Ratio (OR) and 95 percent confidence interval (95%CI) with the p value <0.05 for statistical significance.

Results

A total of 6071 households were included in the survey. Out of the total, 69.4 percent of the households were in the rural sector, 25.0 percent in the urban sector and 5.6 percent in the estate sector. Of the total 27,862 individuals who were usually resident in the selected households, 7604 (27.3 percent) were women aged between 15.0 and 49.9 years (Table 1).

Thirty nine percent of the households had a monthly income less than Rs.9000 and 8.5% had Rs.≥32,000. Percentage of households classified as belonging to the lowest wealth quintile varied from 4.6 percent in the Colombo district to 40 percent in Jaffna district. Conversely, households belonging to the highest wealth quintile ranged from 5.1 percent in Jaffna to 46.6 percent in Colombo district (Table 2).

A total of 2146 non-pregnant and non lactating women aged between 15 to 49 years were included in the assessment of body mass index. As shown in Figure 1, of the total sample, 18.2 percent had BMI less than 18.5 (thin), 52.6 percent had BMI between 18.5 and 24.9 (normal), 22.5 percent with values between 25 and 29 (overweight) and 6.7 percent, with BMI values 30 or above (obese). When the Asian cutoff was applied 18.2 percent had BMI less than 18.5 (thin), 37.8 percent had BMI between 18.5 and 23.0 (normal), 28.7 percent with values between 23.01 and 27.5 (overweight) and 15.2 percent, with BMI values above 27.5 (obese).
Prevalence and associations of overweight among adult women in Sri Lanka

Table 1. Distribution of women 15-49 years by sector and district

<table>
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<tr>
<th>Sector/District</th>
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<td><strong>Total</strong></td>
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Table 2. Distribution of households according to income and wealth index, by district

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<th>Hambantota</th>
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<td>%</td>
<td>No.</td>
<td>%</td>
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<td>%</td>
<td>No.</td>
<td>%</td>
<td>No.</td>
<td>%</td>
<td>No.</td>
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<td><strong>Monthly household income (LKR)</strong></td>
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<td>&lt; 9,000</td>
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<td>17.3</td>
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<td>59.8</td>
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Available national data for non pregnant women aged 15-49 years showed a rising trend in overweight prevalence over time with falling rates in underweight prevalence. Rates of increase seems most marked from 2000 to 2006 (Figure 2). It is interesting to note that the percentage of category of women within the normal BMI levels were almost the same.
The prevalence of underweight (BMI less than 18.5) was high in the 15-19 age group (40.5 percent) with a substantial decline in the age groups 20-29 years (22.5 percent) and 30-39 years (12.9 percent). Of all non-pregnant and non-lactating women studied, 29.2 percent were either overweight or obese. This percentage increased with increasing age, most marked after 30 years of age (Table 3).

Table 3. Prevalence of thin, normal and overweight/obese in non-pregnant women by background characteristics

<table>
<thead>
<tr>
<th>Background Characteristics</th>
<th>BMI category (%)</th>
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<tr>
<td></td>
<td>Underweight (BMI &lt; 18.5)</td>
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<td>16.9</td>
</tr>
<tr>
<td>Badulla</td>
<td>24.1</td>
</tr>
<tr>
<td>Colombo</td>
<td>12.1</td>
</tr>
<tr>
<td>Colombo MC</td>
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</tr>
<tr>
<td>Hambantota</td>
<td>20.4</td>
</tr>
<tr>
<td>Jaffna</td>
<td>20.5</td>
</tr>
<tr>
<td>Kurunegala</td>
<td>19.2</td>
</tr>
<tr>
<td>Nuwaraeliya</td>
<td>22.5</td>
</tr>
<tr>
<td>Ratnapura</td>
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<tr>
<td>Trincomalee</td>
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<td>Women’s education level</td>
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<tr>
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<tr>
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<td>20,000 - 31,999</td>
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<td>Richest</td>
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<tr>
<td>Overall</td>
<td>18.2</td>
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</table>
Marked inter-sectoral differences were seen, with the estate sector showing the highest percentage (42.6 percent) of women with BMI less than 18.5, compared to 11.3 percent in the urban sector. Conversely, in the urban sector, there was a high percentage of women who were overweight (28.3%) and obese (15.0%).

Comparison between districts show that the percentage with low BMI ranged from 12.1 percent in Colombo RD to 25.3 percent in Ratnapura. Conversely, overweight ranged from 11.8 percent in Nuwara Eliya district and 32.3 percent in Colombo MC. Obesity varied from 0.8 percent in Ratnapura district to 19.7 percent in Colombo MC. There was a declining pattern in the prevalence of underweight with increasing income levels and wealth quintiles. The prevalence of overweight and obesity showed an increase with higher income levels and wealth quintiles.

As shown in Table 4, overweight and/or obesity in women were significantly higher after 30 years of age, in the urban sector, Colombo MC and Colombo RD, highest income and wealth quintiles.

Table 4. Prevalence (95% confidence interval), odds ratio (95% confidence interval), and significance testing (p values) of overweight and obesity in non-pregnant and non lactating women by background characteristics

<table>
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<tr>
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<th>%</th>
<th>95% CI</th>
<th>OR</th>
<th>95% CI</th>
<th>p value</th>
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<td>0.09</td>
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(Continued)
Prevalence and associations of overweight among adult women in Sri Lanka

Women in the estate sector had lower (OR=0.21) risk of being overweight/obese compared to urban sector. Compared to the Colombo MC, risk of overweight/obesity was low in certain districts: Ratnapura (OR=0.46), Jaffna (OR=0.50), Colombo RD (OR=0.53), Hambantota (OR=0.57), and Badulla (OR=0.56). Increasing level of husband's education and wealth quintiles were strong correlates for the risk of having overweight/obesity in women.

Discussion

In 2008, 35% of adults aged 20+ were overweight (BMI ≥ 25 kg/m²) (34% men and 35% of women) in the world. The worldwide prevalence of obesity has more than doubled between 1980 and 2008. In 2008, 10% of men and 14% of women in the world were obese (BMI ≥30 kg/m²), compared with 5% for men and 8% for women in 1980. An estimated 205 million men and 297 million women over the age of 20 were obese – a total of more than half a billion adults worldwide.

Data from Sri Lanka Demographic and Health Survey (DHS) 2000 and 2006/07 were taken for comparison of the nutritional status of women due to similar target groups used in the present study and DHS study. It was considered, useful to compare the main findings as both studies were based on large household samples, using the same indicators and methods in the assessment of nutritional status and were carried out within a last 10 year period.

The present study shows that 22.5 percent and 6.7 percent of women aged 15-49 years were overweight and obese respectively. Comparable data from DHS 2006/07 indicate the prevalence of overweight and obesity being 24.0 and 7.2 percent, respectively. This reduction of overweight and obese percentages in women in the present study may be due to the exclusion of lactating mothers. Using the Asian cutoff showed a higher prevalence of overweight and obesity, increased by 6.2% and 8.5% respectively.

Associated factors for thinness among this group of women when compared with the DHS 2006/07 showed similarities except for the inter district differences. Both studies show that the percentage of ‘thin’ women was significantly higher among those aged less than 30 years, especially among the teenagers, in the estate sector and in the lowest income group, and the poorest wealth quintile. In the present study, the districts of that showed high prevalence of thinness were: Ratnapura, Badulla and

# Prevalence and associations of overweight among adult women in Sri Lanka

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>%</th>
<th>95% CI</th>
<th>OR</th>
<th>95% CI</th>
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<td>27.3</td>
<td>31.2</td>
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</table>
In conclusion, among non pregnant and non lactating Sri Lankan women aged 15-49 years, 17.0% are thin, 22.8% are overweight and 6.6% are obese; with half of women in the Colombo MC area being overweight or obese. Overweight or obesity was associated with increasing level of husband’s education and higher wealth quintiles. It is recommended that adult women should be screened for overweight or obesity periodically, especially during each health encounter and be offered appropriate counseling and referral. All overweight or obese women should be counseled about the health implications associated with their weight.

Acknowledgements

This study was supported by the UNICEF and WFP Colombo. The authors thank Dr. Dulitha Fernando, Dr. Upul Senarath and Indika Siriwardana for analyzing the data and for their support in preparing the detailed report of the study. We thank all staff of the Department of Nutrition for supporting the data collection.

References

No link to cardiac valvulopathy was seen in cabergoline treated patients

K Dharshini¹, Noel Somasundaram², H M D P K Senevirathna³, S Raj Kumar⁴


(Index words: prolactinoma, cabergoline, valvulopathy)

ABSTRACT

Objective: To evaluate the association between use of cabergoline in patients with prolactinoma and risk of developing clinically relevant cardiac valvular disease.

Method: This was a descriptive cross sectional study conducted at Endocrinology and Pituitary clinics at National Hospital of Sri Lanka. Patients with macro and micro prolactinoma who were on medical therapy with cabergoline for more than 24 weeks duration were selected for the study. Patients with pre-existing congenital valvular heart disease, history of rheumatic heart disease and ischemic heart disease were excluded from the study. All the included patients were evaluated with 2D echocardiogram for the presence and degree of valvulopathy.

Results: Out of 45 patients included in this study, 12 (26.6%) had mild valvular regurgitation. Twenty four patients received more than the median cumulative dose of 104 mg and the prevalence of valvulopathy was not significantly different (Chi-Squared test; p=0.34) from those receiving less than the median cumulative dose. Similarly 23 patients received treatment longer than the median duration of 48 months and the prevalence of valvulopathy was not significantly different (Chi-square test; p=0.92) from those received less than the median duration.

Conclusion: Our study shows no significant association between the cumulative dose and the duration of cabergoline therapy with the development of valvulopathy among patients with prolactinoma.

Introduction

Medical therapy has become the main treatment modality in treating prolactinomas and dopamine agonists such as cabergoline, quinagolide and bromocriptine are the commonly used drugs in clinical practice. Due to the convenience of weekly dosing and lesser side effects compared to the other dopamine agonist, cabergoline has become the drug of choice for most of the patients. Cabergoline is efficacious and well tolerated and has shown to reduce the prolactin level as well as the pituitary adenoma volume. Cabergoline has a high affinity for 5-hydroxytryptamine receptor 2B (HTR2B) located on heart valves. There is a suggestion that activation of these receptors might lead to mitogenesis and fibroblast proliferation in cardiac valves. Two population-based studies in patients with Parkinson’s disease showed an increased risk of valve regurgitation after treatment with high cumulative dose of pergolide and cabergoline (1,2). This raises serious concerns with respect to the safety of the long-term use of cabergoline in the treatment of prolactinoma.

There were eleven cross-sectional studies, which have been published recently, with a total of 795 patients with prolactinoma (3-13). Five of those studies did not show any association between the treatment with cabergoline and clinically relevant valvular regurgitation during 45-79 months of therapy (3-7). However, the use of cabergoline was associated with an increased prevalence of moderate tricuspid regurgitation in one study (8). Furthermore, the use of cabergoline was associated with increased frequencies of valvular thickening, calcifications and increased mitral tenting area (9). At present, the clinical relevance of these findings is still uncertain, but concern is raised with respect to the safety of the use of cabergoline in the long-term treatment of prolactinomas. There seems to be an individual susceptibility of the HTR2B on cardiac valves for the agonist activity or affinity of cabergoline since polymorphisms of the serotonin

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receptor have been described (14-16). Hence there is a need for assessing the genetic susceptibility of developing clinically relevant valvular disease with cabergoline treatment in our population.

**Objectives**

Our objective was to evaluate the association between use of cabergoline in patients with prolactinoma and risk of developing clinically relevant valvular disease.

**Methodology**

**Study design, setting and study population**

This was a descriptive cross sectional study conducted in the Endocrinology and Pituitary clinics at National Hospital of Sri Lanka. All diagnosed patients with micro and macro prolactinoma who were on medical therapy with cabergoline for more than 24 weeks duration at the date of data collection were included in this study. Age group of this sample was 21 to 54 years.

Diagnosed patients with pre existing congenital valvular heart disease, history of rheumatic heart disease and ischemic heart disease were excluded from the study.

Data collection was carried out for three months starting from 1st of March, 2012. A data sheet was used for data collection and data gathered from clinic records with regard to the following aspects. Age, sex, pre treatment body weight, pre treatment prolactin levels and other hormonal assessment in standard laboratory units (thyroid stimulating hormone, freeT4, serum cortisol, follicular stimulating hormone, luteinizing hormone) were recorded. Diagnosis (macroprolactinoma, microprolactinoma), dose of drug, frequency of administration and duration of therapy were also recorded.

The patients fulfilling the inclusion criteria were investigated with 2D echocardiogram by the same operator (a Senior Registrar in Cardiology), at National Hospital of Sri Lanka. Following aspects were assessed; the presence of valvular regurgitation, the degree of regurgitation (rated in mild, moderate or severe regurgitation according to the recommendations of the American Society of Echocardiography), and the presence of morphological changes such as thickening and/or calcification. Data with regard to post treatment outcome such as post treatment prolactin levels in standard laboratory units and post treatment body weight were gathered.

**Statistical analysis**

Analysis of data was carried out using SPSS 18 version. Mean, median values and standard deviation were estimated for each continuous variable, such as age, body weight, prolactin levels, duration of therapy and cumulative dose; while proportions were estimated for categorical variables. Chi square value was used to compare proportions while Student’s t test was used to compare continuous variables. p<0.05 was considered as the level of significance.

**Results**

From a total of 58 patients, 45 patients (35, 77.7% females) were included in the study. The mean age of the participants was 37.4 (+/- 9.1) years, the mean pre treatment body weight was 62.82 (+/- 12.4) kg and the mean pre treatment prolactin levels were 16074 (+/- 9221) miu/L. The median cumulative dose of cabergoline used was 104mg and the median duration of treatment was 48 months. Twelve patients (26.6%) had mild regurgitation. Twenty four patients received more than the median cumulative dose of 104 mg and the prevalence of valvulopathy was not significantly different (Chi-Squared test; p=0.34) from those receiving less than the median cumulative dose. Similarly 23 patients received treatment longer than the median duration of 48 months and the prevalence of valvulopathy was not significantly different (Chi-square test; p=0.92) from those received less than the median duration (Table 1). The mean post treatment prolactin level was 836 (+/-216) miu/L and the reduction of the prolactin levels from the baseline level due to cabergoline therapy was significant (paired t test; p=0.004).

**Discussion**

We found no clinically significant cardiac valve disease among patients treated with cabergoline for prolactinoma and this is similar to the outcome of previously conducted cross sectional case controlled studies.

Lancellotti and colleagues (9) undertook a reader-blind, cross-sectional study of 102 outpatients who received cabergoline for the treatment of prolactinoma or idiopathic hyperprolactinaemia. The median cumulative dose was 204 mg and the median duration of therapy was 79 months. The frequency of moderate or severe valvular regurgitation did not differ significantly between the treatment and the control groups. Several other studies confirm these findings (3-7). In contrast, Colao and co-workers (8) compared 50 patients receiving a median cumulative dose of cabergoline 280 mg over a median period of 74 months with 50 age and sex-matched healthy controls and 20 untreated patients. The frequency of aortic regurgitation or mitral regurgitation did not differ significantly between the groups in this study. However, the prevalence of tricuspid regurgitation was significantly higher in those receiving more than the median cumulative dose than in those given less than the median cumulative dose.
No link to cardiac valvulopathy was seen in cabergoline treated patients

Table 1. Age category, diagnosis and proportions of valvulopathy in the sample patients

<table>
<thead>
<tr>
<th></th>
<th>Males</th>
<th>Females</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age category (years)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>21-30</td>
<td>2</td>
<td>10</td>
<td>12 (26.6%)</td>
</tr>
<tr>
<td>31-40</td>
<td>4</td>
<td>15</td>
<td>19 (42.2%)</td>
</tr>
<tr>
<td>41-50</td>
<td>3</td>
<td>8</td>
<td>11 (24.4%)</td>
</tr>
<tr>
<td>More than 50</td>
<td>1</td>
<td>2</td>
<td>3 (6.6%)</td>
</tr>
<tr>
<td>Diagnosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Macroprolactinoma</td>
<td>10</td>
<td>15</td>
<td>25 (55.5%)</td>
</tr>
<tr>
<td>Microprolactinoma</td>
<td>0</td>
<td>20</td>
<td>20 (44.5%)</td>
</tr>
<tr>
<td>Presence of valvulopathy</td>
<td>4</td>
<td>8</td>
<td>12 (26.6%)</td>
</tr>
<tr>
<td>MR</td>
<td>3</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>TR</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>PR</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>MR and TR</td>
<td>2</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>MR and PR</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Absence of valvulopathy</td>
<td>6</td>
<td>27</td>
<td>33 (73.3%)</td>
</tr>
</tbody>
</table>


Table 2. Prevalence of valvulopathy with cumulative dose and duration of therapy

<table>
<thead>
<tr>
<th></th>
<th>Valvulopathy</th>
<th>No valvulopathy</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cumulative dose of cabergoline</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Less than median dose</td>
<td>7 (33.3%)</td>
<td>14 (66.7%)</td>
<td>21</td>
</tr>
<tr>
<td>More than median dose</td>
<td>5 (20.8%)</td>
<td>19 (79.2%)</td>
<td>24</td>
</tr>
<tr>
<td>Duration of therapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Less than median duration</td>
<td>6 (27.2%)</td>
<td>16 (72.8%)</td>
<td>22</td>
</tr>
<tr>
<td>Longer than median duration</td>
<td>6 (26.1%)</td>
<td>17 (73.9%)</td>
<td>23</td>
</tr>
</tbody>
</table>

This shows the median cumulative dose (the horizontal line in the box), 25th to 75th percentiles and the range excluding outliers (5 and 34) among patients with and without valvulopathy.

Figure 1. Stem and leaf plot.
Our study showed a prevalence of 26.6% mild valvular regurgitation and there was no significant association with the cumulative dose of cabergoline and the duration of therapy. Small sample size was one of the main limitations of our study and the lack of a baseline (pre treatment) echocardiography was another drawback. However, this does not invalidate our findings and prospective studies with sufficient power are required to investigate the true prevalence of cardiac valve disease related to the modest doses of cabergoline that are normally used in patients with prolactinoma.

References
Vitamin D: what clinicians need to know

Sunil J Wimalawansa


(Index words: auto-immune diseases, supplements, bone mineral density (BMD), fractures, osteomalacia, osteoporosis, rickets)

Abstract

Recent literature on vitamin D is full of controversies regarding its measurement, benefits, diagnosis, and management of its deficiency. In addition to addressing the consequences of deficiency, benefits of its replenishment, and clinical recommendations for supplements, this review addresses extra-skeletal effects of vitamin D. Vitamin D is essential for skeletal health and prevention of falls and injuries. Vitamin D enhances intestinal calcium absorption and mineralization of osteoid tissues. Rickets in children and osteomalacia in adults are classic manifestations of severe vitamin D deficiency. Cohort studies suggest that low 25 hydroxyvitamin D [25(OH)D] affects numerous and diverse physiologic functions, such as control of cell growth including cancer cells, protection against autoimmune disorders, and muscular coordination. Emerging data also suggest that low vitamin D levels may worsen disorders, including cancer, metabolic syndrome, obesity and diabetes, infectious diseases, and autoimmune disorders. Whether increased incidences of these diseases are consequences of widespread vitamin D deficiency is to be determined. Moreover, many reported relationships between vitamin D deficiency and diseases are based on epidemiological observations. Measurement of serum 25(OH)D is the way to evaluate vitamin D status. Serum 25(OH)D levels below 20 ng/mL are considered deficient, whereas optimum levels are between 30 and 50 ng/mL. An additional 1,000 IU of vitamin D per day generally is sufficient for lighter-skinned individuals; elderly, obese, and dark-skinned individuals and other groups of patients may need an additional 2,000 IU or more per day to maintain physiologic serum 25(OH)D levels.

Introduction

The definition of vitamin D deficiency, how and in whom to measure 25-hydroxyvitamin D [25(OH)D], and optimal approaches to vitamin D repletion are topics of controversy. Emerging evidence indicates that vitamin D deficiency may be pandemic (1,2). Vitamin D deficiency (serum levels less than 20 ng/mL) is the most under-diagnosed and perhaps the most common medical condition in the world. It is estimated that about 1.8 billion people worldwide have vitamin D deficiency (3-6). Deficiency and insufficiency (i.e., those with serum vitamin D levels less than 30 ng/mL) are estimated to occur in approximately 3.2 billion, about half of the world’s population.

Vitamin D plays important functions in many tissues, including intestinal absorption of calcium and skeletal development, maintenance, and mineralization. Vitamin D deficiency causes rickets in children and osteomalacia, muscle weakness and falls, osteoporosis, and fractures in adults. Key causes of vitamin D deficiency include less sun exposure, climatic changes, atmospheric pollution (7), lifestyle changes, obesity, and changes in dietetic patterns.

Sensible exposure to sunlight and a better intake of dietary and supplemental vitamin D can prevent this deficiency.

The major function of vitamin D is to regulate the provision of adequate calcium and phosphorus to the body to maintain optimal metabolic functions. In addition, vitamin D has profound effects on the immune system (8), pancreas (9), brain (10), and muscle (3,11). It plays an important role in combating infections such as mycobacterium tuberculosis; viral infections, including influenza (12,13); inflammatory bowel disease (14); preventing muscle weakness and falls and fractures (15); improving fertility and reproductive success (16); and preventing cardiovascular disease, depression, insulin resistance, and certain cancers (17). Direct effects of vitamin D in controlling the cell cycle may be one of the key mechanisms of reduction of cancers (18). Moreover, data suggest that sufficient blood concentrations of vitamin D may reduce excess deaths associated with heart disease (19-20); breast, colon, and prostate cancer (21-22); strokes secondary to hypertension (23); and autoimmune conditions (8). However, most of these data are based on cross-sectional and observational studies and may have confounders, such as drug interactions, sunlight exposure,

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physical activity, intensity of skin pigmentation, variability in measurement of vitamin D, co-morbidities, and overall nutritional status (6).

Prevalence of vitamin D deficiency

A comparison of the National Health and Nutrition Examination Survey (NHANES) 1988-1994 and 2001-2004 databases revealed that the average serum 25(OH)D levels have declined in the United States population. It is likely to be the case in some other countries as well. In the United States, in both genders the prevalence of serum 25(OH)D levels of above 30 ng/mL decreased from 45% to 23% across all ethnic and age groups (1). There is controversy regarding whether declining vitamin D levels are caused by changes in assay methods or standards (24-26), escalating incidence of obesity, or a true decrease in serum vitamin D levels (6). Studies have reported more than 50% of North American women receiving anti-osteoporosis therapies (27) and 88% of women with fractures have serum 25 (OH)D levels below 20 ng/mL (28). Low serum vitamin D levels have a negative effect on the skeleton, being associated with lower bone mineral density (BMD), increased bone turnover, and increased serum parathyroid hormone (PTH) levels, especially when serum 25(OH)D concentrations are less than 20 ng/mL (29-30).

Vitamin D physiology

Types of vitamin D

There are two forms of vitamin D. Ergocalciferol (vitamin D₂) is a plant product. For commercial purposes it is produced by irradiation of yeast or plant sterol ergosterols. Its circulatory half-life is about 8 to 12 days (31). Cholecalciferol (vitamin D₃) is animal-derived, synthesized in the skin, and has a half-life of approximately 25 to 30 days.

Studies have reported that administration of 50,000 IU of D₂ or D₃ produced similar increases in the serum concentration of vitamin D (32). Although both agents produced a similar initial increase in serum 25(OH)D levels, the D₃-treated subjects had additional increases, peaking at day 14 (33). However, when the two forms are administered daily or weekly, equal serum 25(OH)D levels are achieved (34), and thus are considered by some as equivalent (34-35). However, several other studies have reported higher potency of vitamin D₃ compared with D₂ (33,36). Intermittent administration regimens have shown cholecalciferol (D₃) to be twice as potent as ergocalciferol (D₂) in elevating serum 25 (OH)D and modulating serum PTH levels (31). In light of the half-life differences, it seems logical to use D₃ when supplementing at longer intervals. Vitamin D₃ has become the gold standard for vitamin D supplementation (6).

Generation of vitamin D

The synthesis of cholecalciferol, the “sunshine vitamin”, starts with the conversion of 7-dehydrocholesterol (7-DHC) to previtamin D upon photolytic, non-enzymatic reaction after skin exposure to solar ultraviolet-B rays (3). In the skin, this pre-vitamin D₃ isomerizes to vitamin D₃, which has a several-fold higher affinity to the vitamin D-binding protein (DBP), and thus is preferentially transported via the bloodstream from the skin to the liver. In liver parenchymal cells, cytochrome (CYP) P450 enzyme converts it to 25 (OH)D in a substrate-dependent manner. Circulatory 25 (OH)D is bound to DBP and albumin. In a highly regulated process in the proximal renal tubular epithelia, 25 (OH)D is converted to active vitamin D, 1,25-hydroxyvitamin D₃ [1,25 (OH)₂D₃] via C¹-hydroxylation by mitochondrial hydroxylase CYP27B1. This enzyme is stimulated by PTH and inhibited by calcium, phosphorus, and fibroblast growth factor-23 (FGF-23). FGF-23 is primarily produced by osteocytes and osteoblasts. 1,25 (OH)₂D₃ stimulate FGF production (37). Under or over-production of FGF-23 affects vitamin D metabolism and phosphate handling. For example, in patients with chronic kidney disease with elevated FGF-23 contributes to renal bone disease and osteomalacia.
The serum level of 1,25(OH)\(_2\)D is approximately 1,000-fold less than that of 25(OH)D, but active vitamin D has a 1,000-fold higher affinity to the vitamin D receptor (VDR). Figure 1 shows the pathway of generation of 25(OH)D and 25(OH)D in humans.

Interactions of PTH with PTH/PTH-related peptide receptors in the renal tubular epithelial cell membranes increase 1α-hydroxylase (CYP27B1) enzyme activity. Once the serum calcium is normalized, 1α-hydroxylase enzyme, and thus the PTH-1α-hydroxylase axis, is down-regulated. On the other hand, the FGF-23 activates 24-hydroxylase enzyme (38), thus diverting the conversion of vitamin D to a metabolically inactive form, 24,25(OH)D. 1α-hydroxylase enzyme is also present in extra-renal cells, including keratinocytes, monocytes, macrophages, and T- and B-lymphocytes. However, 1α-hydroxylase enzyme in these cells is not regulated by serum calcium.

Figure 2 illustrates the interactions of vitamin D with other biologically active moieties.

**Figure 2. Hormonal control of serum calcium levels:** vitamin D is generated from 7-dehydrocholesterol (7-DHC) in the skin, hydroxylated in the liver to 25(OH)D, and activated into 1,25(OH)D in the renal tubular epithelium by 1α-hydroxylase enzyme. 1α-hydroxylase also occurs in extra-renal tissues and cells, but to a lesser degree. Once the serum calcium is normalized, as a feedback control, the 1α-hydroxylase enzyme and the PTH-1α-hydroxylase axis are down-regulated.

**Vitamin D receptor**

The vitamin D receptor (VDR) is a member of the super family of nuclear hormone receptors located in the cell nuclei and widely distributed in tissues. Classical functions of 1,25(OH)\(_2\)D, such as calcium metabolism, anti-proliferative effects, and immuno modulatory activities are mediated through the VDR (39-40). 1,25(OH)\(_2\)D and VDR interactions modulate a large number of genes that lead to the vitamin’s biological actions (40). 1,25(OH)\(_2\)D is the high-affinity ligand for the VDR in key target tissues that modulates the expression of vitamin D-dependent genes. Ligand binding to the VDR induces its conformational changes and heterodimerization with the retinoid X receptor (9).

1,25(OH)\(_2\)D also elicits non-genotropic effects (39, 41), including rapid activation of protein kinases and modulation of the electrical state of cells. Abnormalities in the VDR or the inability to activate the VDR in the absence of adequate amounts of 1,25(OH)\(_2\)D lead to manifestations of clinical signs and symptoms of vitamin D deficiency.

Data suggest that PTH-mediated bone resorption may require calcium-stimulated, calcium-sensing receptor (CaSR)-mediated osteoclastic activity (42). This suggests interactions of CaSR, vitamin D, and 1α-hydroxylase, modulating bone turnover and skeletal growth. Vitamin D stimulates osteoblast and stromal cell production of receptor activator of nuclear factor kappa-B ligand (RANK-L), a key regulator of osteoclast recruitment and differentiation (43).

**Diagnosis of vitamin D deficiency**

Worldwide, immunological methods are widely used to measure serum vitamin D levels, but liquid chromatography tandem mass-spectrometric assays (LS/MS/MS) are thought to be the most consistent way of measuring vitamin D (44-45). Although the normal serum levels remain a matter of controversy, the diagnosis of vitamin D deficiency usually is confirmed when the measured serum 25(OH)D levels are below 20 ng/mL (50 nmol/L) (Table 1) (30,46). A serum 25(OH)D level of between 20 and 30 ng/mL (50-75 nmol/L) is considered deficient (6), whereas levels below 10 ng/mL (<25 nmol/L) may be associated with signs and symptoms and are considered severe vitamin D deficiency (47-48).

Vitamin D deficiency leads to secondary hyperparathyroidism, stimulation of renal tubular 1α-hydroxylase activity, and increased production of 1,25(OH)\(_2\)D. Consequently, only at very low levels of 25(OH)D do serum 1,25(OH)\(_2\)D levels begin to decline. Thus, measurement of the 1,25(OH)\(_2\)D level should not be used as a marker in the diagnosis of vitamin D deficiency (49).

Serum vitamin D levels below which secondary hyperparathyroidism appear are not agreed upon (50-52). Most studies reported that a 25(OH)D level below 20 ng/mL is associated with adverse skeletal effects (52-53), but others refute this (54-55). Nevertheless, vitamin D supplementation alleviates secondary hyperpara-thyroidism, increases BMD (56), improves muscle function and reduces falls (57), and reduces hip and other osteoporotic fractures (54-55). Consequently, many endocrinologists prefer their patients maintain serum vitamin D levels between 30 and 50 ng/mL (75-125 nmol/L) (35,58,59).
Healthy blood levels of vitamin D

Most reports indicate that the minimum desirable serum 25(OH)D level is between 28 and 32 ng/mL (70-80 nmol/L) (46, 58), but not everyone agrees with this (52). Moreover, these cut-off points may not necessarily apply to all, especially to vulnerable population groups. The 2010 Institute of Medicine (IOM) report on vitamin D suggests 20 ng/mL is adequate for health (52), but most other studies indicate that at least 30 ng/mL is necessary (1,60). In fact, even higher levels have been suggested (35,59). Recent data from two sub-Saharan tribes with dark skin who do not use sunscreen and wear little clothing reported to have mean serum 25(OH)D level of 46 ng/mL (115 nmol/L) (61).

Extra-skeletal disorders, such as autoimmune diseases, obesity, type 2 diabetes, and cancer prevention, may require a higher level of serum vitamin D (48-49,62).

Institute of Medicine (IOM) 2010 report on vitamin D

The IOM report (52) used a population model based on a healthy North American population. The American Endocrine Society recommendations (35,52) are directed at patients (6). IOM recommendation that same dose (600 IU) of vitamin D is adequate across the spectrum of ages, from one-year old and 70-year old is puzzling. Both the IOM and the Endocrine Society reports recommend increasing the safe intake of vitamin D to 4,000 IU/day (35, 52). Serum levels of vitamin D as high as 60 ng/mL are safe, but the long-term safety of levels higher than 60 ng/mL has not been established (48). Nevertheless, some population-based cross-sectional studies, such as NHANES, give some indication of increased all-cause mortality with high serum levels of vitamin D (63-64). However, many other studies report that the higher the serum 25(OH)D level, the lower the morbidity associated with several non-communicable diseases (65-68).

American Endocrine Society Guidelines

The American Endocrine Society guidelines recommend a minimum serum vitamin D level of 30 ng/mL, but to achieve sufficiency, the guidelines suggest aiming for levels between 40 and 60 ng/mL (35). The report states that in individuals who are not at risk, there is no good evidence for population-based screening for vitamin D deficiency. The report also states that vitamin D$_2$ and vitamin D$_3$ are equally satisfactory in treating and preventing vitamin D deficiency (35).

The guidelines recommend two- to three-fold higher doses of vitamin D for obese patients and those who are taking anticonvulsants, glucocorticoids, antifungals, or medications for AIDS. Guideline increased the tolerable upper limit for vitamin D in healthy adults to ~4,000 IU per day and the safe upper limit to 10,000 IU a day (35). The guidelines confirmed the benefits of vitamin D supplementation in fall prevention. However, due to the lack of data from randomized controlled trials (RCT), administering higher-than-recommended amounts of vitamin D to prevent cancer, cardiovascular, or other diseases or to improve quality of life was not recommended (35).

Table 1. Vitamin D status and terminology

<table>
<thead>
<tr>
<th>Status-Terminology</th>
<th>Serum 25(OH)D levels*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ng/mL</td>
</tr>
<tr>
<td>Severe deficiency:</td>
<td>&lt;10</td>
</tr>
<tr>
<td>Leading to rickets in infants and children and osteomalacia in adults</td>
<td></td>
</tr>
<tr>
<td>Deficiency:</td>
<td>10-19</td>
</tr>
<tr>
<td>Inadequate for skeletal and overall health; thought to increase morbidity associated with various illnesses</td>
<td></td>
</tr>
<tr>
<td>Insufficiency:</td>
<td>20-29</td>
</tr>
<tr>
<td>May impair skeletal health and overall health</td>
<td></td>
</tr>
<tr>
<td>Optimal (healthy) range:</td>
<td>30-50</td>
</tr>
<tr>
<td>Intoxication:</td>
<td>&gt;125</td>
</tr>
<tr>
<td>Considered potentially toxic, as indicated by hypercalcemia and hyperphosphatemia, etc.</td>
<td></td>
</tr>
</tbody>
</table>

* Depending upon the country, serum concentrations of 25(OH)D are reported in nanograms per millilitre (ng/mL) or nanomoles per litre (nmol/L) (1 ng/mL = 2.5 nmol/L). One microgram of vitamin D increases circulatory vitamin D by approximately 1 nmol/L (~0.4 ng/mL); 100 IU of vitamin D supplement is expected to increase the serum vitamin D level by 1 ng/mL.
Asian Indians who immigrate to northern Europe have lower serum 25(OH)D levels and a higher incidence of rickets and osteomalacia than do whites (69). In addition to containing little vitamin D, vegetarian diets contain high amounts of phytic acid and fibre, which reduces intestinal calcium and vitamin D absorption. Consequently, in the absence of adequate exposure to sunshine or supplementation, those who consume such diets, particularly vegans, could become vitamin D deficient and malabsorb calcium. Consequently, irrespective of the age, it would be useful to give 2,000 IU/day of vitamin D to vegans (6).

Vitamin D deficiency is highly prevalent among the elderly and institutionalized persons (54,70). In part this is due to insufficient exposure to sunlight; being homebound, institutionalized, or non-ambulatory; avoiding sunlight exposure; an inability to generate vitamin D in the skin; and consumption of certain medications such as anticonvulsants, glucocorticoids, and any medication that enhances the catabolism of vitamin D (71) (Table 2).

Other groups of patients who are vulnerable to vitamin D deficiency include those with gastrointestinal diseases (e.g., celiac disease, malabsorption syndromes), obesity, and disabilities (71,72). Those who have had rapid weight loss, such as after dieting or bariatric surgery, are particularly vulnerable; they require higher doses of vitamin D (73).

Manifestation of vitamin D deficiency

People with prolonged, severe vitamin D deficiency are likely to present with various clinical signs and symptoms of osteomalacia, such as proximal myopathy, pseudo-fractures, and biochemical evidence of raised bone-specific alkaline phosphates (6). Additional symptoms attributable to vitamin D deficiency include lethargy, increased incidence and severity of infections, and exacerbation of chronic non-communicable diseases, immunological disorders including rheumatoid arthritis and multiple sclerosis, and musculo-skeletal issues such as low backache and bone pain, muscle aches, and inability to lose weight (74).

Improving vitamin D status is a highly cost-effective, modifiable risk factor for reducing falls and fractures (75,76). Except for an isolated or poorly designed study, most clinical studies have reported a positive effect of vitamin D supplementation on falls and fracture reduction. In one study, 500,000 IU of cholecalciferol was administered annually, with a slight increase in falls and fractures recorded in the treated group (77). However, the mean serum 25(OH)D levels achieved in the vitamin D-treated group were below 30 ng/mL for at least 6 months of the year. There is a large fluctuation of the post-dosing peak and the end-of-the-year trough of serum 25(OH)D levels. Such levels and rapid changes are unphysiological and may be harmful (78,79). Moreover, vitamin D supple-

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Table 2. Key risk factors for development of vitamin D deficiency

<table>
<thead>
<tr>
<th>Risk factors for development of vitamin D deficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asian Indians who immigrate to northern Europe have lower serum 25(OH)D levels and a higher incidence of rickets and osteomalacia than do whites (69). In addition to containing little vitamin D, vegetarian diets contain high amounts of phytic acid and fibre, which reduces intestinal calcium and vitamin D absorption. Consequently, in the absence of adequate exposure to sunshine or supplementation, those who consume such diets, particularly vegans, could become vitamin D deficient and malabsorb calcium. Consequently, irrespective of the age, it would be useful to give 2,000 IU/day of vitamin D to vegans (6).</td>
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<tr>
<td>Vitamin D deficiency is highly prevalent among the elderly and institutionalized persons (54,70). In part this is due to insufficient exposure to sunlight; being homebound, institutionalized, or non-ambulatory; avoiding sunlight exposure; an inability to generate vitamin D in the skin; and consumption of certain medications such as anticonvulsants, glucocorticoids, and any medication that enhances the catabolism of vitamin D (71) (Table 2).</td>
</tr>
<tr>
<td>Other groups of patients who are vulnerable to vitamin D deficiency include those with gastrointestinal diseases (e.g., celiac disease, malabsorption syndromes), obesity, and disabilities (71,72). Those who have had rapid weight loss, such as after dieting or bariatric surgery, are particularly vulnerable; they require higher doses of vitamin D (73).</td>
</tr>
<tr>
<td>Manifestation of vitamin D deficiency</td>
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<tr>
<td>People with prolonged, severe vitamin D deficiency are likely to present with various clinical signs and symptoms of osteomalacia, such as proximal myopathy, pseudo-fractures, and biochemical evidence of raised bone-specific alkaline phosphates (6). Additional symptoms attributable to vitamin D deficiency include lethargy, increased incidence and severity of infections, and exacerbation of chronic non-communicable diseases, immunological disorders including rheumatoid arthritis and multiple sclerosis, and musculo-skeletal issues such as low backache and bone pain, muscle aches, and inability to lose weight (74).</td>
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Vitamin D, muscle function, and falls

Vitamin D is necessary for calcium transport and the actin-myosin interaction (80). Vitamin D receptors are present on the fast-twitch muscle fibres, which are the first to respond in a fall. Lower serum 25(OH)D levels are associated not only with sarcopenia and proximal muscle weakness, but also with loss of type II muscle fibres (81). Those with 25(OH)D levels less than 10 ng/mL (25 nmol/L) are twice as likely to have sarcopenia and muscle weakness (82-87). Moreover, serum vitamin D levels below 20 ng/mL (50 nmol/L) are associated with increased body sway and decreased muscle strength (15) and significant increased risk for falls (88). Clinical studies that used more than 800 IU vitamin D supplementation, with or without calcium, has shown improvement in muscle strength and balance (75,89) and physical performance.

The exact mechanism of action in neuromuscular coordination and the fall reduction with vitamin D supplementation needs additional studies, but improvements in muscle functions, balance, mobility, and reflexes have been implicated (15,81,90). Taking these data together, it is rational and cost-effective to initiate programs for routine vitamin D supplementation for residents in nursing homes, long-term care facilities, and developmental disability centres, and also for most elders even without measurement of serum 25(OH)D levels.

Vitamin D, balance, and fall risk reduction

Many studies have reported that vitamin D supplementation significantly reduces falls (55,76,91,92). Approximately 30% of individuals older than 65 years fall at least once each year; approximately 0.5% of these falls result in a fracture. Frequency of falls increases with age, and falls lead to injuries and death (93), especially in those with low serum 25(OH)D levels (94). Thus, fall and injury prevention should be a key component of managing these vulnerable patients and our elderly population.

In a residential set-up, the number of patients needed to be treated with vitamin D to prevent major fractures is about 25 patients per year (6). Management of a hip fracture costs on average $40,000, whereas the cost of vitamin D therapy for a patient per year is approximately $10. Thus, no intervention is more cost-effective in these patient populations than the provision of adequate vitamin D supplements.

Several meta-analyses reported that vitamin D supplementation significantly improves mobility and reduces the risk of falls (57,88) in the ambulatory elderly (76,81,88) and among institutionalized elderly (88,90). Nevertheless, one needs to be cautious in drawing conclusions from some of these meta-analyses because the same sets of data have been used repeatedly (54-55, 75-76,95-101). It is also noteworthy that some studies have reported no correlations between vitamin D supplementation and reduction of falls (77,102).

A meta-analysis of eight randomized trials involving 2,426 older patients demonstrated that daily treatment with between 700 and 1,000 IU of vitamin D lowered the risk for falling by 19% (95). Another meta-analysis has reported 46% reduction of falls after dietary calcium and vitamin D supplementation in ambulatory older women and 65% reduction in less active women (103). Thus, improving vitamin D status is an important modifiable risk factor for reducing falls and fractures. However, because the half-life of vitamin D is in days, administration of vitamin D at
intervals of more than a month or two, is unlikely to be effective and should not be practised.

Muscle weakness and muscular incoordination may be the most important risk factors for falls and consequent fractures that can be corrected with vitamin D supplements (6). Vitamin D supplementation is an inexpensive, well-tolerated, and cost-effective strategy for reducing falls and injuries in older adults and should be incorporated into the clinical practice by those who provide care for the elderly. Nevertheless, to make the treatment effective, attention should be given to other factors contributing to falls, including correction of vision and hearing, improving home safety, and minimizing environmental hazards and so forth that leads to falls. Thus, all osteoporosis and fracture-prevention programs should incorporate these.

Vitamin D and skeletal health

Vitamin D is necessary for the bone mineralization and skeletal health (104); thus, vitamin D deficiency could lead to osteomalacia and also contribute to osteoporosis. Vitamin D deficiency is also associated with reduced calcium absorption (105), bone loss (106), increased bone turnover (71,72), osteoporosis (107), and increased risk of falls and fracture (108,109). Moreover, in the absence of adequate intakes of calcium and vitamin D, none of the potent anti-osteoporosis medications would work; in fact they can be harmful.

Although osteoporosis and osteomalacia can coexist, especially in vulnerable populations such as institutionalized patients with high incidence of vitamin D deficiency, low BMD as measured by dual energy x-ray absorptiometry (DXA) is often only considered as osteoporosis (48). Thus, osteoporosis treatment focuses primarily on anti-osteoporosis therapy, instead of offering inexpensive and effective solutions, such as healthy lifestyle changes, weight-bearing exercises, and calcium and vitamin D supplements. Calcium and vitamin D therapy in such patients could significantly increase their BMD (60) and also prevent fractures (48). The current data suggest that the threshold levels of 1,25(OH)\(_2\)D necessary for beneficial non-skeletal effects seem to be higher than that required for stimulation of intestinal absorption of calcium and release of calcium from bone (110,111).

Vitamin D and fractures

Several epidemiologic studies have reported inverse associations between serum vitamin D levels and fractures (112). Studies also reported that vitamin D sufficiency is associated with a low incidence of fractures (55). The Women’s Health Initiative study suggested that every 10-ng/mL decrease in serum vitamin D levels doubles the risk of hip fractures, especially when the levels are below 30 ng/mL (109). W

A meta-analysis that consisted of five RCTs (n=9,294) of hip fractures and seven RCTs (n=9,820) of non-vertebral fractures with oral vitamin D, with or without calcium, also reported a significant reduction of fractures (55). Vitamin D doses in excess of 700 to 800 IU/day reduced the risk of hip and non-vertebral fractures by 26% compared with calcium alone or placebo, whereas 400 IU/day failed to prevent fractures (Medline and Cochrane Controlled Register [1960-2005] and EMBASE [1991-2005]) (55). Although some studies have suggested that the threshold for fracture reduction is approximately 20 ng/ml (113-114), other studies reported a lack of effect of calcium and vitamin D on fracture reduction (115-121). Nevertheless, these studies have used less-than-optimum doses of supplementary vitamin D (on average, 400 IU/day), had small sample size, were of shorter duration, and/or administered the vitamin too infrequently (77, 117, 122).

A Cochrane review reported that vitamin D, reduced hip fractures but may not reduce other fractures (99); the reason is unclear. Analysis of eight clinical trials revealed a significant reduction in hip fractures in those who received both vitamin D and calcium. Overall, the Cochrane review suggests higher doses of vitamin D are more effective and the provision of calcium with vitamin D could be helpful. Most studies have examined the relationship between the supplemented vitamin D doses and falls and fractures (88,93,96,99). Only a few studies have examined the relationships between serum levels of vitamin D needed or achieved and the reduction in falls or fractures (96,100,101); more such RCT studies are needed.

Sources of vitamin D

Vitamin D from sunlight: To produce enough vitamin D, a fair-skinned person needs an exposure of 25% of the body surface to sunlight for approximately 15 to 20 minutes, four to six times a week. After sun exposure, the peak serum 25(OH)D level is reached in about 7 to 14 days, but the mean levels achieved in individuals are highly variable (6).

Calcium and vitamin D from the diet: High quantities of vitamin D are found naturally only in a few foods, including fatty fish and irradiated mushrooms (6). In some countries, certain foods, such as milk, yogurt, orange juice, margarine, infant formula, and breakfast cereals, are fortified with vitamin D. Some calcium supplements and multivitamins also contain small amounts of vitamin D. Most generic multivitamin tablets contain between 200 and 400 IU of vitamin D and 200 to 600 mg of calcium. However, the recent preparations of multivitamins contain 1,000 IU of vitamin D. For most patients, calcium supplementation of more than 500 to 800 mg a day is not necessary (i.e., total daily calcium intake [diet + supplements] is recommended to be less than 1,500 mg) (http://www.asbmr.org).
Guidance for vitamin D supplementation

Measurement of serum 25(OH)D levels provides the diagnosis of vitamin D deficiency, but additional information, such as renal function, serum calcium, and PTH, is helpful for understanding the deficiency. The measurement of 24-hour urine calcium is also helpful in identifying calcium conservation or wasting status that is associated with hypovitaminosis D or hypercalcemia. The use of artificial ultraviolet-B irradiation and lamps to increase serum vitamin D levels has been explored in short-term studies (123-125), but the long-term safety of such therapies is not established.

Children, pregnant women, institutionalized patients, obese patients and those who have experienced rapid weight loss, gastric bypass patients, those taking anti-epileptic drugs, those living in northern latitudes during winter months, people with darker skin who live in northern latitudes, and those who avoid sunlight should be considered for vitamin D supplementation (3,48). An intermediate group at high risk that also should be treated with vitamin D includes patients with celiac disease, inflammatory bowel syndrome, cystic fibrosis, recurrent infections, chronic liver and kidney disease, and those receiving antiretroviral or long-term glucocorticoid therapy (6,48).

A peak serum 25(OH)D level is achieved between 2 and 3 days after an oral dose of 50,000 IU of vitamin D. The treatment goal is to achieve serum 25(OH)D levels above 30 ng/mL. Recent reports recommend keeping the serum vitamin D levels between 30 and 40 ng/mL (30,35,59). Most patients with vitamin D deficiency require therapeutic doses of vitamin D given over several weeks to bring their serum vitamin D levels above 30 ng/mL, followed with maintenance doses between 1,000 and 2,000 IU a day. Thus, where facilities are available, it is recommended to measure serum 25(OH)D levels approximately 3 to 4 months after the therapeutic course of vitamin D supplementation to assess the adequacy and necessity of additional interventions.

Vitamin D deficiency in primary hyperparathyroidism

Vitamin D deficiency occurs more frequently in patients with primary hyperparathyroidism (PHPT) than in the general population (126-131). Primary hyperparathyroidism should be considered in patients who do not normalize serum PTH levels after correction of vitamin D deficiency (126); however, in some patients, these two disorders may co-exist (132). Therefore, the measurement of serum 25(OH)D levels is essential in all hyperparathyroid patients. Some patients with secondary hyperparathyroidism may take 4 to 6 months to normalize serum PTH levels. Approximately 65% of patients with PHPT have serum vitamin D levels below 25 ng/mL (126-128,130-131). In many of these patients, serum PTH levels will decrease once the vitamin D deficiency is corrected, especially in those with secondary hyperparathyroidism (130), whereas in others it may take a few months to achieve (6).

The current practice and the recommendations of vitamin D supplementation for PHPT are based on the following: (1) high prevalence of vitamin D deficiency in patients with PHPT; (2) vitamin D inadequacy worsens the clinical picture of PHPT; (3) in some patients with PHPT, vitamin D deficiency can mask hypercalcemia and thus obscure the diagnosis; and (4) in patients with PHPT and vitamin D deficiency, vitamin D replacement is safe and only rarely increases serum calcium levels (6).

Normalization of vitamin D in hyperparathyroidism

In patients with PHPT, it is advisable to treat vitamin D insufficiency cautiously to avoid hypercalcemia (133,134), especially in patients with markedly elevated serum calcium levels because vitamin D therapy may worsen hypercalcemia. In patients with PHPT, the goal is to maintain serum vitamin D levels around 25 ng/mL (62 nmol/L) (6). Replacement therapy is discontinued or the dose is lowered once the serum vitamin D level reaches the target level. To prevent exacerbation of hypercalcemia and hyper-calcuria, monitoring of serum and urine calcium levels in PHPT patients receiving vitamin D therapy is suggested (132,135-138). In most patients with PHPT, although serum PTH may decrease a bit, there are no significant increases in serum calcium levels after normalization of serum vitamin D.

It is relatively common to find high serum PTH levels with normal or low-normal serum calcium levels in patients with osteoporosis (132,135-140). In this setting, measurement and appropriate replacement of vitamin D (132) facilitate making the right diagnosis: (A) Secondary hyperparathyroidism: PTH values will return to the normal range with replenishment of vitamin D, whereas calcium levels remain within the normal limits (141); (B) Concomitant PHT and vitamin D deficiency: PHPT-associated hypercalcemia may be masked by co-existing vitamin D deficiency. Thus, vitamin D supplementation may uncover biochemical hypercalcemia with persistent elevation of serum PTH levels (126); or (C) Normocalcemic hyperparathyroidism, characterized by high serum PTH but normal plasma calcium in the presence of normal serum vitamin D levels (135,141).

Extra skeletal effects of vitamin D

Vitamin D has beneficial effects on a variety of tissues and in disorders. Recent epidemiological and observational studies and data from in vitro and in vivo animal studies reveal that vitamin D has a wide range of physiological actions. However, many conditions that are aggravated by vitamin D deficiency unfortunately are labelled as “age-related” morbidities and thus go undiagnosed. These include sarcopenia, falls, overactive bladder, swallowing dysfunction, decreased lung function, macular degeneration, and decline in cognitive functions (6).

Properly designed randomized studies in the future could clarify cause-and-effect relationships of low vitamin
Vitamin D deficiency may also aggravate a host of clinical conditions that impair the health of the individual, including increased susceptibility to bacterial and viral infections, osteoporosis, increased risk of falls and fractures, increased risk of cancers, cardiovascular disease, obesity, type 2 diabetes, oral and gum disease, and autoimmune diseases. Figure 3 illustrates complex interactions between vitamin D and various organ systems.

Vitamin D supplementation

Following are three easy and practical regimens of administering therapeutic doses of vitamin D: (A) When the serum vitamin D level is below 10 ng/mL, administer 50,000 IU three times a week; for a serum level between 11 and 20 ng/mL, administer 50,000 IU twice a week; and for a serum level between 21 and 29 ng/mL, administer 50,000 IU once a week, for eight weeks. (B) Administer a varying single loading dose of vitamin D (e.g., 300,000), followed by 50,000 IU once or twice a week until serum vitamin D levels increase above 30 ng/mL. (C) Administer an extra 100 IU of vitamin D daily for each nanogram per millilitre (2.5 nmol/L) decrement of 25 (OH)D below 30 ng/mL. The latter regimen without the administration of therapeutic doses likely will take several months to normalize serum vitamin D levels.

In most patients who are younger than 65 years, serum vitamin D levels can be maintained in the normal range using 1,000 IU/day. However, for those older than 65 years, higher doses such as 2,000 IU a day or 10,000 IU once or twice a week, or 50,000 IU of vitamin D once a month may be required (149). In the absence of a maintenance dose, serum vitamin D levels will revert to their baseline levels in most patients within months. Certain at-risk individuals, including those who are obese, have had bariatric surgery, have malabsorption syndromes, or are taking medications that affect vitamin D catabolism, should be given higher-than-usually-accepted doses, followed by a higher maintenance doses of 3,000 to 5,000 IU per day or 50,000 IU several times a month (35).

Safety and adverse effects

Because of depletion of vitamin D stores in the body, low-dose daily regimens generally take several months to normalize serum vitamin D levels. However, the use of upfront loading doses or therapeutic doses such as 50,000 IU once or twice a week for a few weeks will bring the serum 25 (OH)D levels to the normal range within weeks, and the patients have early symptomatic improvements. When considering deficits of vitamin D that are in the range of 1 million IU or more in a given patient, there is no reason to be apprehensive about prescribing therapeutic doses of non-activated parental vitamin D for short periods.

Some studies have shown vitamin D dosages as high as 10,000 IU daily (150) for 6 months are safe (79,150). Acute signs and symptoms of vitamin D toxicity mirror those of hypercalcemia: headache, irritability, metallic taste, nephrocalcinosis, vascular calcinosis, renal impairments, pancreatitis, dehydration, nausea, and vomiting. Because of the potential for the development of hypercalcemia and hypercalciuria, vitamin D supplementation should be used cautiously in patients with PHPT, granulomatous diseases, metastatic bone disease, sarcoidosis, and Williams’ syndrome (30,151).

Compared to vitamin D, its metabolites are much expensive and associated with greater than 5,000-fold higher incidence of adverse effects. Thus, there is no rational in prescribing any activated forms of vitamin in D or its metabolites, including 1α products or 1,25 (OH)₂D (calcitriol) for patients with osteoporosis. These agents should be reserved for the management of patients with (A) chronic kidney disease and (B) hypoparathyroidism, to maintain their serum calcium at physiological levels. However, there are independent beneficial effects of vitamin D and 1α hydroxylated metabolites including 1,25...
(OH)_2D in the body. Therefore, to maintain optimal health, patients with chronic kidney disease require both parental vitamin D (any over the counter preparation) and activated vitamin D, 1,25(OH)_2D at appropriate doses. Figure 4 illustrates the activation of the natural and synthetic forms of vitamin D.

![Figure 4. The process of activation of vitamin D cascade for natural (dermal derived and dietary) as well as synthetic 1α vitamin D compounds.](image)

**Recommendations**

Sunlight exposure often is limited by lifestyle, but obtaining enough vitamin D from the diet alone is difficult. Thus, many adults require vitamin D supplementation, generally between 1,000 and 2,000 IU a day. The IOM report was aimed at public health use and the conclusions made are based on healthy individuals and thus are not applicable to patients (52). The IOM recommendations should not be considered for patient care, whereas the American Endocrine Society recommendations are clinically relevant (35).

The introduction of a national policy to routinely supplement adequate amounts of vitamin D to vulnerable populations, such as those with CKD and those living in nursing homes or disability centres, would reduce falls and fractures, and decrease morbidities and deaths with a minimal cost. Considering the variability of assays and the cost of measurement of serum vitamin D, the high safety margin of supplementation, and the high incidence of vitamin D deficiency, it is rational to recommend routinely supplementing these vulnerable groups with 50,000 IU vitamin D3 once or twice a month. This would cost approximately $10 to $15 per patient per year. Supplementing once or twice a month is also more economical and practical than giving daily supplements. Even if this regimen reduces at least one fracture per institution per year, it is would be cost-effective.

Although the excitement over the positive health benefits of vitamin D seems warranted, caution has been urged, in part because of inadequate RCTs. Meanwhile, only a few small clinical trials reported to date used different doses of vitamin D, correlated any outcome associated with the serum vitamin D levels achieved, or attempted to correlate such valuable data with skeletal and extra-skeletal diseases. Nevertheless, available data and observations to date strongly support the role of vitamin D in promoting a variety of health indices, prevention of falls, and good skeletal health (3,152-153).

**Conclusions**

Vitamin D plays a critical role in skeletal health, and its deficiency is associated with increased falls and fractures. In addition to regulating number of clinically important genes and calcium and phosphate homeostasis, vitamin D is involved in the regulation of immunity and cell growth and influences a wide array of common diseases, including cancers, cardiovascular disease, autoimmune conditions, and infections. Hypotheses-driven, adequately powered, well-designed, outcome-based, dose-ranging randomized controlled clinical trials leading to firm conclusions are necessary. Recycling data with multiple meta-analyses will not advance the vitamin D field. Overall data support that the use of recommended doses of vitamin D is highly cost-effective with no adverse effects. Thus, good quality vitamin D supplements (but not active vitamin D metabolites) should be offered to our patients.

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Clinical update


Abstract

Improved survival following childhood malignancy has led to increased recognition of a multitude of late adverse effects in long term survivors, which affect their quality of life. Endocrine complications are among the commonest late effects seen and include dysfunction of the hypothalamo pituitary axis leading to impaired growth, abnormal puberty or hypopituitarism, gonadal dysfunction and infertility, thyroid gland dysfunction and neoplasms, obesity, impaired glucose homeostasis and abnormal bone development. Long term follow up is needed for early recognition and timely intervention to minimise the effects of these complications.

Introduction

The last few decades have seen a tremendous improvement in the survival of children affected by malignancy. The overall survival rate for childhood malignancy now exceeds 80% (1). However, cure has not come without a price. It is being increasingly recognised that survivors of childhood cancer go on to develop a multitude of complications during long term follow up. Among these complications, endocrine consequences are possibly the commonest encountered, affecting up to 50% of this population (2,3). Survivors of central nervous system tumours and those exposed to radiotherapy and high dose alkylating agents are especially at risk of developing endocrine related complications in later life. Endocrine late effects adversely affect the quality of life because of interference with normal growth and development and psychological adjustment. However, many of these problems can be minimised by early detection and appropriate interventions (4).

Hypothalamic-pituitary axis

Pituitary hormone deficiencies can occur in children with pituitary and suprasellar tumours, those undergoing cranial irradiation for other intracranial malignancies, those exposed to radiation therapy for orbital and nasopharyngeal tumours and those undergoing total body irradiation as preconditioning for bone marrow transplant.

The effects of cranial irradiation depend upon age at irradiation, dose, fractionation schedule and duration after therapy. Growth hormone deficiency (GHD) is the most common and often the only hormonal deficiency observed, followed by gonadotropin, ACTH and finally TSH deficiency (2), due to differing radio sensitivity of the different hormone synthetic pathways. Lower radiation doses are associated with later onset of GHD (3). Retardation of linear growth is a relatively common phenomenon in childhood cancer survivors. This can be caused by endocrine causes such as growth hormone deficiency and hypothyroidism, particularly in those with cranial tumours and those exposed to cranial irradiation. Other factors contributing to growth retardation include spinal irradiation and use of high doses of exogenous corticosteroids. Therefore it is recommended that the height, weight and BMI of these children are monitored every six months until growth is completed, and annually thereafter (4).

Growth hormone deficiency (GHD) following cranial irradiation usually manifests only 2 years or more after exposure. Lower doses of radiotherapy are associated with later onset of GHD. Height below the 3rd percentile or a drop of ≥2 percentile rankings on the growth chart or a growth velocity <4-5 cm/year during childhood are possible indicators of GHD. Assessing the bone age is important in such children, and those with a significantly delayed bone age should undergo further evaluation. However a possible pitfall may occur if a child exposed to irradiation develops both precocious puberty and GHD, where the pubertal growth spurt by sex hormones may initially mask the GHD, but compromise the final adult height even further.

In children diagnosed with GHD, GH therapy should be considered. Even though existing evidence indicates that GH therapy in these children does not increase tumour recurrence, prudence would dictate waiting for one year after completion of tumour therapy with no clinical or radiological evidence of further growth before initiating GH therapy (5). As the risk of relapse is greatest within the first 2 years from primary treatment, it is common to delay initiation of GH therapy for 2 years (6).
The effect of growth hormone therapy on final height and change in height SDS are sub optimal in cancer survivors. Possible reasons for this include exposure to spinal irradiation, early puberty, inadequate schedules and delay in initiating therapy (2). There is an argument for combining treatment with a GnRH analog and GH to maximize growth potential in those with concurrent early onset puberty, and evidence to suggest that this is beneficial (5). However, this decision has to be individualised based on the patient's needs as well as height potential and tempo of puberty.

Puberty and, gonadal and reproductive function

Children exposed to cranial irradiation are more prone to develop central precocious puberty, presumably due to disruptive effects on the inhibitory pathways on the hypothalamus (3). While girls are more susceptible than boys at lower doses of radiation (18-24 Gy), both boys and girls are similarly prone to early onset puberty at higher doses (30-50 Gy) (6). Early puberty may be followed several years later by gonadotropin deficiency. Conversely, higher doses of radiation can cause delayed puberty due to hypogonadotrophic hypogonadism.

Gonadal dysfunction can occur in survivors of childhood cancer, due to gonadotropin deficiency or direct damage to the gonads by radiotherapy and chemotherapy. Gonadal dysfunction may manifest as delayed or arrested puberty, hypogonadism, oligosperma, azoospermia or infertility in males and as delayed/arrested puberty, primary or secondary amenorrhea, infertility or premature menopause in females.

The common chemotherapeutic agents associated with gonadal dysfunction include alkylating agents such as Busulfan, Cyclophosphamide and Ifosfamide and heavy metals such as Cisplatin and Carboplatin (7). Gonadal damage can also be caused by pelvic, abdominal, testicular, spinal or total body irradiation.

Periodic evaluation for pubertal onset and tempo, annual evaluation of Tanner staging until sexually mature and screening with baseline FSH, LH together with oestradiol in girls at age 13 and testosterone in boys at age 14 and in those with delayed puberty and features of sex hormone deficiency is recommended. In adulthood evaluation for menstrual and sexual dysfunction and infertility is necessary (7).

Preservation of fertility should be considered in patients undergoing treatment modalities with high risk of infertility. In sexually mature males, cryopreservation of spermatozoa is possible. In young sexually mature females with partners, the collection of mature oocytes for fertilization and subsequent embryo cryopreservation is an established option. Cryopreservation of oocytes is an alternative but is less successful. The options for preserving fertility in pre-pubertal children remain experimental.

Thyroid dysfunction

Primary hypothyroidism following irradiation is the commonest encountered thyroid disorder in childhood cancer survivors, and can be seen in those exposed to neck, cranio-spinal or total body irradiation (3). Although less common, hyperthyroidism and thyroid neoplasia are also associated with radiotherapy.

Children undergoing total thyroidectomy for differentiated thyroid malignancy require lifelong thyroxine replacement therapy to maintain a clinically euthyroid state with serum T4 and T3 in the near normal range, while suppressing TSH to <0.1 μU/mL in most cases and to undetectable concentrations in children with extensive disease.

Body composition and glucose homeostasis

Those children with brain tumours and those receiving cranial radiotherapy are more prone to obesity and the metabolic syndrome secondary to hypothalamic damage. This propensity is also seen in those exposed to high dose prolonged corticosteroid therapy. Annual monitoring of BMI and blood pressure and two yearly measurements of fasting blood glucose and fasting lipid profile is recommended (7).

Reduced bone mineral density is recognised especially in those who received methotrexate, cyclosporine, tacrolimus, long term high dose corticosteroids and radiotherapy as well as growth hormone deficient individuals. Baseline screening with Dual energy x-ray absorptiometry is recommended for those at risk (7).

Impaired glucose tolerance is usually seen as a transient phenomenon in those receiving glucocorticoids and asparaginase, but permanent diabetes mellitus is also described following asparaginase therapy (2).

Importance of long term surveillance/ follow up

The endocrine late effects of cancer therapy often evolve over time. They may cause a significant effect on quality of life of cancer survivors. These ill effects may be remediable with timely interventions. It is essential that survivors receive appropriate education and screening so that late effects can be recognized at their earliest, most treatable stage. A multidisciplinary approach is often necessary (4,8).

The Children’s Oncology Group Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancers is a useful clinical practice guideline intended to promote earlier detection of and intervention for complications that may potentially arise as a result of treatment for paediatric malignancies (7).
Endocrine late effects in paediatric cancer survivors

They are intended for use beginning 2 or more years following the completion of cancer therapy.

A well planned and coordinated long term follow up service for childhood cancer survivors involving paediatric and adult oncologists, endocrinologists, neurologists and community physicians is an increasingly felt and timely need in our country.

References

Pharmacological advances in the management of osteoporosis

Noel P Somasundaram¹, M S A Cooray²


Abstract

Osteoporosis is a worldwide health problem with a high prevalence. Agents for the treatment of osteoporosis are classified as antiresorptives, anabolic agents and drugs with combined anabolic and anti-resorptive actions.

Although many drugs with proven efficacy are available for the treatment of osteoporosis their effectiveness has been limited by side-effects, concurrent comorbidities, and inadequate long-term compliance. Additionally, conventional antiresorptives such as aminobisphosphonates profoundly suppress bone resorption and formation which might contribute to the pathogenesis of osteonecrosis of the jaw.

Various novel antiresorptive agents are in development. This overview aims to discuss in brief some of the most promising novel treatments which include: bazedoxifene a new selective estrogen receptor modulator, denosumab, PTH rP (parathyroid hormone related protein), odanacatib and other bone anabolic agents such antibodies against sclerostin and dickkopf-1.

Denosumab, a fully human monoclonal antibody to receptor activator of nuclear factor kappa B ligand (RANKL) an anti-resorptive agent with a low side effect profile has been proven efficacious. Bazedoxifene has also proven its efficacy. Odanacatib, an inhibitor of cathepsin K, which is an osteoclast enzyme required for resorption of bone matrix is under assessment as an anti-resorptive agent with no anti-anabolic effects and is showing promising results.

Anabolic agents act by stimulating formation of new bone. Novel agents in development include: antibodies to sclerostin and dickkopf-1, proteins that target molecules involved in Wnt signaling, a pathway that regulates gene transcription of proteins that are important for osteoblast function; an antagonist to the calcium-sensing receptor; and an activin receptor fusion protein, which functions as an activin antagonist and has shown promise as an anabolic agent in early human trials.

Introduction

Osteoporosis, the most common metabolic bone disease, is characterized by low bone mineral density (BMD) and microarchitectural deterioration of bone tissue consequently leading to an increase in the susceptibility to fragility fractures. The problem of osteoporosis has become so important due to the ageing population (1). Currently, every third postmenopausal woman and every fifth man older than 50 years suffer from osteoporosis. In a cross-sectional survey of a group of 1642 community-dwelling postmenopausal women in seven provinces in Sri Lanka using peripheral dual-energy X-ray absorptiometry revealed that 736 women (44.9%) were likely to have osteoporosis (2). A similar study reported 5.8% prevalence of osteoporosis among men older than 50 years in Sri Lanka (3).

Bone is a dynamic tissue, which has the ability to adapt its shape and size in response to mechanical loads through constant osteoclastic resorption of damaged bone followed by osteoblast-mediated deposition and mineralization of new matrix. Bone strength, ie, resistance to fracture, depends not only on bone mass, but also on its spatial distribution and the intrinsic properties of the materials that constitute the bone (1). The main aim of treatment of osteoporosis is to reduce the bone fracture risk as far as possible. Although it is not possible to eliminate the entire risk for fractures, currently available medications can substantially reduce that risk. Even small increases in bone mass can substantially reduce the incidence of fracture.

Anti-osteoporosis drugs can be classified on the basis of their action on bone remodeling. Antiresorptive drugs decrease bone resorption and reduce fractures by preserving skeletal microarchitecture. Anabolic drugs on the other hand, reduce fractures by enhancing remodeling. In addition to increasing BMD, they appear to repair bone microarchitecture and improve bone geometry. There are also drugs that decouple the two processes, inhibiting bone resorption and stimulating bone formation (Table 1).

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Important issues and limitations with regards to some of the currently used drugs

Three different aminobisphosphonates (alendronate, risedronate, and zoledronate), teriparatide, strontium ranelate, and hormone replacement therapy have been shown to be effective against both vertebral and nonvertebral fractures. Evidence of efficacy against vertebral fractures is available for ibandronate (an aminobisphosphonate), raloxifene, and PTH 1-84 (1). Unfortunately despite effective therapies, because of patients’ unwillingness to take current therapies or inability to tolerate the therapies, many patients remain untreated.

Bisphosphonates

They are well established, widely used, first line treatment agents to treat osteoporosis, and they act via the inhibition of osteoclasts, leading to reduced bone turnover, increased bone mass, and improved mineralization (5). Bisphosphonates can be given orally or intravenously, and relatively inexpensive and used across a broad spectrum of osteoporosis types, including postmenopausal, male, and steroid-induced osteoporosis, as well as Paget’s disease.

Recent evidence have raised some important issues

- In addition to inhibiting osteoclasts, bisphosphonates (specifically alendronate) may also promote osteoblast proliferation and maturation (4,6).
- Alendronate and zoledronate by binding strongly to the bone matrix and becoming internalized within bone suppresses bone resorption continuously (even after treatment cessation) – this has lead to recent concerns of detrimental changes to bone quality and accumulation of damage (5).

Strontium ranelate

It is a bone-seeking agent capable of increasing bone formation and reducing bone resorption, thereby uncoupling and rebalancing bone turnover in favor of bone formation (7). Although trials have proven efficacy against vertebral and non-vertebral fractures over 5 years in women with postmenopausal osteoporosis no studies have been performed on strontium ranelate efficacy on men (8-9).

Parathormone

Both the full-length parathyroid hormone (PTH 1-84) and its N-terminal fragment, teriparatide (PTH 1-34) are bone-anabolic drugs targeting osteoblasts and are potent stimulators of bone formation that restore bone to an osteopenic skeleton when administered intermittently. They have the potential to increase bone mass and reduce fracture risk dramatically. Currently, the only anabolic agent approved by the FDA for the treatment of osteoporosis in the United States is teriparatide, a 1-34 amino acid fragment of human parathyroid hormone (PTH 1-34). In Europe, a full-length PTH (1-84) molecule also is approved for therapy.

A limitation of PTH is the need for daily subcutaneous administration. Therefore, alternative delivery systems, such as oral, transdermal, and intranasal, have been tested. A recent study comparing the transdermal daily administration of teriparatide verses subcutaneous administration demonstrated a good bioavailability and an increase in vertebral BMD comparable with subcutaneous teriparatide (10,11). Although teriparatide has revolutionized the

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<td>Uncoupling agent</td>
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<td>Teriparatide</td>
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Notes: ↑ increase; ↓ decrease; ↑↑ or ↓↓ strong increase or decrease, respectively. Adapted from International Journal of Clinical Rheumatology, June 2011, Vol. 6, No. 3, Pages 359-369.

Abbreviations: OB, osteoblast; OC, osteoclast; NV, nonvertebral; PTH, parathyroid hormone; V, vertebral.
management of osteoporosis there have been some issues of concern (13-15):

- despite bone mass increase the new bone is less mineralized.
- the protective action of teriparatide on BMD vanishes with time in both genders (but not up to the baseline values) in contrast to bisphosphonates, the effect of which persists for many months after drug withdrawal
- concurrent therapy with antiresorptive therapy, particularly bisphosphonates, has to be avoided
- higher cost
- hypercalcemia – which is associated with increases in osteoclast-driven bone resorption.
- side-effects such as nausea, flushing and muscle cramping.
- the induction of osteosarcoma in a rat model of carcinogenicity (12).

Thus teriparatide therapy is not recommended for more than 2 years, and contraindicated in patients at increased risk of osteosarcoma (these include Paget disease of bone, open epiphyses, a history of irradiation involving the skeleton, or an unexplained elevation of alkaline phosphatase level of skeletal origin).

Although concurrent treatment is not recommended it has been demonstrated that sequential treatment with antiresorptives after teriparatide or PTH prevents accelerated osteoclastic resorption of the new bone tissue built during teriparatide therapy, increases mineralization, and rapidly lowers cortical porosity; leading to further increases in BMD (15).

**Estrogens and selective estrogen receptor modulators (SERM)**

These have effects not only on bone metabolism, but also on the breast, endometrium, and lipid metabolism. Proven effects of SERM on bone density and metabolic bone markers have been generally more modest than that seen with bisphosphonates. In the Multiple Outcomes of Raloxifene Evaluation (MORE) trial, although vertebral fractures were decreased by 37% after four years of raloxifene, a reduction in non-vertebral fractures was not seen (16). Adverse events such as increase in hot flushes and a 3-fold increase in venous thromboembolic events are associated with use of raloxifene.

**New therapies**

Management of osteoporosis is challenging and research continues to design a drug that is not only safe and cost-effective but also with the following characteristics:

- Reduce fracture risk without long-term deleterious effects on the skeleton or other side effects
- Effects of the drug cease with cessation of therapy
- Inhibit bone resorption without inhibiting bone formation

Anabolic agents can target signals increasing the osteoblastic cellular pool or the function of the mature cell. Because of their potential to increase bone mass, extensive research is being carried out in this area. Although emphasis is being placed in the development of new anabolic agents, new antiresorptive agents are being pursued with the hope to develop therapies with good efficacy, tolerability, and simplicity of administration. This overview aims to discuss some of the most promising novel treatments which include:

**Anti-resorptive therapies**

- Bazedoxifene
- Denosumab
- Odanacatib

**Bone anabolic agents**

- Antibodies against the proteins sclerostin and dickkopf-1.
- PTH rP (Parathyroid Hormone related protein)

**Bazedoxifene (BZA)**

Bazedoxifene is a novel third-generation selective estrogen receptor modulator, a molecule developed to act as estrogen receptor agonists in some tissues (eg. bone) and as estrogen receptor antagonists in others, such as breast and endometrium, in order to reduce the risk of breast and endometrial cancers that would be induced by hormone replacement therapy (17-19).

Two large Phase III clinical trials have shown that bazedoxifene increased BMD, decreased levels of bone turnover markers, and significantly reduced the risk of new vertebral fractures in postmenopausal women compared with placebo (17,18). Although the incidence of nonvertebral fractures with bazedoxifene or raloxifene did not differ significantly from that with placebo, a post hoc analysis of a subgroup of women at higher fracture risk revealed that bazedoxifene significantly reduced the nonvertebral fracture risk relative to placebo and raloxifene. There was no evidence of endometrial and breast stimulation in studies. Bazedoxifene use is associated with an improvement in the lipid profile (reduction in the serum concentrations of total cholesterol and low-density lipoprotein cholesterol, with an increase in the serum level of high-density lipoprotein cho-sterol). The incidence of vasodilatation (hot flushes), leg cramps, and venous thromboembolic events were significantly higher with bazedoxifene compared with placebo.
Tissue selective estrogen complex (TSEC)

TSEC is a novel therapy, partnering a selective estrogen receptor modulator (SERM) with one or more estrogens. Based on the favorable effects of bazedoxifene on the breast and endometrium, pairing of bazedoxifene with conjugated estrogens is done for the treatment of menopausal symptoms and prevention of postmenopausal osteoporosis. The pairing of bazedoxifene with conjugated estrogens (CE) has been evaluated in the Selective Estrogens, Menopause, And Response to Therapy (SMART) phase 3 trials and overall, BZA/CE has been shown to be effective in relieving menopausal symptoms and treating osteoporosis while maintaining endometrial and breast safety (1,17).

Although bazedoxifene is a promising new therapy for patients with osteoporosis, further clinical investigations of long-term treatment with this selective estrogen receptor modulator are needed to evaluate the prevention of osteoporotic fractures, breast cancers, endometrial cancers, and cardiovascular events (17).

Denosumab

Denosumab a human monoclonal antibody to RANKL (receptor activator of KB ligand) is a promising new drug for the prevention and treatment of postmenopausal osteoporosis. It has been approved by the Food and Drug Administration (FDA) and European Medicines Agency for the treatment of:

- postmenopausal osteoporosis in women at high risk of fracture.
- bone loss associated with androgen deprivation therapy in men with prostate cancer.

It may be particularly useful in clinical practice for the treatment of patients who have failed or are intolerant to other available osteoporosis therapy, eg. patients with gastrointestinal contraindications, side effects with oral bisphosphonates, or malabsorption. Denosumab has also shown promising skeletal effects in the treatment of cancer and rheumatoid arthritis (20,21). Denosumab 60 mg is given subcutaneously every six months and is simple to administer and well tolerated.

Mechanism of action

The principal regulator of bone resorption is the RANKL/RANK/osteoprotegerin pathway. RANKL is a transmembrane and soluble protein that is highly expressed by osteoblasts; its receptor, RANK, is located on the cell membrane of osteoclasts and preosteoclasts (22,23). RANKL-RANK binding stimulates the formation, activity, and survival of osteoclasts, resulting in increased bone resorption.

Osteoprotegerin (OPG) is a naturally occurring, endogenous regulator “decoy receptor” of the RANKL-RANK pathway. By binding to RANKL and preventing its interaction with RANK, OPG inhibits osteoclast formation, activity and survival thereby reducing bone resorption (24-26). Denosumab acts like osteoprotegerin, diminishing osteoclast activity by binding to RANKL with high affinity and specificity and blocking the interaction of RANKL with RANK (22).

Denosumab in postmenopausal osteoporosis

The FREEDOM (Fracture Reduction Evaluation of Denosumab in Osteoporosis Every 6 Months) is the largest and most important trial of four Phase III studies in testing denosumab in postmenopausal women. In this 3 year trial, 7868 women aged 60-90 years with a bone density T score < -2.5 in the lumbar spine or total hip were randomized to receive either denosumab 60 mg or placebo by subcutaneous injection every six months for three years (27). There was a statistically significant (68%) relative risk reduction and an almost 5% absolute risk reduction in the primary outcome which was a new vertebral fracture diagnosed by spine x-ray. There was a reduction in clinical vertebral fractures as well as non-vertebral fractures and bone mineral density increased relative to the placebo group by 9.2% (spine) and 6% (total hip). Bone turnover markers reflecting both osteoclastic and osteoblastic activity were suppressed by denosumab compared with placebo (20,28).

In DEFEND (Denosumab Fortifies Bone Density), a Phase III trial evaluating the efficacy and safety of denosumab in postmenopausal women with low bone mass (osteopenia), denosumab significantly increased BMD at lumbar spine compared with placebo at 24 months as well as at total hip, distal one-third radius, and total body (28). DECIDE (Determining Efficacy: Comparison of Initiating Denosumab Versus Alendronate) and STAND (Study of Transitioning from Alendronate to Denosumab) both 1-year Phase III trials in postmenopausal women with osteopenia/osteoporosis which compared denosumab 60 mg every 6 months with oral alendronate 70 mg weekly revealed a significantly greater BMD increase with...
denosumab compared with alendronate at total hip and all other measured skeletal sites at 12 months (20,25,28). Discontinuing denosumab (at a dose of 210 mg) after 24 months resulted in a decrease in BMD in the following year comparable to the gains in BMD with 24 months of therapy. Denosumab has a declining residual effect over 1 year, a period called offset time.

**Denosumab in androgen deprivation therapy (ADT)**

Patients with prostate cancer on ADT have a higher risk for fracture, as high as 20% over five years, despite having a good overall survival outlook (29-32). Although effective, adherence to weekly or even monthly oral bisphosphonate has been unsatisfactory in these patients. Thus yearly intravenous zoledronic acid is the preferred agent. Denosumab is also attractive because it can be given subcutaneously at every other administration of ADT therapy, which is usually a gonadotropin hormone-releasing hormone analog provided every three months (33,34).

**Important characteristics of denosumab therapy in comparison to bisphosphonates** (26,27,35):

1. Convenient biannual subcutaneous administration that could translate into improved long-term adherence.
2. Reversibility, because it targets RANKL and not incorporated into the bone mineral thus yielding a much shorter terminal half-life (26). Thus for the patient who has a side effect from therapy, denosumab will be no longer active six months after the last dose and will be an advantage. On the other hand, if patients are not receiving denosumab regularly, the patient's fracture risk might increase after the dose “wears off” (27).
3. Inhibits both osteoclastogenesis and osteoclast activation. These actions at different levels of osteoclast cell-biology could explain why bone biopsy samples from patients treated with denosumab have no osteoclasts in more than 50% of samples (20).
4. Lack of gastrointestinal side-effects.
5. May worsen hypocalcemia in patients with severe renal impairment (creatinine clearance <30 mL/min) or on chronic haemodialysis (21).
6. Cleared by nonrenal metabolism – bisphosphonates are cleared by the kidney and contraindicated in patients with renal insufficiency. Denosumab may prove to be a safe drug in these patients, although studies that directly address this issue need to be done.
7. Serious skin infections, as well as infections of the abdomen, urinary tract, and ear, are more frequent in patients treated with denosumab. Epidermal and dermal adverse events (eg. dermatitis, eczema, and rashes) occurred at a significantly higher rate in the denosumab group compared to the placebo group in the FREEDOM trial (28).
8. The FREEDOM trial reported no cases of osteonecrosis of the jaw (ONJ) in either denosumab or placebo group (28). Although this may be an advantage over bisphosphonates patients should be monitored for consequences, including ONJ, atypical fractures, and delayed fracture healing as the effect of long-term treatment are unknown (20,21).

**Odanacatib**

Odanacatib is currently the most advanced inhibitor of cathepsin K under clinical investigation. It is orally available and effective in a once-weekly 50 mg dose (36). Cathepsins are lysosomal proteases that belong to the papain-like cysteine protease family. Out of the eleven different types that have been described (B, C, F, H, K, L, O, S, V, X, and W), cathepsin K (being a key lysosomal enzyme of the mature activated osteoclast) is the most important with respect to bone remodeling, since it is a protease with intense collagenase activity. It is predominantly expressed in osteoclasts and degrades the two main types of collagen I and II. It is essential to dissolve calcic hydroxyapatite, the main mineral component of bone with respect to acid pH and is an attractive target for selective inhibition to reduce bone resorption (37-39).

**Important characteristics of cathepsin K inhibitors** (36, 40):

- Cathepsin K inhibition has shown a quality that is not present among other classes of antiresorptive agents in that it has resulted in greater suppression of bone resorption than bone formation, suggesting a dissociation between bone resorption and bone formation. This is due to preservation of osteoclast viability despite suppressed osteoclast function. These effects might allow osteoclast-to-osteoblast signalling that maintains bone formation while suppressing bone resorption. These uncoupling effects of odanacatib contrast with other antiresorptive drugs such as bisphosphonates and denosumab, which enhance osteoclast apoptosis.
- The onset and resolution for the antiresorptive effect of cathepsin K inhibitors is rapid. While a rapid resolution of effect might be preferable if there are concerns about side effects with prolonged exposure, it could also increase the risk of fracture shortly after discontinuation of treatment. This becomes particularly important in clinical practice where intended and unintended interruptions in therapy, including noncompliance, are very common.
Phase I and II studies conducted in postmenopausal women showed odanacatib to be safe and well tolerated. After 5 years, women who received ODN 50 mg weekly showed significant BMD increases from baseline of 11.9% at the lumbar spine, 9.8% at the femoral neck, 10.9% at the hip trochanter, and 8.5% at the total hip. A low antiresorptive activity with only slightly reduced bone-specific alkaline phosphatase was maintained through 5 years of treatment. In women who switched from ODN to placebo after 2 years, bone turnover markers reverted to baseline levels after 12 months off medication. Adverse experiences in the ODN-treated group were not significantly different from the placebo group. However, there is yet no fracture data for ODN. Three Phase III studies with ODN are ongoing, two in postmenopausal women and one in men to assess its safety, efficacy and effects on fracture risk (41-43). The results of the BMD efficacy and safety of odanacatib in postmenopausal women trial, a clinical, randomized, double-blind trial with 16,716 patients, are expected in the latter half of 2012 (43).

Parathyroid hormone-related protein (PTHrP)

PTHrP is a naturally occurring polypeptide that is closely related to PTH and activates the same receptor as PTH (PTH1-34). It is expressed in many tissues, but is found in high levels at the growth plate, in osteoblasts and within mammary tissues. It was initially identified as the circulating cause of hypercalcemia of malignancy after being cloned from cancer cells. Although originally thought to be a potent stimulator of bone resorption and hence hypercalcemia, experimental studies using intermittent PTHrP have shown that it has significantly similar anabolic properties to PTH1-34 (44-46).

Unlike PTH, which is a mixed anabolic and catabolic agent, PTHrP displays features suggesting that it may be a pure anabolic agent when intermittently administered. Studies have shown that short-term, high-dose treatment with PTHrP has yielded encouraging results (44,45). A study done by Horwitz MJ showed that intermittent PTHrP was administered safely and without serious adverse events in subjects receiving 500 and 625 microg/d for 3 wk. Subjects receiving 750 microg/d developed mild hypercalcemia (44). Bone turnover markers suggested that even at the highest doses, daily sc PTHrP may not activate bone resorption, i.e. may be purely anabolic. Interestingly, when hypercalcemia occurred, it may have resulted not from bone resorption but from activation of intestinal calcium absorption by 1,25 dihydroxyvitamin D. Thus, human PTHrP (1-36) is one of the promising drugs for treatment of osteoporosis. However, the long-term safety and fracture efficacy will only be determined by a large Phase III clinical trial (46).

Calcilytic drugs

These act as antagonists of the Calcium Sensing Receptor (CaSR) and mimic hypocalcaemia, thus evoking a short pulse of PTH secretion which translates into a bone-anabolic effect. The mechanisms responsible for the anabolic effect of the calcilytic agent in bone have not been reported, but it is likely that they are analogous to those of PTH. This hormone has mitogenic properties for cells of the osteoblastic lineage and increases the synthesis of IGF I by osteoblasts, resulting in an increase in bone collagen synthesis and bone formation (47). Calcilytics are given orally and obviate the need for injections, as opposed to PTH treatment. Currently newer calcilytic drugs with an improved pharmacological profile are being assessed. The most advanced compound of this class is MK-5442, which is currently in phase-2 trials for postmenopausal osteoporosis (47,48).

Sotatercept

An antagonist to the calcium-sensing receptor and an activin receptor fusion protein, which functions as an activin antagonist, have shown promise as anabolic agents in early human trials. Sotatercept, a soluble activin receptor type 2A IgG-Fc fusion protein is being extensively evaluated in preclinical studies, in particular in models of cancer- and osteoporosis-related bone loss. In a phase I clinical trial in postmenopausal females, sotatercept increased hematocrit levels, and, in a phase II trial in patients with multiple myeloma, a trend toward improvement in osteolytic lesions as well as antitumor activity was observed (48).

Inhibitors of Wnt antagonists and antibody therapies

Wnts constitute a family of proteins important in cell differentiation. The Wnt/β-catenin signaling pathway plays a critical role in osteoblastic the differentiation of mesenchymal cells toward mature osteoblasts and bone formation (49). Secreted Wnt antagonists include sclerostin and Dickkopf (Dkk-1).

Antiscerostin antibodies – Sclerostin, the product of the sst gene, inhibits osteoblastogenesis. Humanized monoclonal antibodies to sclerostin cause enhanced Wnt signaling. Phase I study in humans demonstrated that antiscerostin antibodies can increase BMD and biochemical markers of bone formation in humans. Phase II study is currently under way to assess the impact of a humanized antiscerostin antibody on BMD in postmenopausal women with low BMD (49).

Dkk-1 antibodies – Dkk-1 functions as an inhibitor of Wnt signaling and could be a potential therapeutic target for osteoporosis. Dkk-1 neutralization causes an increase
in BMD, trabecular bone volume, osteoblast surface, and bone formation in rodents, suggesting that Dkk-1, like sclerostin, neutralization could be pursued as an anabolic approach in the treatment of osteoporosis, but no studies in humans have been reported (50).

The downside is that indiscriminate Wnt activation could result in unwanted side effects and possible tumorigenicity in nonskeletal tissues. Activating mutations of the Wnt signaling pathway are associated with colorectal cancer, hepatocellular carcinoma, and other malignancies (51).

**Other anabolic agents under investigation**

- Glucagon-like peptide 2 – prevents the nocturnal rise in bone resorption without affecting bone formation.
- Insulinlike growth factor 1 (IGF-1) – enhances the differentiated function of osteoblasts and bone formation (52).

**Conclusion**

Improved understanding of the molecular and cellular regulators and mediators of bone remodeling has lead to the identification of new targets for therapeutic intervention of osteoporosis. Denosumab, a fully human monoclonal antibody to Receptor Activator of Nuclear factor Kappa B ligand (RANKL), an anti-resorptive agent inhibits bone resorption and is approved for the treatment of women with postmenopausal osteoporosis at high risk of fractures. An inhibitor of cathepsin K, odanacatib, is in phase III clinical trials for the treatment of postmenopausal osteoporosis; it decreases bone resorption while seeming to suppress bone formation less than other antiresorptive agents (53).

Anabolic therapies are also fast developing. Investigational monoclonal antibodies to sclerostin have osteoanabolic properties with the potential to improve clinical outcomes in patients with osteoporosis (54).

PTHrP remains a potentially important future anabolic treatment for osteoporosis, particularly if this agent increases bone formation more than bone resorption.

Novel interventions that target newly recognized regulators of bone remodeling are promising agents for the treatment of osteoporosis and it is invariable that the number of available agents for the treatment of osteoporosis will dramatically increase in the coming years.

Multiple novel anti-osteoporotic compounds are in advanced clinical trials and are proving to be efficacious, convenient as well as with lesser side effect profile. However, long term clinical data will be needed before they are approved for clinical use.

**References**


Clinical update


Primary hyperparathyroidism – a diagnostic approach

S Pathmanathan¹, Noel P Somasundaram²


Abstract

Primary hyperparathyroidism (PHPT) is characterized by the autonomous production of parathyroid hormone (PTH), in which there is hypercalcemia or normal-high serum calcium levels, in the presence of elevated or inappropriately normal serum PTH concentrations. Diagnosis of PHPT is biochemical. Advances in imaging technology, intraoperative parathyroid hormone measurement, and surgical technique now allow parathyroidectomy to be performed using a focused approach without the absolute need of a four-gland exploration. This brief review summarizes the various diagnostic modalities available for successful preoperative localization and management of the modern day PHPT patient.

Introduction

Primary hyperparathyroidism (PHPT) occurs as a result of increased and uncontrolled secretion of parathyroid hormone because of hyperfunction of one or more parathyroid glands. The cause of hyperfunction of parathyroid glands is, in the majority of cases, an adenoma/multiple adenomata, followed by hyperplasia in 1 to 15% of patients, and carcinoma only in 1 to 2% of cases. Adenomas may be found in ectopic locations in about 16% of cases – commonly the thymus, tracheoesophageal groove, mediastinum and the thyroid. The frequency of primary hyperparathyroidism is 1-4/1000 individuals in the general population (1,2). Women are twice as likely to be affected as men, and the commonest age of presentation in between 50 and 60 years of age (3).

With increased detection by means of routine calcium screening, the clinical profile of primary hyperparathyroidism in Western countries has shifted from a symptomatic disease, characterized by hypercalcemic symptoms, nephrolithiasis, overt bone disease, and neuromuscular symptoms to one with subtle or no specific symptoms (“asymptomatic” primary hyperparathyroidism) (2,3,4). In the developing world, the symptomatic variant still dominates (6). In our part of the world where serum calcium is not measured as part of the routine screening, PHPT must always be evaluated in patients with clinical histories of nephrolithiasis, nephrocalcinosis, osseous pain, subperiosteal resorption, and pathologic fractures, as well as in those with age inappropriate osteoporosis-osteopenia on dual-energy X-ray absorptiometry (DXA) (6,7). Evaluation may be also useful in patients with resistant dyspepsia or chronic vague gastrointestinal symptoms.

Diagnosis of primary hyperparathyroidism

Laboratory diagnosis

The diagnosis of hyperparathyroidism is usually first suspected because of the finding of an elevated serum calcium concentration. If hypercalcemia is confirmed on a repeat sample, the serum parathyroid hormone (PTH) concentration should then be measured. The diagnosis of primary hyperparathyroidism is usually made by finding a frankly elevated PTH concentration or one that is within the normal range but inappropriately elevated given the patient’s hypercalcemia. A 24-hour urine calcium measurement is necessary to rule out familial hypocalciuric hypercalcaemia (FHH). Other laboratory findings include mild hyperchloremic acidosis, hypophosphatemia, increased alkaline phosphatase and mild-to-moderate increase in urinary calcium and inorganic phosphorus excretion rate (1,2,3,7).

Parathyroid hormone (PTH)

Parathyroid hormone (PTH) is a single-chain polypeptide containing 84 amino acids. It exerts its effects through the interaction of its first 34 amino acids with the type 1 PTH/PTHrP receptor (PTH1). PTH has a plasma half-life of two to four minutes. PTH undergoes proteolysis to yield N-terminal fragments and longer lived C-terminal and mid region fragments. The N-terminal fragment contains the region that confers bioactivity. Generally less than 5 to 25% of total immunoreactive PTH is intact hormone. The remaining 75 to 95% is inactive midregion/carboxyl fragments. The first generation assays included the whole PTH molecule. Second generation assays (intact PTH) measure the active PTH (35-84), which is actually the fragment of PTH present in highest amounts in blood.
and also PTH (7-84) as well. In most people, this fragment is present in much lower amounts than PTH (1-84), so this is not a concern. In kidney failure, a common setting for measuring PTH levels, PTH (7-84) levels increase compared to PTH (1-84), and sometimes over half of what is measured as PTH represents this N-terminal truncated fragment. To overcome this problem the newer 3rd generation (Bio-intact PTH (BI-PTH)) assays has come into practice (8).

BI-PTH by chemiluminescence eliminates interference from inactive PTH fragments, specifically the 7-84 PTH fragments and offers improved sensitivity and specificity to diagnose secondary hyperparathyroid disease in individuals with early and end-stage renal disease. There is no overall difference between second- and third-generation assays for the diagnostic evaluation of PHPT; however, both of these newer generation assays represent an improvement over the first-generation PTH assay (8).

**Problems in the diagnosis of PHPT**

**Familial hypocalciuric hypercalcaemia**

Familial hypocalciuric hypercalcaemia (FHH) is a rare disorder that can also present with hypercalcaemia and mildly elevated or inappropriately normal PTH levels, and as a result it must be carefully distinguished from PHPT. FHH is autosomal dominant in inheritance and in the majority of cases is due to a heterozygous mutation in the calcium-sensing receptor (CaSR) gene, the main regulator of parathyroid cell response to calcium. The diagnosis of heterozygous FHH is confirmed by the measurement of the calcium/creatinine clearance ratio (Ca/Cr). In FHH the Ca/Cr clearance ratio is usually less than 0.01. In pHPT the Ca/Cr clearance ratio is typically greater than 0.02 (9).

**Normocalcemic hyperparathyroidism**

Hypercalcaemia is not always present in all patients with PHPT. For some patients the serum calcium may be at the upper end of the normal range in association with inappropriate elevation of the PTH. This condition is called normocalcemic or subclinical HPT. Two observational studies of normocalcemic PHPT have shown that 19% will go on to develop classic primary hyperparathyroidism. However, 40% developed evidence of disease progression with development of kidney stones, fractures, marked hypercalciuria or >10% decline in BMD. In the differential diagnosis of patients with normocalcemia and elevation of PTH, potential causes of secondary hyperparathyroidism should also be ruled out. Thus, the possibilities of renal insufficiency, vitamin D deficiency or hypercalciuria must be evaluated. If vitamin D deficiency is suspected a trial of calcium and vitamin D supplements can markedly reduce PTH levels and may preclude unnecessary surgery (10).

**Preoperative localization**

Localization techniques were originally used primarily to search for ectopic parathyroid tissue in patients with recurrent or persistent hyperparathyroidism after unsuccessful neck exploration. Currently, with the increased popularity of minimally invasive surgery, parathyroid localization is required to determine whether or not patients are candidates for this approach. It is important to emphasize, however, that preoperative localization studies are only performed to help plan the operative approach. They should not be used to diagnose or confirm the diagnosis of primary hyperparathyroidism. Localization studies should therefore be reserved for patients in whom the biochemical diagnosis of primary hyperparathyroidism is secure. Localization of abnormal parathyroid glands preoperatively can reduce operative time, postoperative morbidity and the requirement for repeat surgery. Imaging techniques for localizing abnormal parathyroid glands and guiding in surgical management include bone densitometry, high resolution ultrasonography (USG), CT, MRI and the radionuclide imaging. Plain skeletal radiography is not routinely recommended in the diagnosis except in resource poor settings where they can favour the diagnosis (11,12).

**Imaging techniques**

**Bone densitometry and plain skeletal radiography**

PTH has a catabolic effect on cortical bone, and sites enriched in cortical bone are preferentially reduced. Most patients have reduced bone mineral density at the distal third of the forearm with relative preservation at the lumbar spine and intermediate values at the hip. Plain radiographic findings include resorption and sclerosis of the middle phalanges of the index and middle fingers (primarily on the radial aspect), phalangeal tufts (acro-osteolysis), the lamina dura around the teeth, the medial aspect of the tibia, the humerus, the femur, and the distal clavicle. In cases of severe primary hyperparathyroidism, skeletal radiographs show pathognomonic changes such as salt-and-pepper degramulation in the skull and brown tumours of the cortical bones. Common sites include the mandible, clavicle, ribs, pelvis, and femur. Plain skeletal radiography is not routinely recommended except in very severe cases (11,12).
Primary hyperparathyroidism

High resolution USG

High resolution USG is one of the most common imaging methods used for neck evaluation and it is practically the first option in the primary hyperparathyroidism assessment. On USG, parathyroid adenoma is seen typically as round or oval homogenous, hypoechoic nodule localized behind the thyroid gland and at the lower aspect of paratracheal or paraeosophageal region. It is clearly separated from thyroid gland due to its capsule. Morphological differences such as hyperechoic component, cystic changes and calcification may be seen particularly in large adenomas. More than 90% of parathyroid adenomas include intraparenchymal hypervascular pattern in the color flow imaging (8).

Ultrasonography offers the advantage of depicting potential concomitant thyroid disease, which is present in approximately 40% of patients with parathyroid disease. Ultrasonography is approximately 75% sensitive in identifying adenomas, but this technique has low sensitivity in identifying ectopic lesions (13).

CT

Standard CT scanning has inadequate sensitivity. Newer techniques of CT scanning with dynamic contrast images (4D-CT) have shown promise, with accuracy rates as high as 88%. One of the advantages of CT over USG is its ability to determine particularly ectopic parathyroid adenomas in the mediastinum (13,14).

MRI

Sensitivity of MR in the determination of parathyroid adenoma varies between 65-80%. On T1-weighted images, adenomas appear as low-signal-intensity masses, whereas intermediate or high signal intensity is seen on T2-weighted images. MRI can be useful, particularly in cases of recurrent or persistent disease and in ectopic locations such as the mediastinum (13,15).

Radionuclide imaging of the parathyroid glands

Parathyroid scintigraphy remains an important tool for guiding clinical and surgical decisions. Sestamibi with 99mTc is the most commonly used radiotracer for imaging the parathyroid glands and has been extensively studied in the setting of primary hyperparathyroidism. Sestamibi is taken up by both the thyroid and parathyroid glands. It clears from the thyroid with a half-life of about 30 minutes but is usually retained by abnormal parathyroid glands. In dual-phase planar imaging, the thyroid and parathyroid glands are imaged at 5 minutes after tracer injection; images are repeated at 2 hours. Initial images will show both thyroid and parathyroid tissue whereas on delayed images, an abnormal parathyroid is seen as a persistent focus of activity. The scan’s sensitivity for detecting solitary adenomas has varied widely in the literature but generally is reported as 60-90%. The main weakness of this test is in diagnosing multiglandular disease. In this case, sensitivity drops to approximately 50%. When combined with single-photon emission computed tomography (SPECT) scanning, it can be used effectively to localize parathyroid adenomas. The scan can include the mediastinum and, thus, is extremely useful in cases of an ectopic adenoma or previously failed surgical exploration. Various studies have shown that 99mTc-sestamibi and 99mTc-tetrofosmin have equal sensitivity for the localization of abnormal parathyroid glands (15,16). Dual-tracer subtraction scintigraphy combines dual-phase 99mTc-tetrofosmin with administration of a second radiopharmaceutical that accumulates specifically in the thyroid gland and not in the parathyroid tissue; images are then subtracted to allow detection of focal uptakes specific for abnormal parathyroid tissue. This study is not found to be superior to 99mTc- sestamibi or 99mTc-tetrofosmin scanning (17). In Sri Lanka 99mTc-tetrofosmin scanning is available in the government sector whereas 99mTc-Sestamibi scans are available in the private sector which would cost about 24,000 LKR (Figure 2).

Figure 2. Sestamibi scan showing right parathyroid adenoma.
Selective venous sampling of the parathyroids

Selective venous sampling and PTH measurements are performed to determine the general location of a parathyroid adenoma. A parathyroid arteriogram should be performed first because it serves as a guide or road map to the more variable parathyroid venous pathways. An end-hole catheter without side holes should be used to prevent the mixing of blood from adjacent veins. Sampling of small veins is the goal. After each sample is obtained, a small amount of contrast material is injected, and a spot image is obtained to document the location of the catheter tip and sampling site. Lastly, a peripheral vein sample is obtained. A 2-fold gradient between the PTH concentration in the sampled vein and that of the peripheral vein is considered to be diagnostic. With modifications, this technique has also been used during surgery to confirm success in removing the source of increased PTH production. The sensitivity of parathyroid venous sampling is 70-80% (18,19).

Parathyroid fine-needle aspiration (FNA) with parathyroid hormone washout

Ultrasound guided parathyroid fine needle aspiration was first described by Doppman et al in 1983. It became more frequently used during the late 1990s and today it is a novel, reproducible, and highly successful method of preoperative localization suitable for focused parathyroidectomy. This technique is almost restricted to reoperative patients. In a reoperative setting when scarring, distortion of anatomic landmarks, and a higher number of ectopic parathyroid glands in this subgroup make another intervention more difficult, correct localization is pivotal. It allows identification of parathyroid adenoma via a minimally invasive approach, especially in cases where a sestamibi scan is inconclusive. FNA is performed under USG or CT guidance followed by a washout procedure using isotonic saline. Then the blood tinged fluid is submitted for PTH assay. PTH >1,000 pg/ml in the needle-washing fluid is considered positive. With newer techniques different institutions are using different cutoff values. So these values need to be revalidated in future. This procedure has a sensitivity and specificity of 91%-100%. The main limitation of parathyroid FNA with PTH washout are its dependence on identification of a suspicious lesion by USG or CT and the number of false negative results (20).

Intraoperative PTH (IOPTH) monitoring

PTH monitoring takes advantage of the short half-life (three to five minutes) of PTH and utilizes a rapid immunochemiluminescence assay technique that allows measurements while the patient is still in the operating room. A drop in rapid PTH levels of greater than 50% at 10 minutes after excision of hyperfunctioning tissue is predictive of postoperative normocalcemia in patients with hyperparathyroidism. Patients with no drop in intraoperative PTH levels have generally remained hypercalcemic immediately after surgery. Numerous studies have shown that rapid intraoperative PTH testing, in the setting of primary hyperparathyroidism, is accurate in predicting surgical success. Cure rates of >95% have been reported in several studies. However, several so-called false-negative results have been reported where a delayed (up to 30 minutes) drop in PTH levels has occurred and there have been complete cure. In addition, rapid PTH levels may initially rise within the first few minutes after excision of a hyperfunctioning gland, possibly because of manipulation of parathyroid tissue with augmented systemic release of PTH into the bloodstream before excision (21).

Rapid IOPTH monitoring is particularly useful in reoperative parathyroidectomy. Combined use of the rapid PTH assay with preoperative Sestamibi localization may prevent unwanted dissection of previously operated patients who have recurrent or uncured disease. The ability of the rapid PTH assay to detect the presence of multiglandular parathyroid hyperplasia is unclear. Some studies have suggested that IOPTH levels will typically fall in a sequential manner as each of the hyperfunctioning glands is removed. IOPTH monitoring is extremely costly even in the best centers and it is not available in Sri Lanka.

Conclusion

Diagnosis of PHPT is straight forward. Preoperative localization is not necessary in the traditional four gland exploration. Preoperative localization studies are only performed to help plan the operative approach and they should not be used to diagnose or confirm the diagnosis of primary hyperparathyroidism. Ultrasonography and Sestamibi scanning are used commonly. The optimal preoperative localization technique is best decided on local availability in consultation with an experienced surgeon or who has done a large number of parathyroid surgeries.

References

Primary hyperparathyroidism


Grave’s orbitopathy – an approach to clinical evaluation and management

T W N Karunasena¹, M W S Niranjala²


Abstract

Grave’s orbitopathy (GO), is a potentially sight threatening condition which constitutes a major clinical and therapeutic challenge and occurs in about 50% of patients with Grave’s disease with only 3-5% cases posing threat to sight. This autoimmune condition is mediated via cytokines secreted by T lymphocytes infiltrating in to the orbital cavity and thyrotropin receptor antibodies (TRAbs) stimulating thyrotropin receptors (TSHR). Clinical assessment for disease activity and severity in GO is important for decision making in management of both hyperthyroidism and GO. Sight threatening GO should be identified promptly and treated with high dose intravenous (IV) glucocorticoids and/or orbital decompression.

Introduction

Grave’s ophthalmopathy also called Grave’s orbitopathy, is a potentially sight threatening condition which constitutes a major clinical and therapeutic challenge. It is often mild and self-limiting and probably declining in frequency, with only 3-5% of cases posing a threat to sight (1). Subtle ocular changes of GO occurs in almost all patients with Grave’s disease, with clinically recognizable disease only in 50% and 20-30% will have significant ocular disease which needs treatment (4). Its onset may precede or follow the onset of hyperthyroidism, however thyroid disease and GO occur concomitantly or within a few months from each other in more than 80% of cases (2). GO can occur in hypothyroid or euthyroid patients as well. Although clinically apparent unilateral GO is seen occasionally, orbital imaging with either Magnetic resonance imaging (MRI) or computer tomography (CT) confirms asymmetrical bilateral disease in majority of them.

Pathogenesis of Grave’s orbitopathy (GO)

GO is an autoimmune process of which precise pathogenic process is not fully unraveled, but is better understood now than ever before. In GO extraocular muscles and adipose tissues are swollen due to accumulation of extracellular matrix of glycosaminoglycans that are secreted by the fibroblasts under the influence of cytokines such as interferon γ, interleukin (IL)-1α and TNFα, which are secreted by T lymphocytes infiltrating the orbital cavity (5). Accumulation of glycosaminoglycans disrupts and impairs the function of ocular muscles leading to fibrosis as the inflammation ceases. The close clinical and temporal relationships between Grave’s hyperthyroidism and GO suggest that both conditions derive from a single systemic process and share the thyrotropin receptor (TSHR) as the auto antigen (3). It is now established that full-length TSH receptor is expressed in orbital adipocytes and fibroblasts of GO patients, which are activated by TSHR stimulating antibodies (TRAbs) (5). This is further supported by the fact that patients with most severe orbitopathy have the highest titters of TRAbs and severity of orbitopathy correlates with the level of TRAbs. The type I insulin-like growth factor receptor (IGF-1R) may be another important autoantigen in Grave’s ophthalmopathy which is expressed in higher levels in the orbital fibroblasts of patients with Grave’s orbitopathy (6).

Clinical presentation of Grave’s orbitopathy

Symptoms of GO occur in about 50% of patients with Grave’s hyperthyroidism, including a dry and gritty ocular sensation, photophobia, excessive tearing, double vision, and a pressure sensation behind the eyes. The most common clinical features of Grave’s ophthalmopathy are upper eyelid retraction, edema and erythema of the periorbital tissues and conjunctivae, and proptosis. Proptosis and exophthalmos can lead to failure of eye lid closure increasing the risk of exposure keratitis. Only about 3 to 5% of patients with GO have severe disease with intense pain, inflammation, and sight-threatening corneal ulceration or compressive optic neuropathy (6). Assessment of visual acuity, colour vision and fundoscopic examination for papilloedema are mandatory to identify sight threatening Dysthyroid Optic Neuropathy.
Grave’s orbitopathy

(DON). Smoking is the single most important risk factor for the development of GO and it is related to the current number of cigarettes smoked per day (7).

**Disease activity and severity assessment in GO**

Disease activity and severity of orbitopathy should be assessed in all the patients in each visit, and the management be guided upon them. European Group on Grave’s Orbitopathy (EUGOGO) has formulated criteria for assessment of clinical activity and severity (Box 1). A clinical activity score (CAS) $\geq 3/7$ (one point assigned to each feature) indicate active GO whereas a CAS $<3/7$ is considered as inactive disease (1). In follow up patients three additional features should be added which includes, increase of $>2$ mm in proptosis, decrease in uniocular ocular excursion in any one direction of $>8^\circ$, decrease of acuity equivalent to 1 Snellen line, giving a total score of 10.

Grading the severity of GO is fraught with difficulties; however, classifying patients into broad categories as mild, moderate-to-severe or sight threatening facilitates decision making. Careful assessment of the impact of GO on quality of life (QoL) by disease-specific questionnaire is fundamental in deciding whether treatments used for moderate-to-severe GO are justified in patients with mild GO (1).

Sight-threatening GO is defined as presence of Dysthyroid Optic Neuropathy (DON) which is characterized by reduced visual acuity and color vision, presence of relative afferent papillary defect or disc oedema and/or corneal breakdown, which warrants immediate intervention. A visual acuity $<6/18$, failure to identify $>2$ plates in isihara chart, corneal opacification, papilloedema and globe subluxation are indications for urgent referral to an ophthalmologist (1). Moderate-severe GO is a disease without sight-threatening GO whose eye disease has sufficient impact on daily life to justify the risks of immunosuppression or surgical intervention and they usually have any one or more of the following: lid retraction $\geq 2$ mm, moderate to severe soft tissue involvement, exophthalmos $\geq 3$ mm above normal for race and gender, inconstant or constant diplopia. Mild GO is a disease which have only a minor impact on daily life insufficient to justify immunosuppressive or surgical treatment. They usually have only one or more of the following: minor lid retraction ($<2$ mm), mild soft tissue involvement, exophthalmos $<3$ mm above normal for race and gender, transient or no diplopia, and corneal exposure responsive to lubricants.

**Management of Grave’s orbitopathy**

All patients with GO should be advised to quit smoking and other general measures should be considered where appropriate (Table 1). It is also imperative to make them euthyroid if they are in hyperthyroid state which raises the important question whether the different treatment modalities used to control thyrotoxicosis can affect the course of the eye disease. Most researchers have found that subtotal or total thyroidectomy and thionamide drug therapy do not influence orbitopathy unless they lead to the development of hypothyroidism (8,9). However, long term follow up study by Leo et al (10) on outcome of GO after total thyroid ablation and glucocorticoid treatment has shown that total thyroid ablation with thyroidecomy followed by $^{131}$I treatment allows best possible outcome and improvement of GO within a shorter period of time as compared to thyroidecomy alone. The effect of radioiodine treatment on GO is researched considerably and several randomized control trials have shown that approximately 15% patients develop new eye disease or experience the progression of existing GO within 6 months after radioiodine therapy (11). This is more likely to occur in patients who already have GO prior to radioactive iodine (RAI) therapy, smoke, have more severe hyperthyroidism and high levels of TRAbs or whose post RAI hypothyroidism is not promptly corrected by thyroxine replacement therapy (11). In these at-risk patients a relatively short course of moderate doses of oral glucocorticoids prevents progression of eye disease and often cures preexisting GO.

**Table 1. General measures in management of GO**

<table>
<thead>
<tr>
<th>Problem</th>
<th>Treatment</th>
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</thead>
<tbody>
<tr>
<td>Photophobia and excess tears</td>
<td>Dark glasses</td>
</tr>
<tr>
<td>Grittiness</td>
<td>Artificial tears and simple eye ointment</td>
</tr>
<tr>
<td>Eyelid retraction</td>
<td>Tape eyelids in the night to prevent corneal damage</td>
</tr>
<tr>
<td>Proptosis</td>
<td>Head elevation during sleep</td>
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<tr>
<td>Diuretics</td>
<td></td>
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<tr>
<td>Ophthalmoplegia</td>
<td>Prisms in the acute phase</td>
</tr>
</tbody>
</table>
Clinical update

Sight threatening GO

Systemic glucocorticoids (GCs) and surgical decompression of the orbit are the only treatments proved to be effective in patients with DON. High dose IV GCs are the first line of treatment for DON and prompt orbital decompression should be carried out if there is inadequate response to IV GCs or poor response after 1-2 weeks, or the dose/duration of steroid required induces significant side effects. Orbital radiotherapy is not recommended in the case of DON unless as an adjunct to proved therapies. High dose IV GCs administered in pulses are more efficacious and associated with fewer adverse effects than oral or retrobulbar steroids (1). The currently recommended treatment for patients with active and moderate to severe GO is a course of 0.5 g of methylprednisolone IV once a week for 6 weeks, followed by 0.25 g/wk for 6 weeks(1). The response rate of this therapeutic regimen is approximately 80% (12). Although IV GCs are tolerated better than oral GCs, acute liver damage and a risk of life threatening liver failure has been reported in association with very high cumulative doses in 0.8% of patients (13). Hence the cumulative dose of IV GCs should not exceed 8 g.

In severe, sight-threatening corneal breakdown hourly topical lubricants are indicated, however this intervention alone may be insufficient to prevent ulceration, thinning, and perforation. In such cases, specific measures to improve eyelid closure such as blepharorrhaphy, tarsorrhaphy, or botulinum toxin injections can help until corneal healing occurs (1). The effect of GCs on severe corneal exposure has never been specifically evaluated. Orbital decompression helps to reduce symptoms associated with exposure keratopathy. Rarely severe corneal ulcers may be refractory to decompression surgery if lagophthalmos persists.

In sight threatening GO hyperthyroidism must be treated by anti thyroid drugs (ATDs) to restore euthyroidism and definitive treatment with RAI or thyroidectomy, if required, should be postponed until DON has improved and orbitopathy has become inactive.

Moderate to severe GO

The treatment of choice for moderate to severe and active (CAS ≥3/7) GO is pulses of IV glucocorticoids, as for sight threatening GO. Orbital irradiation (OR) should be considered in patients with active disease who have diplopia or restricted motility. OR with lower cumulative doses (10 Gy) may be as effective as and better tolerated than with higher doses (20 Gy) and doses>20 Gy are not recommended (1). Orbital radiotherapy is contraindicated in patients with diabetic retinopathy or severe hypertension. The combination of oral GCs (dose of 1mg/kg) with OR is thought to be more effective than either treatment alone, but randomized clinical trials indicating that the combination of IV GCs with OR is better than IV GCs alone are still lacking (1).

Moderate to severe disease with CAS <3/7 (inactive) warrants no immunosuppressive therapy and should be treated with rehabilitative surgery (1), which includes a sequence of orbital decompression, squint correction, lid lengthening and blepharoplasty. Indications for orbital decompression are disfiguring exophthalmos, troublesome retroocular pain/discomfort, and/or grittiness associated with minor exposure keratopathy not amenable to topical therapies (14). Rehabilitative surgery should be performed only in patients who have had inactive GO for at least 6 months (1).

Here the choice of treatment for hyperthyroidism is most controversial. Some argue in favour of ATDs due to prompt correction of hyperthyroidism and stable maintenance of euthyroidism with ATDs. Another argument is that thyroid ablation removes intrathyroidal autoreactive T-lymphocytes and thyroid antigens thereby helping abate the orbital process. Based on these assumptions, after restoration of euthyroidism with ATDs, even in this category of patients the thyroid can be

<table>
<thead>
<tr>
<th>Grave’s orbitopathy</th>
<th>Management of hyperthyroidism</th>
<th>Management of GO</th>
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<tbody>
<tr>
<td>Mild active</td>
<td>ATDs, RAI with steroid prophylaxis or surgery</td>
<td>Watch and wait</td>
</tr>
<tr>
<td>Mild inactive</td>
<td>ATDs, RAI or surgery</td>
<td>Watch and wait ± rehabilitative surgery</td>
</tr>
<tr>
<td>Moderate to severe active</td>
<td>ATDs, RAI with steroid prophylaxis or surgery</td>
<td>High dose steroids ±orbital radiotherapy</td>
</tr>
<tr>
<td>Moderate to severe inactive</td>
<td>ATDs, RAI or surgery</td>
<td>Rehabilitative surgery</td>
</tr>
<tr>
<td>Sight threatening</td>
<td>ATDs</td>
<td>IV glucocorticoids and/or orbital decompression</td>
</tr>
</tbody>
</table>

Table 2. Management of hyperthyroidism and orbitopathy of Grave’s disease in different clinical settings
promptly ablated while managing GO with appropriate therapy (15). If RAI is given in these patients, it should be combined with low dose steroid prophylaxis (0.2mg/kg/day for 6 weeks) (16). In moderate to severe inactive disease, treatment depends on standard criteria and if RAI treatment given steroid prophylaxis can be avoided in the absence of other risk factors for progression of GO.

**Mild GO**

Local measures and an expectant strategy are sufficient in most cases of patients with mild GO (active/inactive). Glucocorticoids are rarely justified in mild GO as the risks outweigh the benefits. However, if quality of life is profoundly affected, it may be justified to treat as for moderate to severe disease. Rehabilitative surgery can be considered for cosmetic and functional reasons in inactive disease. Treatment of hyperthyroidism in these patients is largely independent of the orbital disease and based on established criteria. Steroid prophylaxis is indicated only if RAI is the treatment of choice in active disease.

**Novel treatment modalities**

With the better understanding of pathogenesis of GO immunomodulating agents like Rituximab, which is a monoclonal antibody against CD20, has shown promising outcome in management of Grave’s disease. Several small studies have shown that rituximab infusion significantly reduces CAS in patients with Grave’s orbitopathy (17,18). However large randomized control studies are lacking to recommend rituximab for treatment of GO.

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**Box 1**

**Activity and severity assessments in GO – EUGOGO recommendations**

(a) **Activity measures based on the classical features of inflammation**

1. Spontaneous retrobulbar pain
2. Pain on attempted up or down gaze
3. Redness of the eyelids
4. Redness of the conjunctiva
5. Swelling of the eyelids
6. Inflammation of the caruncle and/or plica
7. Conjunctival edema
   
   A CAS ≥3/7 indicates active GO

(b) **Severity measures**

1. Lid aperture (distance between the lid margins in mm with the patient looking in the primary position, sitting relaxed, and with distant fixation)
2. Swelling of the eyelids (absent/equivocal, moderate, severe)
3. Redness of the eyelids (absent/present)
4. Redness of the conjunctivae (absent/present)
5. Conjunctival edema (absent, present)
6. Inflammation of the caruncle or plica (absent, present)
7. Exophthalmos (measured in millimeter using the same Hertel exophthalmometer and same intercanthal distance for an individual patient)
8. Subjective diplopia score (0=no diplopia; 1=intermittent, i.e. diplopia in primary position of gaze, when tired or when first awakening; 2=inconstant, i.e. diplopia at extremes of gaze; 3=constant, i.e. continuous diplopia in primary or reading position)
9. Eye muscle involvement (ductions in degrees)
10. Corneal involvement (absent/punctate keratopathy/ulcer)
11. Optic nerve involvement (best-corrected visual acuity, color vision, optic disk, relative afferent pupillary defect (absent/present), plus visual fields if optic nerve compression is suspected
Clinical update

References


Sertoli-Leydig cell tumour: a rare cause of androgenic alopecia in post-menopausal women

S Siyambalapitiya¹, J Fernado², R N G Rajapakse³

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(Index words: Sertoli-Leydig cell tumour, ovarian tumour, postmenopausal women, hyperandrogenism, alopecia)

Abstract

Objective: Sertoli-Leydig cell tumour (SLCT) is a rare ovarian tumour often detected in young females between the ages of 20 and 30 years who usually presents with virilising features. We are describing an unusual case of Sertoli-Leydig cell tumour in a 57 year old postmenopausal woman who presented with progressive male pattern hair loss. She had high testosterone levels with poor response to medical therapy and underwent bilateral oophorectomy. Histology showed a Sertoli-Leydig cell tumour in the right ovary with benign characteristics and surgery resulted in an almost complete cure for the patient.

Introduction

Sertoli-Leydig cell tumour (SLCT) is a rare ovarian tumour belonging to the group of sex-cord stromal tumours. These neoplasms account for less than 0.5% of all ovarian tumours and are more often detected in young females between the ages of 20 and 30 years who usually become virilised (1) and very rarely in postmenopausal women. SLCTs are characterized by the presence of testicular structures that produce androgens. Most tumours are unilateral and confined to the ovaries. With this background, we describe an unusual case of Sertoli-Leydig cell tumour in a postmenopausal woman who presented with progressive hair loss. Despite, similar cases of SLCT of ovary in post-menopausal women have been reported (2-9), we believe this to be a useful addition to the literature.

Case report

A 57-year old married woman was referred to the endocrine clinic from the out patient department with progressive male pattern hair loss for 2 years’ duration. She was married with 2 children. She had breast fed uneventfully and she had experienced the menopause at the age of 52. She noticed progressive hair loss especially from the forehead and the central area of the scalp over the last 2 years. She never had a similar problem, any other chronic medical illness or any skin disorder in the past.

On examination, she had male pattern hair loss (Figure 1) and persistently elevated blood pressure. Her glucose levels were repeatedly in the diabetic range. There was no hirsutism or clitoromegaly. CT scan of the abdomen showed normal ovaries and adrenals. The test results indicated excessive androgenic activity in the form of elevated serum testosterone levels (3.39 ng/mL; normal, 0.2-1.2 ng/mL) with normal dehydroepiandrosterone sulfate (DHEAS) levels.

Figure 1. Figure shows the hair loss from forehead and central region of scalp.

Diabetes due to insulin resistance, hyperandrogenism and normal ovaries and adrenals in abdominal CT were in favour of ovarian hyperthecosis and we put her on the anti-androgens; spironolactone and finasteride. Metformin, glibenclamide, enalapril and atorvastatin were prescribed for treatment of diabetes and hypertension. Her blood glucose and the blood pressure were normalized with the medication. However, she had minimal response
to anti-adrogen therapy and continued to loose hair. Therefore, we offered her the surgical treatment option, bilateral oophorectomy.

During surgery, the right ovary measuring $5 \times 1.8 \times 2$ cm and the left ovary measuring $3 \times 2 \times 1$ cm were removed. Cut surface of the right ovary showed a greyish white, well circumscribed nodule (measuring $2.5 \times 1.6 \times 1$ cm) towards the outer surface of the right ovary (Figure 2). Sections of this ovary showed well circumscribed tumour composed of sheets and clusters of cells with abundant eosinophilic cytoplasm. Some cells exhibited intracytoplasmic lipids with lipofuchsin pigment and there were clusters of nuclear rich areas separated by nuclear free areas. There were no nuclear atypia or increased mitotic activity. These findings were compatible with a benign Sertoli-Leydig cell tumour of the ovary (Figure 3). Cut surface of the left ovary showed a unilocular cyst (measuring 1 cm) within the ovarian tissue, which was compatible with a serous cystadenoma. However, rest of the left ovary appeared unremarkable.

Four weeks after the operation, we reviewed the patient with the histo-pathological report and repeated testosterone results. The testosterone level had decreased to normal levels. The patient’s symptoms have improved substantially and she had no further hair loss after the surgery. We discussed the results with the patient and decided to follow up her without subjecting to any further treatment.

**Discussion**

The majority of patients of SLCT are being detected during the second and third decades of life and SLCT at postmenopausal age is extremely rare. Very rarely, the SLCT can be associated with DHEAS secreting adrenal adenomas (7). Most important prognostic factors in these tumours are their stage and degree of differentiation. A histopathological review done by Young and Scully in 1985 (1), has shown that all well-differentiated tumours were benign, whereas 11% of tumours with intermediate differentiation, 59% of tumours with poor differentiation, and 19% of those with heterologous elements were malignant. In another study, patients who had intermediate or poorly differentiated SLCT, a survival rate of 92% was noted at both 5 and 10 years (10).

Most of these tumours are unilateral and diagnosed early; hence a conservative surgery is the only treatment that is needed. Adjuvant chemotherapy is considered for patients who have poor prognostic factors (10). Our patient had a well-differentiated tumour with benign characteristics and surgery alone was adequate for her as treatment.

In conclusion, SLCT is a rare ovarian sex-cord tumour that usually occurs unilaterally in young females and extremely rare in post-menopausal women. It is a rare cause of hyperandrogenism that needs to be considered in patients with virilising symptoms and signs.

**References**


Case report

Investigating for the aetiology of Cushing’s syndrome: where we can go wrong

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Abstract

The diagnosis of Cushing’s syndrome as well as delineating its aetiology can be often challenging, especially in the mild cases with atypical features. Although the combined clinical features such as the age, gender and the severity of the hypercortisolism can usually help to differentiate between pituitary ACTH hypersecretion from an ectopic ACTH source, this may sometimes be inaccurate. The presence of caveats in most biochemical testing and imaging modalities as well as the relative unavailability of certain dynamic tests and catheter based studies can contribute to the dilemma.

Introduction

Differentiation between the two main aetiologies of ACTH dependent Cushing’s syndrome, an ACTH-producing pituitary adenoma and an ectopic ACTH-producing tumor, can be challenging when an obvious source of ACTH hypersecretion is absent. Cushing’s disease accounts for about 90-95% of the cases of ACTH dependent Cushing’s syndrome. Although many patients have clinical and/or biochemical features suggestive of one of the two diagnoses, no one biochemical test or imaging procedure correctly identifies the source of ACTH hypersecretion in all cases. The evaluation of ACTH-dependent Cushing’s syndrome has been greatly improved by the availability of bilateral inferior petrosal sinus sampling (BIPSS). Here we report a case of a patient with Cushing’s syndrome, whose pituitary source of ACTH secretion was ultimately diagnosed with BIPSS after extensive investigation with other methods for more than two years.

Case report

Mr C, a previously healthy businessman was detected to be hypertensive at the age of 35 years and was started on Losartan K 50 mg twice daily. However, his blood pressure remained uncontrolled despite good compliance for treatment, generally above 160/110. About one year later Mr C began to notice an increase in bodyweight and change in facial appearance. He also noticed skin petechiae, mainly in the upper and lower limbs. He had not noticed a recent increase in skin pigmentation. On examination, he had truncal obesity with a body mass index of 28.1 kg/m². He also had dorso-scapular fat deposition, facial fullness, acne and facial plethora. His blood pressure was 160/100 while on medication and the fundoscopy revealed grade 2 hypertensive retinopathy. There was clinical evidence of a grade 4 proximal myopathy of all limbs. He also had enlargement of the thyroid gland with 2 firm nodules over the right lobe.

His basic investigations revealed a persistently low serum potassium, usually in the range of 3-3.5 mmol/l. The rest of the haematological and biochemical investigations were normal. Since the clinical features were suggestive of Cushing’s syndrome, a low dose dexamethasone suppression test was performed which showed an unsuppressed cortisol value of 327 nmol/l (normal <50) at 48 hours. His 24 hour urinary free cortisol was 683 nmol (0-283). Therefore Cushing’s syndrome was biochemically confirmed. His serum ACTH value was unsuppressed at 49.7 pg/ml (0-46) suggesting that this was ACTH dependent disease. A pituitary MRI was performed as pituitary ACTH secretion was responsible for 90-95% of ACTH dependent Cushing’s syndrome, which failed to reveal a lesion. A gadolinium enhanced dynamic pituitary imaging, which has a higher sensitivity for pituitary lesions was also negative. We did not have facilities in Sri Lanka to perform bilateral inferior petrosal sinus (BIPSS) sampling at that time. A high dose Dexamethasone suppression test failed to suppress cortisol to more than 50% of the basal value suggesting that this was more likely to be ectopic ACTH secretion. The fact that this was a male patient and the presence of persistent hypokalemia were also supportive of this. We performed a CT scan chest and abdomen to identify a source of ACTH secretion which showed multiple nodules in the right lobe of the thyroid gland with mixed echo

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pattern. Thymic area showed a few foci of soft tissue density material with no definitive mass. The possibility of a thyroid or thymic carcinoid secreting ACTH was considered but needed to be confirmed further with investigations. We planned to carry out further investigations to identify an occult ACTH secreting tumour while managing the patient medically to minimize the adverse effects of persistent hypercortisolism. Mr C was started on oral metyrapone 250 mg bid and oral ketoconazole 100 mg bid which brought his cortisol levels to within normal limits after a few weeks.

A fine needle aspiration biopsy of the thyroid nodules revealed a colloid storing goiter with degenerative changes only. Colonoscopy and bronchoscopy failed to reveal any lesions suggestive of carcinoids. As the possibility of a carcinoid, which is known to cause low grade Cushing’s syndrome due to ectopic ACTH secretion, was high, we performed several biochemical tests which are tumour markers of carcinoids. The 24 hour urinary 5 hydroxy indolacetic acid (5HIAA) and serum Chromogranin A levels were normal. A 99 m In-Octreotide scan was performed to detect any sites of occult neuro-endocrine activity with ACTH secretion; this was normal.

As the patient’s problem was still unresolved and as the patient was on longterm treatment with drugs with a number of possible adverse effects, we contemplated a combined thyroidectomy and a thymectomy for the only possible sites of ectopic ACTH secretion that we have identified. However, as bilateral inferior petrosal sinus sampling (BIPSS) became available at the National Hospital of Sri Lanka we planned for that procedure considering the fact that 90-95% of ACTH dependent Cushing’s syndrome was due to pituitary disease. We also included mediastinal vein sampling as we were also considering thyroid or the thymus as the possible sites of ACTH secretion.

Results of BIPSS

![Image of BIPSS results]

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The ACTH values of the right inferior petrosal sinus was about six times higher than the other values of the periphery (femoral vein); a central to peripheral gradient of more than 2 in an unstimulated test is considered significant with a diagnostic sensitivity of nearly 100% (1). Therefore venous sampling clearly identified the site of ACTH secretion as the pituitary as opposed to an ectopic site, most likely involving the the right side of the pituitary gland.

The immediately pre operative MRI scan of the pituitary identified an ill defined 4 mm × 3 mm non enhancing mass in the right lobe of the pituitary suggestive of an adenoma. The patient underwent transphenoidal excision of the pituitary with an uneventful post operative period. The pathological specimen consisted of a 4×4 mm well defined mass lesion with cells containing round nuclei, dispersed chromat in and eosinophilic granular cytoplasm on histology. The serum cortisol levels were <50 nmol/l post operatively, indicating a cure from the disease. Most of his symptoms improved following surgery, and the blood pressure normalized.

**Discussion**

This case illustrates the importance of bilateral inferior petrosal sinus sampling in the diagnosis of the aetiology of ACTH dependent Cushing’s syndrome.

The vast majority (90-95%) of patients with ACTH dependent Cushing’s syndrome have a pituitary corticotroph microadenoma (1). Because the pretest probability of Cushing’s disease is so high, any differential diagnostic test must be very accurate. Simple clinical measures have been shown to have good predictive value in establishing the presence of Cushing’s disease. A woman with mild to moderate hypercortisolism, a normal or slightly elevated plasma ACTH, and normokalemia has at least a 95% likelihood of having Cushing’s disease. In contrast, a patient with overt hypercortisolism, hypokalemia, and marked elevations of plasma ACTH may be more likely to have an occult ectopic ACTH-secreting tumor (2). Our patient was a young man with persistent hypokalemia, unusual features for pituitary ACTH production, which made us consider ectopic ACTH production as a possible aetiology. Although ectopic ACTH production would be expected to have higher values of ACTH production and overt hypercortisolism than in our patient, low grade Cushing’s is still possible with certain ectopic ACTH sources like carcinoids. Studies have shown that certain neuroendocrine tumours such as bronchial and thymic carcinoids can present with covert ectopic ACTH secreting syndrome and may actually have marginally high ACTH levels resembling pituitary disease (3).

Pituitary imaging with MRI is the initial study required when investigating for a cause for ACTH dependent Cushing’s syndrome. Unfortunately, as in our patient, 40-50% of corticotroph microadenomas causing Cushing’s syndrome in adults are not visible with this technique (4). The use of dynamic MRI (with iv gadolinium) with spoiled gradient sequences may increase the sensitivity (5). It is also important repeat the MRI after a reasonable time interval if the initial scans were negative but the patient remains symptomatic. Because as hypercortisolaeam evolvs, it is possible for the repeat scans to demonstrate microadenomas which were undetected previously due to the minute size, just as it occurred in our patient. Although there is a consensus that the presence of a pituitary lesion greater than 6 mm in a patient with a classical presentation and concordant dynamic results provides a definite diagnosis of Cushing’s disease (6), further evaluation in the absence of a pituitary lesion is not so clearly defined.

There are a number of non invasive tests that can be used concurrently when the pituitary imaging is negative, but none of them have the diagnostic accuracy alone to differentiate the source of ACTH production. The high dose dexamethasone suppression test, using the criterion of a cortisol suppression of >50% of the baseline level after high-dose dexamethasone has a sensitivity and specificity of 88 and 57% (7). Low grade Cushing’s, as in a carcinoid syndrome can give a false negative result and overt hypercortisolism in Cushing’s disease can sometimes give a false positive value.

Although the CRH stimulation test is considered the most reliable dynamic non invasive test for the differential diagnosis of ACTH-dependent Cushing’s syndrome, this test cannot make a 100% differentiation between pituitary and ectopic causes. From literature data, the sensitivity and specificity using ACTH criteria is approximately 90%. However, there is yet no consensus on the criteria for interpreting the test as positive. Variability in interpretation depends on the type of CRH used, the weight based or fixed dose of CRH, and the wide range of response parameters (8). CRH is not currently available in Sri Lanka.

On the contrary, BIPSS is considered the gold standard for establishing the origin of ACTH secretion. Given the fact that 95% of the patients with ACTH dependent Cushing’s syndrome would harbour a pituitary lesion, BIPSS is recommended to be done in patients like ours who either have a negative MRI or have discordant imaging and biochemical results (5). Furthermore, ectopic ACTH secreting tumours are only responsible for about 5-10% of the ACTH dependent Cushing’s syndrome. Localization of these tumours is also often challenging and extremely difficult, imaging correctly identifies the tumour at first investigation in only 65% of cases. In up to 30% of cases, the tumour remains occult for a long time after diagnosis of Cushing’s syndrome (9). Although tumour markers such as plasma calcitonin, gastrin, glucagon, or somatostatin may often be elevated in patients with ectopic ACTH syndrome, they are rarely helpful in identifying the source of the neoplasm (10). Somatostatin receptor scintigraphy, such as the Octreotide
scan which was used in our patient, may not sometimes
detect the ACTH secreting neuro-endocrine tumours, due
to inadequate resolution of the scans to detect these small
lesions (1). Most of these tests are very expensive and
not freely available in Sri Lanka. Therefore although BIPSS
is an invasive test that is only performed in certain tertiary
centres currently, it should be performed in all patients
prior to embarking on a tedious search for a source of
ectopic ACTH secretion. Extensive imaging without
performing BIPSS may result in false-positive studies and
lead to surgical misadventures.

This case illustrates the difficulties that are sometimes
encountered when investigating for the aetiology of ACTH
dependent Cushing’s syndrome and the important role of
BIPSS in the investigation pathway. It also highlights the
need for making BIPSS a more widely available procedure
in a resource poor setting like ours, where the performance
of a multitude of other tests on each patient would not be
feasible.

Abbreviations

ACTH – adrenocorticotropic hormone, CRH –
corticotrophin releasing hormone, IJV – internal jugular
vein, BIPSS – bilateral inferior petrosal sinus sampling.

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Ionized salts present in body fluids are known as electrolytes. Commonly measured human electrolytes for clinical purposes are sodium, chloride, potassium, calcium, magnesium, phosphates and bicarbonates. Electrolytes control the fluid balance in the body and are important in muscle contraction, energy generation, and almost every major biochemical reaction in the body.

Many physicians consider disease as the only cause of abnormal test results. Many factors besides diseases affect the composition of body fluids. These factors are broadly classified into 3 areas, namely pre-analytical, analytical and post analytical. Errors in interpretation of electrolyte results are encountered in certain occasions due to inadequate evaluation of pre-analytical and analytical status or conditions through which the samples are processed from the time of sample collection.

Analytic process refers to the part of the total testing process that involves measurement and analysis, as opposed to the pre-analytic part that deals with all the steps prior to performing the test and the post-analytic part that deals with all the steps after the test result is available.

There are many practices and procedures which lead to pre-analytical errors in clinical assays. These include selection of sample type (blood, serum, or plasma) appropriate to the patient, method of sample collection, site of collection (capillary, venous, arterial or proximity to IV line and conditions of sample transport and storage. Interfering substances (drugs, metabolites etc.) which are present within the sample at the time of sample analysis affect the assay procedure resulting generation of errors in the final result. Therefore it is critical to understand the impact of analytical and pre-analytical interferences in routine assays for correct interpretation.

For determination of electrolyte in serum various methods are used. The most commonly adopted methods in routine clinical laboratories include flame photometry, either direct or indirect Ion Selective Electrodes (ISE) and atomic absorption spectrophotometry.

Sodium

Pseudohyponatraemia is a state where serum sodium measurement appears low when it is actually higher than the indicated value. It is an artifact of measurement. It is not associated with concomitant reduction in serum osmolality. There should be a high index of suspicion regarding this condition to avoid misinterpretation of results when sodium is measured using flame photometer or indirect ISE. Serum is composed of aqueous (water and water soluble substance) and non-aqueous (lipids and non-aqueous portion of proteins) fractions, 7% and 93% in approximate volumes respectively. Sodium is present in the serum in aqueous fraction. Lipids and proteins (non-aqueous portions) consume a portion of the volume of specimen delivered to the instrument avoiding contribution of ions for measurement. This is known as water displacement or solvent exclusion effect. This will lead to an error when the displacement occurs in abnormal proportions. The degree of error will be proportionate to the volume occupied by the non-aqueous portion of the specimen.
giving rise to normal sodium levels (pseudonormonatraemia). This pseudo effect is reversed with a decrease in the serum protein concentration resulting in pseudohypernatraemia. The fluid management based on these results that mask the true physiological condition can lead to errors resulting in serious clinical consequences. Those hyper- and hypo-pseudo effects are equally applicable to Cl⁻ as well.

These pseudo effects should be suspected in conditions such as severe hyperproteinemia (usually more than 10g/dL) and severe hyperlipidaemia (usually a triglyceride level more than 1000mg/dL) with low sodium.

Measuring serum osmolality is a suitable approach to determine whether hyponatraemia represents a true hypo-osmolar state. Suspicion should also be raised when there is a discrepancy between measured osmolality and calculated osmolarity. Several formulae have been proposed to calculate serum osmolality. The most commonly used formula is Calculated Osmolality (mOsm/kg) = 2 [Na mmol/L] + Glucose mg/dL /18 + BUN mg/dL / 2.8. In normal physiological state, the difference between measured osmolality and calculated osmolarity, the osmolar gap is approximately 12 mOsm/Kg (range 7-19).

These pseudo effects can be excluded when direct ISE is used where the activity of the relevant analyte is not affected by the concentration changes of lipids or proteins in the sample. However, a high glucose level can affect direct ISE resulting in artefactual increase in the sodium level. If direct ISE is not available, corrected sodium value can be calculated by estimating serum water fraction.

Low sodium in a patient with diabetes mellitus with poorly controlled hyperglycaemia can be a true hyponatraemia secondary to osmotic effects of hyperglycaemia. Yet this per se does not cause a hypo-osmolar state. This should be differentiated from pseudohyponatraemia secondary to associated hyperlipidaemia.

Other indirectly measured analytes such as K⁺ and Ca²⁺, are subjected to same effects as sodium but the absolute change in sodium is greater because it has a higher concentration in the serum.

Sodium values can also be affected by heparin which may be used in certain sampling devices (e.g. heparin capillary tubes used in blood gas machines) and high concentrations in samples collected through a dialysis catheter, resulting in low sodium values. The negative bias is thought to be due to chelation of Na⁺ by heparin.

**Potassium**

The commonest pre-analytical factor that can lead to falsely high K⁺ is haemolysis. Blood for serum electrolytes are collected into plain bottles. If by mistake blood is collected into a tube containing potassium EDTA as an anticoagulant or sodium fluoride/potassium oxalate a blood glucose test preservative, a falsely high level of potassium or sodium or both will result due to contamination. Haemolysis should be prevented using a proper technique and usage of a correct needle with appropriate gauge and size. Haemolysis easily occurs if the blood is drawn rapidly with force to obtain samples from small gauge peripheral catheters or needles. During blood collection fist clenching should be avoided. A delay in transport of samples to the laboratory can lead to red cell break down and leakage of potassium rich intracellular fluid into the sample giving rise to falsely high values. Pseudohyperkalaemia can also occur in skin puncture derived blood (neonatal heel prick and finger prick), particularly with difficult collections. These involve excessive squeezing which leads to significant haemolysis and artefactual contamination from interstitial and intracellular fluids as well. Thus, care in sample collection for serum potassium is very important.

Occasionally falsely elevated K⁺ levels can be encountered with fragile leucocytes in patients with leukaemia, and with thrombocytosis. It is important to note that severe hypokalaemia may be masked in these conditions, giving rise to falsely high potassium levels in vitro.

**Calcium**

The most frequently used methods for determining plasma calcium concentration, measure total calcium, although ionized (free) calcium can be measured using ion selective electrode (ISE). Special consideration is needed in the interpretation of ionized calcium since pH changes in blood can affect ionized calcium values.

When the pH in a specimen is increased, both free calcium and free magnesium concentrations decrease due to the stronger binding of these ions with proteins in the more alkaline environments. The reverse occurs in specimens with low pH.

Gradual acidification of the sample or lowering of pH would occur, if the venous samples are left for a long period without separating serum from cells due to metabolic activity of the cells. Elevation of the pH in the specimen would result, if the venous samples are kept open and air contact is allowed, facilitating loss of CO₂ into the environment. Same consequences occur with air bubble formation during sample collection. These changes may alter the true value of ionized calcium (Ca²⁺) to a clinically significant level. Certain instruments are provided with a facility to report results to an estimated or “normalized pH”, in other words to a pH value of 7.4.

Sample collection practices should be adopted to minimize these effects on ionized calcium. A half an hour rest is required prior to blood collection with no muscular action and a minimum time of tourniquet application (less than a minute) or avoiding the use of a tourniquet to prevent changes in pH and free ions binding to proteins, mainly
albumin. Exercise causes a decrease in pH due to lactic acid production and an increase in Ca\(^{2+}\). Samples should preferably be collected into an evacuated tube containing a gel to separate serum from cells or the tube should be completely filled avoiding contact of blood with air and transported to the laboratory immediately in ice.

Similar effects can occur in ionized magnesium (Mg\(^{2+}\)) measurement, where binding of Mg\(^{2+}\) to proteins and ligands in plasma or serum is pH dependent.

When Ca\(^{2+}\) measurements are done in samples collected to heparin containing tubes, falsely low Ca\(^{2+}\) levels could be obtained. To minimize this Ca\(^{2+}\) titrated heparin tubes can be used.

Change in posture from standing to supine causes fluid shifts into the vascular compartment, decreasing albumin concentration within approximately 10 minutes. A drop of albumin by 1g/L causes total calcium to decrease by 0.02 mmol/L leading to possible misinterpretation of results. These changes are not applicable to ionized calcium (Ca\(^{2+}\)). To prevent this, corrected calcium concentration should be used which indicates the total calcium concentration to be expected if the albumin concentration was normal (40g/L).

Sodium specifically affects plasma ionized calcium values independently to pH, presumably via modulating process of calcium binding to plasma proteins. Being aware of this fact is important in acute dilution hyponatraemia where disturbances in Na\(^+\) concentration could alter the Ca\(^{2+}\).

In general, erroneous results can be seen when blood is taken from catheters or cannulas which deliver IV fluids. Thus, these require flushing before collecting samples for analysis. Most frequently encountered errors occur from contamination with IV fluids containing Na\(^+\), K\(^+\), Cl\(^-\), Ca\(^{2+}\) and Mg\(^{2+}\). Other less common or unusual interferences occur related to lines used for infusion of drugs (e.g. ticarcillin which contains high concentrations of sodium), blood and blood products, parenteral feeds, dialysis etc. The mechanism is either additive or through binding of compounds contained in the infusions.

Therapeutic compounds can interfere with electrolyte assays by binding to electrolytes of interest or affecting the analytical procedure. Ascorbic acid (vitamin C) being a strong reducing agent, when given in high doses to cancer patients, can falsely elevate Na\(^+\), K\(^+\), Ca\(^{2+}\) and falsely reduce Cl\(^-\) levels. The activity of Ca\(^{2+}\) and Mg\(^{2+}\) ions decreases in patients receiving large volumes of blood transfusions due to chelation of these by citrate resulting in decreased measured activity.

Therefore, it is always important to interpret these results considering the clinical status of the patient and it is in fact up to the clinician to provide adequate clinical details to the pathologist for correct validation of reports.

**References**

To the Editor,

Re: Camurati-Engelmann disease


I would like to comment on Camurati-Engelmann disease which appeared in your Journal 2011 Aug; 1(1): 54, authored by Pathmanathan S. et al.

This condition has been reported previously in Sri Lanka by Dharmadasa K et al in the Ceylon Medical Journal, 1981; 26: 178-179. The two patients described in that article, subsequently came under my care at Kurunegala. The daughter of the index patient (case 2) was brought to me because she threatened to commit suicide precipitated by the severe unrelenting pain in the lower limbs. After perusing some literature, I prescribed prednisolone 40mg daily for one week on a trial basis. The severe bone pains receded completely within one week. I then tailed off the steroids over the next month. She did not have a relapse of the pain even up to 4 years while she was under my care. She married at the age of 18 and was thereafter lost to follow up. The mother who was the index patient mentioned in the aforesaid article had no bone pains and was not given steroids.

Subsequently I corresponded with Dr. Irwin A. Schafer and Dr. Luigi Luzzatti of the Stanford University School of Medicine in USA in February 1981. They replied that they had two patients with the same disease who had been given steroids, one of whom benefited and the other developed steroid side effects and the steroids were withdrawn.

The purpose of this correspondence is to highlight the first description of this condition in Sri Lanka by Dharmadasa K, et al and to bring to the readers notice that short term steroid therapy may benefit these patients when they have unrelenting bone pain.

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