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Patient motivation in the management of diabetes

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Looking at the alarming statistics, South Asians have a disproportionately higher incidence of diabetes and compared to the general population and the disease develops 5 to 10 years earlier. This is a profoundly worrying prospect for a disease that shortens lifespan by 5 to 15 years; a leading cause for vision loss, renal failures, heart attacks, strokes and non-traumatic limb amputations. Despite clear evidence that managing diabetes with dietary changes, regular exercise, and adherence to appropriate medications leads to a 53–63% reduction in complications and a 46% reduction in mortality, diabetes management and control remain poor in South Asian patients (1). Moreover, the introduction of nearly 40 drugs and drug combinations, including several types of insulin, the proportion of diabetics achieving adequate blood-sugar control remains low.

The complexity of the diabetes care to maintain health and quality of life is a key reason for this failure. Since patients with diabetes should handle majority of their day-to-day care, it is necessary to promote self-management. Researches indicate there are seven essential self-care behaviours in people with diabetes which predict good outcomes. Those are healthy eating, being physically active, monitoring of blood sugar, compliant with medications, good problem-solving skills, healthy coping skills and risk-reduction behaviours. All these seven behaviours have been found to be positively correlated with good glycemic control, reduction of complications and improvement in quality of life (2).

Though multiple demographic, socio-economic and social support factors can be considered as positive contributors in facilitating self-care activities in diabetic patients, role of clinicians in promoting self-care is vital and has to be emphasized.

The biggest challenge for us as health care providers to promote self-care is dealing with non-adherence. Although there are many reasons for non-adherence, poor attitude towards the disease, complexity of the drug regimens, cost, and negative patient perceptions about the efficacy of treatment are the crucial ones.

Studies show that South Asians are less likely to exercise or follow a healthy diet. Among South Asian patients with diabetes prescribed oral hypoglycemic agents, ACE inhibitor and statin therapy, only 40–45% were adherent to these medications, majority (55%) of South Asian patients were above recommended A1C targets, 36% were above blood pressure targets and 58% were above lipid level targets for diabetes (1).

Patients in our country view self-efficacy negatively; generally appreciate and rely on physicians to provide diabetes advice, not prefer self-management or autonomy. Majority of patients also find it challenging to disclose to physicians if they failed to comply with physician recommendations. Compared to western countries where allied healthcare workers spending more time with patients and have better understanding and concerns, our patients have limited time with the physician.

Among our patients some communities have difference in body image perception where a larger body size is considered more prosperous and healthy. There are misconceptions on benefits of exercise, many elderly think they should just rest. Females experience numerous barriers to engage in regular exercise outside of home, such as safety, wearing appropriate cloths for exercise, and negative attitude that exercising outside is culturally inappropriate.

Adopting a diabetic diet is another challenge for many of our patients. In our society there is a considerable social pressure to eat during social events and family gatherings, as food plays a significant role in maintaining social relationship. Also our traditional diet often contain high quantity of carbohydrate and saturated fat with low protein.

As healthcare providers we should actively involve in developing self-care regimens for each individual patient. Before making recommendations, perceived patient barriers to self-care behaviours must be evaluated. These modifications should be specific for each patient and should be altered depending on the patient’s response. The best possible regimen which is practical and realistic to the patient should be prescribed, so that he or she can follow it.

Other important step at the primary care level will be implementing good diabetes self-management education programs with emphasis on motivating good self-care behaviours especially lifestyle modification (3). But the success is on sustaining the healthy behaviour which definitely need periodic reinforcement, adequate social support systems such as allied health care workers, support groups, etc. The system which focus on improving communication; discussing common misperceptions in our community on diabetes management and leveraging cultural beliefs and family as a resource may help to improve diabetes control.
References


The 12 month impact of continuous insulin infusion therapy on glycaemic control in adults with type 1 diabetes, at the Townsville hospital, Queensland - A retrospective study.

Suji Prabhaharan, Vasant Shenoy, Kunwarjit Sangla

The Townsville Hospital, Queensland, Australia.

Abstract

Aims: The purpose of this study was to assess the impact of continuous subcutaneous insulin infusion therapy (CSII) on glycosylated haemoglobin level (HbA1c), total daily dose of insulin (TDD), weight, episodes of diabetic ketoacidosis (DKA), severe hypoglycaemia, hospital admissions due to any other causes at 12 months of CSII therapy and to identify the predictive factors for good response to treatment, in patients attending the Townsville hospital diabetes centre.

Methodology: This is a retrospective quality assurance single centre study. A total of 105 type 1 diabetes patients on continuous subcutaneous insulin infusion (CSII) were identified from 1st January 2001 to 31st December 2014 of whom; only 52 patients had sufficient data to be included in the study. The HbA1c, total daily dose of insulin and weight were collected 4 months before, after and at 12 months of CSII therapy. Patients demographic details, variables related to disease, treatment and follow up were also recorded.

Results: Among the 52 patients analysed, 34.6% were males. The baseline median HbA1c for females and males were 8.5% and 8.6% respectively. A significant reduction in baseline median HbA1c (8.6%) was noted both at 4 months (p=0.035) and 12 months (0.7% (p=0.001)) of continuous subcutaneous insulin infusion therapy. The statistically significant reduction in HbA1c at 4 months was maintained at 12 months (p=0.025). At 12 months of CSII therapy a median HbA1c level of 7.7% was noted in those more than thirty years and 8.6% in less than 30 years of age. The median HbA1c was 7.8% in those who had diabetes for more than 10 years and 8% in less than 10 years. There was no difference in the median HbA1c in females (7.8%) and males (7.9%) at 12months of CSII therapy. At 4 months, the greatest reduction in HbA1c (1.1%) was observed in those who had a baseline HbA1c of > 10%. A significant reduction in baseline median total daily dose (TDD) of insulin (57 units) noted both at 4 months (29.9 units (p<0.001) and 12 months (25u (p<0.001). There was no significant variation noted in the weight over 12 months.

Conclusions: This study adds to the existing literature that continuous subcutaneous insulin infusion therapy significantly improves glycaemic control, reduced the total daily dose of insulin and had no effect on weight over 12 months. In our study age < 30 years and HbA1c of > 10% prior to commencement of therapy are predictors of poor glycaemic outcome at 12 months. Duration of diabetes and gender did not influence the glycaemic outcomes at 12 months.

Introduction

The incidence and prevalence of diabetes continues to rise, with more than 552 million people worldwide expected to be affected by this disorder by 2030 (1). Type 1 diabetes is an autoimmune disease, which requires lifelong insulin treatment for euglycaemia and prevention of complications due to glycaemic variability. Type 1 diabetes most commonly occurs in childhood and adolescence with increasing incidence in older age group (2). In Australia, the prevalence rate is 139 cases per 100,000 population which, places it as the 10th highest among the developed countries (3). Type 1 diabetes causes a massive burden on individual's, the community and the health care system (4). The financial burden of type 1 diabetes is estimated to be $570 million annually in Australia (5).

The cornerstone of management of diabetes mellitus is intensive glycaemic control to prevent chronic hyperglycaemia induced microvascular and macrovascular complications (6,7). The current model of care for most adult type 1 diabetes patients in Australia is multiple daily dose insulin as opposed to continuous subcutaneous insulin infusion therapy due to the financial burden.

Intensive insulin therapy is well proven to reduce micro and macro vascular complications in diabetes (6). However intense therapy is associated with severe hypoglycaemic events (6).

CSII therapy delivers small dose of rapid-acting insulin throughout the day (the basal rate). A bolus dose of insulin is delivered at meal-times and additional boluses can be administered to correct high blood glucose levels. CSII therapy has a number of advanced features that enable them to closely mimic normal pancreatic physiology. According to
American Diabetes Association (ADA) guidelines, type 1 diabetic patients with wide glycaemic variability, recurrent diabetic ketoacidosis, frequent hypoglycaemia and hypoglycaemic unawareness are most eligible for CSII therapy (8).

All patients who are eligible for CSII therapy should be proficient in carbohydrate counting and should receive a structured education programme; therefore it is standard practice that patients will be on multiple daily insulin injections prior to initiation of CSII therapy (9).

Multiple studies have looked at the efficacy of continuous subcutaneous insulin infusion (CSII) on glycaemic control and have shown improvement in HbA1c levels compared to MDI (4, 7, and 13). The studies that looked at the long term efficacy of CSII therapy on glycaemic targets also shows CSII therapy is better in both short term and long term glycaemic control compared to MDI (15, 16, 17).

CSII therapy is associated with decreased risk of severe hypoglycaemia and the need for emergency medical care (18, 19). The latter translates into reduction in the cost of care and utilization of health care resources (9). The sensor augmented CSII therapy with automated insulin suspension devices has proven to reduce moderate to severe hypoglycaemic events compared to standard CSII therapy (10).

Quality of life measures have shown improvement with CSII therapy compared with MDI (11). The cost associated with consumables, pump failure, hypoglycaemia, diabetic ketoacidosis, lipohypertrophy and skin infection are recognised disadvantages of CSII therapy (12).

The aim of this study is to assess the glycaemic outcomes, total daily dose of insulin and weight of type 1 diabetes patients on CSII therapy and identify the predictive factors for good response to treatment. This study will provide guidance for efficient and effective patient selection criteria, implementing local guidelines or recommendations for safe and sustainable service and optimise existing patient management.

Methodology

This study is a retrospective quality assurance chart audit conducted at the Townsville hospital diabetes outpatient clinic. According to both inclusion and exclusion criteria a total of 105 patients on CSII therapy were identified from 1st January 2001 to 31st of December 2014. The inclusion criteria were all patients with type 1 diabetes, age more than 18 years and completed minimum of 12 months of CSII therapy at the time of data collection. The exclusion criteria were pregnant women, patients with chronic kidney disease stage 5, end stage liver disease with Child- Pugh score C, discontinuation of CSII therapy in less than 12 months, patients with solid tumours on chemotherapy and organ transplant. Of the 105 patient’s, 53 patients had insufficient data even though they met the inclusion criteria. The patients who were excluded due to insufficient data were those who did not have information on HbA1c, weight and total daily dose of insulin for both at 4 and 12 months of CSII therapy. Similarly those who did not have data for number of episodes of diabetic ketoacidosis (DKA), severe hypoglycaemic episodes and hospital admissions due to any causes both at 12 months before and after CSII therapy were excluded. Therefore at the end of data collection only 52 patients had sufficient data to include in the study.

Data were collected from handwritten patient medical records as well as public, private laboratory investigations and point of care testing (POC-A1c). HbA1c, weight and total daily dose (TDD) of insulin were collected before 4 months and at 4 months and 12 months of CSII therapy. Episodes of DKA, severe hypoglycaemic events and number of hospital admissions due to any other causes were collected both before and after 12 months of CSII therapy. We also collected information about age, gender, duration of diabetes, types, duration and complications of CSII therapy. Micro and macrovascular complications data were collected according to International classification of diseases 10th revision, Australian modification (ICD-10 AM). The number of specialist clinic visits, point of care and phone call review with diabetic educators were recorded before and after 4 months and 12 months of CSII therapy.

The number of hospital admissions due to DKA or any other causes and severe hypoglycaemic episodes were very few both before and after CSII therapy. Therefore these data were not analysed.

Clinically significant improvement in glycaemic control was defined as a reduction of HbA1c of > or = 0.5% from baseline. Severe hypoglycaemia was defined as events that needed help from a family member, friend or required emergency service or hospital admission.

Given the fact it was a observational study no patients were involved in setting the research question, or outcome measures, nor were they involved in the design or implementation of this study.

Statistics

Descriptive statistics were used for all variables (median, frequencies, and cumulative percentages). Comparison were made using Wilcoxon’s signed rank test as these are repeated – measured variables. We considered a P value < 0.05 to be statistically significant and a P value of <0.01 to be highly significant. A subgroup analysis was performed on patients with baseline HbA1c more than 10% and similar statistical analysis methods were used. The data analysis was conducted through SPSS version 22.

Results

A total of 52 patients were analysed in this study. Of the 52, 34.6% were males. The base line characteristics are highlighted in table 1. Both male and female patients were similar in their baseline characteristics. A significant reduction in baseline median HbA1c (8.6%) was noted both at 4 months (0.6%, (p=0.035)) and 12 months (0.7% (p=0.001)) of continuous subcutaneous insulin infusion therapy (CSII). The statistically significant reduction in HbA1c at 4 months was maintained at 12 months (p=0.025). Only those who had a median HbA1c of > 8% prior to initiation of CSII therapy had HbA1c reduction of >0.5% at 4 months (table 3). The greatest reductions (11.1%) was observed in those who had a base line HbA1c of > 10% (table 3). At 12 months of CSII therapy a reduction in the base line median HbA1c was noted (8.6% to 7.7%) in those
more than thirty years but an increase in median HbA1c was noted in those who are less than 30 years (8.0% to 8.6%). The median HbA1c was 7.8% in those with diabetes more than 10 years and 8% in less than 10 years. There was no difference in the median HbA1c in females (7.8%) and males (7.9%) at 12 months of CSII therapy.

A significant reduction in baseline median total daily dose (TDD) of insulin (57 units) noted both at 4 months (29.9 units [p<0.001]) and 12 months (25 units [p<0.001]) of CSII therapy. The reduction in total daily dose of insulin at 12 months of CSII was not significant (p=0.07) compared to median total daily dose of insulin at 4 months (Fig 2).

No statistically significant change noted in the baseline weight both at 4 months (73.0 kg [p=0.13]) and 12 months (73.5kg [p=0.12]) of continuous subcutaneous insulin infusion therapy (Fig 3). There was no significant variation noted in the weight over 12 months. A subgroup analysis was performed on patients with baseline median HbA1c of more than 10%. The base line characteristics of these patients are highlighted in Table 2. A statistically significant reduction in median HbA1c (11.1%) was noted both at 4 months (1.1%, [p=0.025]) and 12 months (1.1%, p=0.01) of CSII therapy (Fig 4). The reduction in HbA1c from 4 months to 12 months was not statistically significant (0%, [p=0.262]).

<table>
<thead>
<tr>
<th>Variable (median)</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
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<td>29</td>
</tr>
<tr>
<td>Duration of diabetes (years)</td>
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<tr>
<td>HbA1c (%)</td>
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<td>8.5</td>
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<tr>
<td>Weight (kg)</td>
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<td>73</td>
</tr>
<tr>
<td>Total daily dose of insulin (units)</td>
<td>57</td>
<td>57.5</td>
</tr>
</tbody>
</table>

**Table 1: Baseline characteristics of the study population (n=52)**

**Figure 1: Median HbA1c with duration of CSII therapy**

** P value <0.01
* P value <0.05.

CSII = continuous subcutaneous insulin infusion
Table 2: Base line characteristics of patients with HbA1c >10% (n=13)

<table>
<thead>
<tr>
<th>Variable (median)</th>
<th>female</th>
<th>Male</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
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<td>4</td>
</tr>
<tr>
<td>Age (years)</td>
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<td>22</td>
</tr>
<tr>
<td>Duration of diabetes (years)</td>
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<td>7.5</td>
</tr>
<tr>
<td>HbA1c (%)</td>
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<td>10.7</td>
</tr>
<tr>
<td>Weight (Kg)</td>
<td>70</td>
<td>59</td>
</tr>
<tr>
<td>Total daily dose of insulin (units)</td>
<td>68</td>
<td>83.5</td>
</tr>
</tbody>
</table>
Discussion

In accordance with previous studies (4, 7, 13) our study also demonstrated a statistically significant reduction in the median HbA1c following CSII therapy. The reduction in median HbA1c at 4 months was regardless of the HbA1c prior to CSII therapy (Table 3). Clinically significant reduction was observed both at 4 months (0.6%) and 12 months (0.7%) of continuous subcutaneous insulin infusion therapy. However the reduction in HbA1c was clinically insignificant (0.1%) from 4 to 12 months.

The Diabetes Control and Complication Trial (DCCT) demonstrated a decrease in HbA1c by 0.5% reduced long term micro vascular complications (7). According to American Diabetes Association guidelines (26), adhering to a strict follow up protocol both at initiation and continuation phase of CSII therapy is important for good glycaemic outcomes.

Even though the greatest reduction in HbA1c at 4 months (1.1%) was observed in a subgroup of patients with HbA1c >10% prior to CSII therapy, the median HbA1c remained the same both at 4 and 12 months (10%). These patients median duration of diabetes and age were noted to be less than the rest of the study population (Table 2). In consistent with previous studies the transition period from adolescents to younger adults is associated with poor glycaemic control (16, 21). Those who had excellent HbA1c (<7%) while on multiple daily dose regimen and opted for CSII therapy due to life style reasons maintained a HbA1c of < 7% at 1 year. Thus it appears CSII therapy facilitates to maintain better glycaemic control but does not change the pre-existing disease management behaviour.

In this study the baseline HbA1c prior to continuous subcutaneous insulin infusion therapy is a predictor of long term glycaemic control (Table 3). This is likely that pre-existing risk factors that have led to the poor glycaemic control could have continued after initiation of CSII therapy.

Our study demonstrates that age less than 30 years and HbA1c of > 10% at base line associated with poor glycaemic targets at 12 months but there was no association between glycaemic outcomes and the duration of diabetes and gender.
In terms of total daily dose of insulin (TDD), our study results were concordant with multiple previous studies. A significant reduction in total daily dose of insulin noted both at 4 and 12 months of CSII therapy compared to multiple daily dose of insulin (4, 6, 17, 25, and 28). The reduction in total daily dose (TDD) of insulin was not statistically significant at 12 months compared to 4 months of CSII therapy, however the reduction was clinically significant. The initial reduction in the total daily dose of insulin could be related to close monitoring and follow up during the intense period of CSII therapy.

Insulin causes weight gain through multiple mechanisms (23). A small case control study on adolescents type 1 diabetes, demonstrated that CSII therapy itself does not usually leads to weight gain and reinforced the importance of education on calorie content and eating habits. (19).

Multiple studies have shown there is no significant difference in weight while on CSII therapy when compared to multiple daily dose of insulin (13, 18, and 25). In accordance with previous studies we also noted a stable weight throughout the 1 year period. The reasons for weight gain with insulin therapy are either due to higher doses or frequent hypoglycaemia (26). In our study, we did not observe weight loss with reduced total daily dose of insulin. Since we did not have data on confounding variables such as calorie intake, appetite and level of exercise, the stable weight could be due to lifestyle factors. However frequent CSII therapy education sessions also have had an impact.

The number of hospital admissions from diabetic ketoacidosis (DKA) and due to any other causes to the Townsville hospital were few. Under reporting or inaccurate coding could have led to few numbers both before and after CSII. Hypoglycaemic events may be under recorded and under reported by patients in clinics. This is mainly due to lack of patient's adherence to glycemic monitoring. In addition, every patient's indications for CSII therapy or their hypoglycaemic awareness were not available. The evidence is variable with regards to impact of CSII therapy on hypoglycaemic events (6, 18, and 19).

Implications and recommendations

Continuous subcutaneous insulin infusions therapy is an established effective mode of treatment for type 1 diabetes. Our study adds to the existing literature that 12 months of CSII therapy significantly improves glycemic control, reduced the total daily dose of insulin and had no effect on weight. Even though CSII therapy is an established treatment, it may not be the effective treatment for all.

We did not identify the exact indications for continuous subcutaneous insulin infusion therapy in our study population due to lack of documentation. However about 13.5% of patients had HbA1c less than 7% before CSII. Even though these patients had satisfactory glycemic control on multiple dose of insulin, they may have opted for CSII therapy for life style reasons. In these patients regardless of the mode of therapy the glycemic targets remained well within the acceptable range.

A subgroup of patients with HbA1c more than 10% while on multiple dose insulin therapy (MDI), still had a median HbA1c of 10% both at 4 and 12 months of CSII. In this group, mode of treatment did not change the underlying patient disease management behaviour and hence the treatment targets. In Australia CSII therapy is not provided through Medicare, adult patient's eligible for CSII needs private health insurance and this can lead to selection bias (31). Therefore, socioeconomic status becomes one of the most important determinants for CSII therapy rather than the standard indications as described in American Diabetes Association (ADA) guidelines (8).

According to Australian institute of health and welfare CSII therapy was more prevalent in high socioeconomic status due to the cost associated with devices and consumables. High socioeconomic status patients with type 1 diabetes achieve better glycemic control than low economic status patients (32,33). Hence in our study the patients would have achieved a good glycemic control regardless of the mode of therapy. Therefore the improvement in glycemic targets could have been an expected outcome. Hence the results cannot be generalised to all type 1 diabetes patients attending the diabetes centre.

Even though there was clinically significant reduction in HbA1c at both 4 and 12 months of CSII therapy the reduction in HbA1c from 4 months to 12 months was clinically insignificant. This may be due to less number of educational sessions, clinic appointments and lack of motivation from patients after the initial phase of treatment.

As the study did not show a HbA1c reduction from 4 months to 12 months period, we identified the need to intensify structured educational sessions and follow up after 4 months therapy. There is a necessity to develop better selection criteria to enroll patients for CSII therapy with consideration given to existing patient disease management behaviour.

The current existing model of care includes, phone call review by the diabetic educators and specialists clinic appointments. The follow up appointments can be very demanding both during the initiation and continuation phase of CSII therapy with the existing resource.

Defined protocols for an effective follow up will minimize resource exhaustion. Group education instead of individual sessions are efficient way to manage time. Treatment goals and follow up frequency needs to be discussed with patients at the beginning of therapy to ensure adherence. An afterhours on call system involving the diabetic educators or a clinical nurse practitioner will enhance patient contact with health care system in a timely manner. Nurse practitioner lead clinics to rural and remote areas through tele health service will reduce patient travel time. This will enhance followup and improve glycemic outcomes.

Maintaining a database helps to identify patients who are not achieving desired glycemic targets. This will allow critical appraisal of clinical benefit and cost effectiveness of CSII therapy both at the patient and institutional level. This data also can be used for future prospective larger studies.

The strengths and limitations

This is a single centre study, thus all enrolled patients were under the same care model. This is the first study in North
Queensland to ascertain the impact of CSII therapy in type 1 diabetes. Each patient serves as their own control, since their previous insulin regimen was multiple dose insulin therapy.

It is a retrospective, single centre, observational study therefore it is difficult to generalise the outcome to all type 1 diabetes patients attending the outpatient. The HbA1c levels were analysed through both public and private laboratories and point of care testing (POC-A1c). HbA1c levels obtained from point of care testing are lower than laboratory testing (34). The lack of standardization of HbA1c is a limitation in our study.

The CSII technology had advance with time to improve glycaemic outcomes. The advanced devices have been shown to improve both pre-prandial glycaemic control and overnight hypoglycaemia (35). Hence the difference in CSII devices among patients is a limitation in our study.

A significant change in diabetes care came with the development of continuous glucose monitoring system (CGMS). It is an indwelling subcutaneous sensor that check the interstitial fluid glucose readings every 3 to 5 min. CGMS identifies glycaemic excursions and hypoglycaemia over 24 hours and helps to improve both hyper and hypoglycaemia (36). The in-cooperation of (CGMS) in some patients, over the study period, could have contributed to better glycaemic outcomes.

Chronic anaemia due to any reason can falsely reduce the HbA1c level. We did not exclude patients with anaemia apart from those with end stage renal disease. The number of DKA, hospital admissions due to any cause and severe hypoglycaemic events were very small, hence unable to ascertain the impact of CSII therapy on these variables.

Conclusion
This study adds to the existing literature that CSII therapy significantly improves glycaemic control, reduced the total daily dose of insulin and had no effect on weight over 12 months. Our study identifies age less than 30 years and HbA1c of > 10% at base line are predictors of poor glycaemic control at 12 months. Duration of diabetes and gender did not influence the glycaemic outcome. This study identifies the need for defined eligibility criteria for CSII therapy and the need for intense follow up and education beyond 4 months. We did not objectively look at the patient disease management behaviour which is one of the important predictors of glycaemic outcomes. A prospective quality assurance study is needed to reanalyse the outcomes once recommendations are implemented.

References

Serum Magnesium Status and its Correlation with Insulin Resistance in Newly Diagnosed Patients with Type 2 Diabetes Mellitus

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Abstract

Hypomagnesemia has been reported in type 2 diabetes mellitus (T2DM) and an association of low serum magnesium (Mg) with insulin resistance has been observed. In this cross-sectional study, 65 new T2DM patients and 65 healthy controls were investigated to assess the Mg status and see the association between Mg level and insulin resistance. Oral glucose tolerance test, HbA1c, serum Mg, and fasting insulin were measured and the level of insulin resistance was calculated by using the homeostasis model assessment for insulin resistance (HOMA-IR). Serum Mg level was similar in T2DM and control groups; a higher frequency of hypomagnesemia was observed in the T2DM than control group (26.2% vs. 12.3%) though it was not statistically significant (p= 0.074). Level of insulin resistance (HOMA-IR) was higher in the T2DM group and a higher frequency of subjects had insulin resistance in this group compared to controls. No significant differences in age, body mass index (BMI), waist circumference (WC), waist-hip ratio (WHR), fasting plasma glucose (FPG), HbA1c, fasting insulin level and HOMA-IR were observed between normomagnesaemic and hypomagnesaemic T2DM subjects. In the T2DM group, age, BMI, WC, WHR, FPG, fasting insulin and HOMA-IR correlated with serum Mg level though in the control group Mg had significant inverse correlations with BMI and fasting insulin. New T2DM subjects and healthy controls had similar Mg status although the frequency of hypomagnesemia was higher (not significant) in the T2DM group and serum Mg level had no correlation with glycemic status, fasting insulin and HOMA-IR in T2DM patients.

Keywords: type 2 diabetes, magnesium, insulin resistance, HOMA-IR

Introduction

Type 2 diabetes mellitus (T2DM) is a multifaceted disease characterized by insulin resistance, impaired insulin secretion, excess hepatic glucose production, and abnormal fat metabolism. In the early stage, insulin resistance plays the major role in the pathogenesis of T2DM. Pathogenesis of insulin resistance (IR) is multifactorial. Although obesity, genetic predisposition, less physical activity, food habits, and nutritional factors are well-known trigger factors for insulin resistance and T2DM, more new factors are coming forwards (1). Recently the role of minerals (such as chromium, magnesium, vanadium, zinc, manganese, molybdenum, selenium) and vitamins in the pathogenesis of insulin resistance has gained particular scientific interest (2, 3, and 4).

Magnesium (Mg) is an important mineral involved in the glucose homeostasis, plays a key role in regulating insulin action and sensitivity, insulin-mediated glucose uptake and vascular tone, and has an association with oxidative stress (5). Mg is also an anti-inflammatory molecule (6). Hypomagnesemia is common in T2DM occurring at a prevalence of 13.5 to 47.7% (7). Population-based studies and meta-analyses showed a positive correlation between low magnesium intake and risk of developing insulin resistance and T2DM (6, 8, 9). Newly diagnosed T2DM patients were found to have lower Mg levels than no diabetic controls (10, 11, 12, 13, and 14). Mg levels were also found to be lower than healthy controls in previously diagnosed T2DM subjects (15-19). In T2DM patients, serum Mg has been found to be negatively associated with fasting glucose and glycated haemoglobin (HbA1c) (11, 13, 15, 19, 20, 21). Significant negative associations of serum Mg level have also been reported with fasting insulin concentration and HOMA-IR (10, 14, 17, and 20).

There is inadequate data reflecting the relationship of magnesium status with the level of glycemia, insulin level and insulin resistance in Bangladeshi T2DM patients. This study was undertaken to address the lacun.
Methods

This observational cross-sectional study was conducted in the Department of Medicine of a tertiary hospital of Bangladesh from January 2016 to December 2017, with the permission of institutional review board of the hospital. All patients with newly diagnosed T2DM attending the Medicine Outpatient Department of the hospital during the study period were considered as the study population. Non-probability convenient sampling technique was applied and 65 newly diagnosed non-pregnant adult patients with T2DM according to the American Diabetes Association (ADA) criteria, aging 35 to 65 years before initiation of any pharmacological treatment for DM were included in the sample (22).

Equal numbers of age and sex-matched healthy controls selected from healthy attendants of the patients and health care professionals were included in the control group. Diabetic patients presented with any acute or chronic complications of DM, or with an acute illness, those having diarrhoea or other mal-absorptive states, those taking alcohol or drugs like diuretics, and those with a history of small bowel surgery were excluded. Informed written consent was taken from each study subject before enrollment; relevant history was taken, physical examination including anthropometric measurements was done; collected data were recorded in a pre-specified data collection sheet. Obesity status was determined by body mass index (BMI) categories applicable to the Asian Indians and waist circumference ≥90 cm in male and ≥80 cm in female were used to define abdominal obesity (23). All study subjects were requested to attend medicine OPD on another day with overnight fasting when they were tested by standard 75 gram oral glucose tolerance test (OGTT), WHO protocol was used for OGTT (22). The fasting blood sample was also used for estimation of HbA1c, serum magnesium, and plasma insulin levels.

Biochemical analysis:

Plasma glucose was estimated by using glucose oxidase-peroxidase method (Colotimetric method) by a semi-auto analyzer (Screen Master 3000 manufacturer: Biochemical System International, Italy), HbA1c was assayed by immuno-fluorescence assay on NGSP certified quantitative immunoassay analyzer Getein 1100 (Getein Biotech, Inc, China), serum magnesium was measured by enzymatic method read by a semi-auto analyzer (Screen Master 3000 manufacturer: Biochemical System International, Italy) and serum fasting insulin was assayed by quantitative ELISA method (Human Insulin ELISA Test Kit, Catalog No: 10801, manufacturer: JAI international, Inc, USA) with Elisa reader (Plate reader, manufacturer: das srl, Italy). Homeostasis model assessment for insulin resistance (HOMA-IR) was used as insulin sensitivity indices which correlate well with the gold standard method (24). The methods are well validated in the South Asian population (25). HOMA-IR was calculated by using the following formulae: HOMA-IR = [Fasting insulin (μIU/mL) × fasting glucose (mg/dL)] / 405. Participants were considered as insulin resistant when HOMA-IR ≥2.6 (24). Serum Mg level <1.8 mg/dL was used as the cut-point for defining Mg deficiency according to the reference range of the corresponding laboratory.

Statistical analysis:

Statistical analysis was done using Statistical Packages for Social Sciences (SPSS) software version 23.0 (IBM Corp. Released 2015. IBM SPSS Statistics for Windows, Version 23.0, Armonk, NY: IBM Corp.). The categorical variables were represented as percentages and measurable variables as mean ± standard deviation (SD) or median and inter-quartile range (IQR) as applicable. Student’s t-test, Mann-Whitney U test, and Chi-square test were performed as applicable for comparing the variables between different groups. Pearson’s correlation test was used to observe the correlation of Mg level with other variables. P value ≤0.05 was considered to be statistically significant.

Results

Demographic characteristics of the study participants are shown in table 1. The T2DM group and control group subjects did not differ in respect to age, gender, BMI, being overweight or obese, waist circumference, and having first-degree relative with T2DM, though the waist-hip ratio and the frequency of abdominal obesity was higher in the T2DM group.
### Table 1: Demographic characteristics of the study subjects

<table>
<thead>
<tr>
<th>Variables</th>
<th>Subjects with T2DM (n=65)</th>
<th>Healthy controls (n=65)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), mean ± SD</td>
<td>46.88 ± 8.48</td>
<td>45.35 ± 7.61</td>
<td>0.283a</td>
</tr>
<tr>
<td>Male Gender, %</td>
<td>38 (58.5%)</td>
<td>38 (58.5%)</td>
<td>1.000b</td>
</tr>
<tr>
<td>BMI (kg/m²), mean ± SD</td>
<td>25.02 ± 3.89</td>
<td>25.24 ± 5.48</td>
<td>0.788a</td>
</tr>
<tr>
<td>BMI ≥23 (kg/m²), %</td>
<td>48 (73.8%)</td>
<td>38 (58.5%)</td>
<td>0.095a</td>
</tr>
<tr>
<td>WC (cm), mean ± SD</td>
<td>92.81 ± 10.22</td>
<td>89.85 ± 14.28</td>
<td>0.176a</td>
</tr>
<tr>
<td>Abdominal Obesity, %</td>
<td>48 (73.8%)</td>
<td>35 (53.8%)</td>
<td>0.028a</td>
</tr>
<tr>
<td>Waist-Hip ratio, mean ± SD</td>
<td>0.98 ± 0.05</td>
<td>0.94 ± 0.08</td>
<td>0.001a</td>
</tr>
<tr>
<td>First degree relative with T2DM, %</td>
<td>22 (33.8%)</td>
<td>21 (32.3%)</td>
<td>1.000b</td>
</tr>
</tbody>
</table>

BMI = Body mass index, WC = Waist circumference; a by Student’s t-test, b by Chi-square test after adjustment by Bonferroni method.

### Table 2: Metabolic parameters of the study subjects

<table>
<thead>
<tr>
<th>Variables</th>
<th>Subjects with T2DM (n=65)</th>
<th>Healthy controls (n=65)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>FPG (mg/dL), median (IQR)</td>
<td>142.0 (116.5 – 141.0)</td>
<td>88.0 (80.5 – 98.0)</td>
<td>&lt;0.001a</td>
</tr>
<tr>
<td>HbA1c (%), median (IQR)</td>
<td>8.57 (7.12 – 10.66)</td>
<td>5.71 (5.25 – 6.0)</td>
<td>&lt;0.001a</td>
</tr>
<tr>
<td>F. insulin (µIU/mL), median (IQR)</td>
<td>8.29 (3.73 – 13.45)</td>
<td>7.76 (3.39 – 10.46)</td>
<td>0.511a</td>
</tr>
<tr>
<td>HOMA-IR, median (IQR)</td>
<td>3.14 (1.18 – 5.67)</td>
<td>1.76 (0.84 – 2.47)</td>
<td>&lt;0.001a</td>
</tr>
<tr>
<td>Insulin resistance (%)</td>
<td>40 (61.5%)</td>
<td>14 (21.5%)</td>
<td>&lt;0.001b</td>
</tr>
<tr>
<td>5. Magnesium (mg/dL)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>2.23 ± 0.50</td>
<td>2.27 ± 0.40</td>
<td>0.582c</td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>2.10 (1.80 – 2.70)</td>
<td>2.20 (2.20 – 2.50)</td>
<td>0.468a</td>
</tr>
<tr>
<td>Range</td>
<td>1.10 – 3.30</td>
<td>1.50 – 3.20</td>
<td></td>
</tr>
<tr>
<td>Mg Deficiency (%)</td>
<td>17 (26.2%)</td>
<td>8 (12.3%)</td>
<td>0.074b</td>
</tr>
</tbody>
</table>

FPG = Fasting plasma glucose, IQR = Inter quartile range, a by Mann-Whitney U test, b by Chi-square test after adjustment by Bonferroni method, c by Student’s t-test.
Table 3: Comparison of Variables in subsets of T2DM subjects with deficient and normal Mg

<table>
<thead>
<tr>
<th>Variables</th>
<th>Subjects with Mg Deficiency (n=17)</th>
<th>Subjects without Mg Deficiency (n=48)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), mean±SD</td>
<td>48.82 ± 8.53</td>
<td>46.19 ± 8.44</td>
<td>0.274a</td>
</tr>
<tr>
<td>BMI (kg/m²), mean±SD</td>
<td>23.62 ± 3.99</td>
<td>25.51 ± 3.77</td>
<td>0.086a</td>
</tr>
<tr>
<td>WC (cm), mean±SD</td>
<td>88.94 ± 11.96</td>
<td>94.18 ± 9.28</td>
<td>0.069a</td>
</tr>
<tr>
<td>WHR (mean±SD)</td>
<td>0.97 ± 0.05</td>
<td>0.98 ± 0.05</td>
<td>0.448a</td>
</tr>
<tr>
<td>FPG (mg/dL), Median</td>
<td>136.0</td>
<td>143.0</td>
<td>0.946b</td>
</tr>
<tr>
<td>HbA1c (%),Median</td>
<td>8.07</td>
<td>8.78</td>
<td>0.107b</td>
</tr>
<tr>
<td>F. Insulin (µIU/ml), Median</td>
<td>7.86</td>
<td>8.56</td>
<td>0.433b</td>
</tr>
<tr>
<td>HOMA-IR, Median</td>
<td>3.13</td>
<td>3.62</td>
<td>0.474b</td>
</tr>
</tbody>
</table>

WC = Waist circumference, WHR= Waist-hip ratio, BMI = Body mass index, FPG = Fasting plasma glucose, HOMA-IR = Homeostasis model assessment for insulin resistance, a by Student’s t-test, b by Mann-Whitney U test

Table 4: Correlations

<table>
<thead>
<tr>
<th>Variables</th>
<th>T2DM (n=65)</th>
<th>Control (n=65)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>r</td>
<td>p</td>
</tr>
<tr>
<td>Age and Mg</td>
<td>-0.194</td>
<td>0.121</td>
</tr>
<tr>
<td>BMI and Mg</td>
<td>0.181</td>
<td>0.148</td>
</tr>
<tr>
<td>Waist Circumference and Mg</td>
<td>0.178</td>
<td>0.157</td>
</tr>
<tr>
<td>Waist : Hip Ratio and Mg</td>
<td>0.103</td>
<td>0.413</td>
</tr>
<tr>
<td>FPG and Mg</td>
<td>-0.056</td>
<td>0.657</td>
</tr>
<tr>
<td>HbA1c and Mg</td>
<td>0.138</td>
<td>0.274</td>
</tr>
<tr>
<td>Fasting Insulin and Mg</td>
<td>0.011</td>
<td>0.932</td>
</tr>
<tr>
<td>HOMA-IR and Mg</td>
<td>-0.034</td>
<td>0.788</td>
</tr>
</tbody>
</table>
Table 2 shows the metabolic parameters of the study subjects. T2DM subjects had statistically higher FPG, HbA1c, and HOMA-IR than controls; fasting insulin level was also higher in diabetic group though it did not reach the level of statistical significance. A higher number of subjects had insulin resistance in diabetic group in comparison to control group. Serum Mg level did not differ in between the two groups; the frequency of Mg deficiency was higher in the diabetes group though it was not significant.

The comparison of different variables between T2DM subjects with deficient and normal Mg is given in table 3.

The two groups did not differ significantly in age, BMI, waist circumference, waist-hip ratio, FPG, HbA1c, fasting insulin level and HOMA-IR. Correlations of serum Mg level with other variables in T2DM and control subjects are given in table 4. Serum Mg did not show significant correlation with any of the variables in the T2DM group and had negative correlations with BMI and fasting insulin level in the control group.

**Discussion**

Diabetes mellitus is the most common endocrine and metabolic cause of Mg deficiency (7). A low Mg intake and an increased Mg urinary loss appear the most important mechanisms causing Mg depletion in T2DM patients, while Mg absorption and retention of dietary Mg seems not to be impaired in them. Mg deficiency may not be just a secondary consequence of T2DM but may precede and contribute itself to the development of insulin resistance and altered glucose tolerance, and even T2DM (5). There are accumulating evidence to suggest that Mg deficiency may be a preceding factor in insulin resistance and hyperinsulinaemia (2, 3, 4, and 6). The exact mechanism by which magnesium deficiency may lead to IR has not yet been fully elucidated. Intracellular magnesium has key roles in regulating insulin action, insulin-mediated glucose uptake, and vascular tone. Intracellular Mg deficiency results in a defective tyrosine-kinase activity, post-receptorial impairment in insulin action, and increased insulin resistance. Cellular magnesium is a critical cofactor for the activities of various enzymes involved in glucose transport, glucose oxidation, insulin release, and is a cofactor for ATPase and adenylyl cyclase enzymes. Chronic magnesium deficiency has also been associated with increased free radical induced cellular damage, and this may also contribute to post-receptor insulin resistance (4, 5).

Our study observed a higher frequency of hypomagnesaemia in the T2DM group (26.2%) than the control group (12.3%) though the difference failed to reach the level of statistical significance (p= 0.074). We found no significant difference in serum Mg levels between the two groups (2.23±0.50 mg/dl vs. 2.27±0.40 mg/dl, mean±SD). Masood et al and Tiwari et al also found similar Mg level in T2DM patients and healthy controls (26,27). On the contrary, newly diagnosed T2DM patients were found to have lower Mg levels than nondiabetic controls in studies done by Chutia et al., Hussain et al, Khan et al, Karim et al and Sukesha et al (10,11,12,13,14). Our study result goes contrary to the proposal of lower magnesium in the etiopathogenesis of insulin resistance and T2DM. However, recognizing the signs of magnesium deficiency and measurement of intracellular magnesium may be important as the deficiency can occur long before it is reflected in the serum values, but this was not done in this study (7).

Researchers have found negative correlations of serum Mg level with FPG in T2DM patients (13, 17, 19, and 21). In our study, no difference in FPG was observed between Mg-depleted and Mg-sufficient T2DM subjects and also no correlation was between Mg and FPG was found, which is similar to the observations of Khan et al and Ikay et al (12,28). Odusan et al found similar FPG in normomagnesemic and hypomagnesemic T2DM patients (16).

HbA1c was found similar in T2DM subjects with low and normal Mg which is contrary to previous observation by Odusan et al who found higher HbA1c in Mg-depleted diabetic patients (16). Mg was found to have a negative correlation with HbA1c in some studies (11, 15, 17, 20, and 21). On the contrary, our study failed to demonstrate any correlation between Mg and HbA1c. Tiwari et al also observed no significant correlation between Mg and HbA1c in T2DM subjects (26).

Fasting insulin level was higher in diabetic subjects than healthy controls in our study though it was no statistically significant. A significantly higher fasting insulin in new T2DM patients in comparison to the healthy controls was found by Chutia et al (10). HOMA-IR was significantly higher in T2DM patients and the frequency of subjects having insulin resistance was higher in the T2DM group. Chutia et al had similar observations (10). We found similar fasting insulin level and HOMA-IR in diabetic patients with normal and deficient Mg. On the contrary, others found higher insulin level and HOMA-IR in Mg-deficient diabetic patients (20).

A higher level of insulin resistance is associated with lower Mg level and Mg has been found to have negative correlations with fasting insulin and HOMA-IR (10, 14, 17, and 20). But in our study, we found no significant correlation of fasting insulin level and HOMA-IR with serum Mg level. El-said et al found no correlation of Mg with insulin level (17). Jahanshahi et al observed no correlation between serum Mg level and HOMA-IR (18).

We found no difference in age, BMI, WC, and WHR between T2DM subjects with normal and depleted Mg though hip circumference was higher in normomagnesemic patients. Odusan et al found no difference of age between normal and Mg-deficient diabetic patients (16). El-said et al found no correlation of Mg with age and BMI; and Ikay et al observed no correlation of Mg with BMI, waist circumference, hip circumference and the waist-hip ratio between normo- and hypo-magnesemic T2DM subjects (17, 28).
Limitations of the study:

Our sample size was small and randomization of sampling was not done. Dietary assessment for Mg intake was not quantified. It was a cross-sectional study; no follow up evaluation of the study subjects was done. This was a single tertiary level hospital-centered study, so the result may not reflect the whole community. Clinical evaluation of magnesium deficiency and measurement of intracellular magnesium was not done. The median HbA1c of the controls was 5.71%, which indicates that a fair proportion of them had pre diabetes, which may influence their Mg status and other metabolic profiles.

Conclusion

We found no significant difference of serum magnesium level between newly diagnosed T2DM subjects and healthy controls although the frequency of hypomagnesemia was non-significantly higher in the T2DM group. Serum magnesium level showed no correlation with glycemic status, fasting insulin and HOMA-IR in T2DM patients. However, it needs further wide-scale studies to understand the association of serum magnesium with insulin resistance properly.

References


Frequency and predictors of hyperglycemia in patients with various thyroid disorders attending a tertiary hospital of Bangladesh.

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3National Institute of Cancer Research and Hospital
4Shahid Sayeed Nazrul Islam Medical College, Bangladesh
5Bangabandhu Sheikh Mujib Medical University, Bangladesh

Abstract

Thyroid diseases and diabetes mellitus are the two most common endocrine disorders encountered in clinical practice having a mutual influence on each other, and an association between both conditions has long been reported. This cross-sectional study aimed to explore the frequency of hyperglycemia among newly detected patients with thyroid disorders. Four hundred subjects, newly diagnosed with different forms of thyroid disorders, previously not known to have diabetes or prediabetes, underwent a standard oral glucose tolerance test (OGTT). Plasma glucose values were assessed by the glucose-oxidase method. Out of them, 211 (52.7%) subjects were found to have glucose intolerance (35.5% prediabetes and 19.3% diabetes). Subjects with glucose intolerance had higher mean age, body mass index (BMI), waist circumference, systolic BP, free T4, and lower TSH than euglycemic ones. No statistical difference in glycemic status was observed among the hypothyroid, hyperthyroid, and euthyroid groups. Having a family history of hypertension and abdominal obesity were associated with significantly higher odds of glucose intolerance in the study subjects. Glucose intolerance is frequently found in patients with thyroid disorders. This study emphasizes the importance of screening for glucose intolerance among patients with thyroid disorder.

Keywords: diabetes, glucose intolerance, thyroid dysfunction, hyperthyroidism, hypothyroidism

Introduction

Thyroid disorders and diabetes mellitus are two of the most common endocrine conditions, occurring with greater frequency along with each other (1). Insulin and thyroid hormones are intimately involved in cellular metabolism and thus excess or deficit of either of these hormones can result in the functional derangement of the other (2). Both hypothyroid and hyperfunctioning of thyroid gland influence carbohydrate metabolism at the level of pancreatic islets and glucose-utilizing target tissues, imparting important therapeutic and diagnostic implications (3). Thyroid hormones are positively associated with insulin resistance not only in diabetic patients but also in subjects with a normal glucose tolerance (4).

While Graves' disease may be associated with type 1 diabetes in autoimmune polyglandular syndrome, thyrotoxicosis by itself is diabetogenic. Variable glucose intolerance is seen in up to 50% of patients with Graves’ disease and frank diabetes occurs in 2-3% of hyperthyroid patients (2). On the other hand, subjects with overt and subclinical hypothyroidism demonstrated both insulin resistance and diminished early insulin secretory response (5, 6, 7, 8). Moreover, the frequency of metabolic syndrome was found to be higher in both subclinical and overt hypothyroidism compared to healthy controls (9).

Very limited data are available regarding the frequency of hyperglycemia among patients with thyroid disorders both in our country and internationally. The current study was undertaken to know the frequency of glucose intolerance in newly detected patients with various thyroid disorders.

Methods

This cross-sectional study was conducted at the Endocrine Outpatient Department (OPD) of a tertiary hospital of Bangladesh from March 2015 to May 2015, with the approval of the Institutional Review Board of the institute.
Newly detected adult (≥18 years) patients with various forms of thyroid disorders attending the OPD were considered as the study population and samples were collected consecutively by purposive sampling technique. Thyroid function tests were interpreted according to the normal range of the laboratory (TSH: 0.35-5.5 μIU/mL, FT4: 0.80-1.80 ng/dL) and classified into three groups: hypothyroid, hyperthyroid and euthyroid, according to the criteria set by American Thyroid Association (10, 11). Patients with normal thyroid function but having structural thyroid abnormality such as diffuse or nodular goiter and thyroid malignancy were grouped under euthyroid thyroid disorder group. Patients with diagnosed thyroid disease on treatment, patients with known diabetes or prediabetes, patients with acute illness (sepsis, acute myocardial infarction, severe heart failure, recent admission in intensive care unit) or other co-morbidities (hepatic and renal impairment), pregnant and lactating women, those taking drugs that may cause dysglycaemia (e.g. glucocorticoids) and those having other secondary causes of diabetes were excluded. Patients who gave informed written consent were interviewed and examined for relevant demographic and clinical information. A semi-structured data collection sheet was used to collect and record data which included general information on demographic characteristics, personal history of hypertension, family history of thyroid disease, diabetes, hypertension and dyslipidemia, and history of smoking, alcohol etc. Height, weight, waist circumference and blood pressure were measured by well-calibrated instruments, and body mass index (BMI) was calculated from height and weight. Obesity status was determined by body mass index (BMI) categories applicable to the Asian Indians and waist circumference ≥90 cm and ≥80 cm were used to define abdominal obesity for men and women respectively (12, 13). Hypertension was defined according to JNC VII criteria (14). All of the participants were asked to attend the OPD on another convenient day with overnight fasting for at least 8 hours and all attending patients underwent standard oral glucose tolerance test (OGTT) according to the procedure described by World Health Organization (15). Plasma glucose was assayed immediately by the glucose-oxidase method in the automated analyzer (Dade Behring, Germany). Normal glucose tolerance, prediabetes, and diabetes were diagnosed on the basis of the American Diabetes Association (ADA) criteria for the diagnosis of diabetes in non-pregnant adults (16).

Statistical analysis

Statistical analysis was done using Statistical Packages for Social Sciences (SPSS), version 23.0 software (IBM Corp. Released 2015. IBM SPSS Statistics for Windows, Version 23.0, Armonk, NY: IBM Corp.). All data were expressed as mean±SD (or ±SE), median or in percentages as appropriate. Student’s t-test or Chi-square test was used for comparison of the values of variables among different groups as applicable. Pearson correlation test was used to see correlation among different variables. Binary logistic regressions were used to see the influence of individual predictors on the presence of abnormal glucose tolerance (AGT). A p-value ≤0.05 was considered to be statistically significant.

Results

The demographic, clinical and biochemical characteristics of the study population and the comparison of those variables between subjects with normal glucose tolerance (NGT) and abnormal glucose tolerance (AGT) are shown in Table 1. Subjects with AGT had higher mean age, higher frequency of family history of hypertension and diabetes, higher BMI, waist circumference, systolic blood pressure, TSH, FT4, and higher fasting and 2-hour post 75-gm OGTT values.
<table>
<thead>
<tr>
<th>Variables</th>
<th>Total Subjects (N=400)</th>
<th>Subjects with NGT (N=189)</th>
<th>Subjects with AGT (N=211)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years, mean±SD)</td>
<td>37.21±11.65</td>
<td>36.68±12.27</td>
<td>38.58±10.92</td>
<td>0.013</td>
</tr>
<tr>
<td>Female Gender (%)</td>
<td>310 (77.5%)</td>
<td>147 (77.8%)</td>
<td>163 (77.3%)</td>
<td>0.905</td>
</tr>
<tr>
<td>Smoker (%)</td>
<td>37 (9.3%)</td>
<td>20 (10.6%)</td>
<td>17 (8.1%)</td>
<td>0.394</td>
</tr>
<tr>
<td>Family H/O Thyroid Disease Present (%)</td>
<td>54 (13.5%)</td>
<td>22 (11.6%)</td>
<td>32 (15.2%)</td>
<td>0.310</td>
</tr>
<tr>
<td>Family H/O DM Present (%)</td>
<td>156 (39.0%)</td>
<td>63 (33.3%)</td>
<td>93 (44.1%)</td>
<td>0.031</td>
</tr>
<tr>
<td>Family H/O HTN Present (%)</td>
<td>169 (42.2%)</td>
<td>60 (31.1%)</td>
<td>109 (51.7%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Goiter Present (%)</td>
<td>322 (80.5%)</td>
<td>149 (78.8%)</td>
<td>173 (82.0%)</td>
<td>0.450</td>
</tr>
<tr>
<td>BMI (kg/m², mean±SD)</td>
<td>25.57±5.28</td>
<td>24.98±5.09</td>
<td>26.10±5.39</td>
<td>0.033</td>
</tr>
<tr>
<td>Waist Circumference (cm, mean±SD)</td>
<td>87.0±12.13</td>
<td>85.2±11.7</td>
<td>88.6±12.3</td>
<td>0.005</td>
</tr>
<tr>
<td>Systolic BP (mmHg, mean±SD)</td>
<td>125±14</td>
<td>122±13</td>
<td>128±15</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diastolic BP (mmHg, mean±SD)</td>
<td>81±8</td>
<td>81±7</td>
<td>82±9</td>
<td>0.115</td>
</tr>
<tr>
<td>FPG (mmol/L, mean±SD)</td>
<td>5.33±1.47</td>
<td>4.67±0.51</td>
<td>5.93±1.76</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PG 2 hr after OGGT (mmol/L, mean±SD)</td>
<td>8.26±3.09</td>
<td>6.14±0.95</td>
<td>10.16±3.12</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>S. TSH (µIU/mL, mean±SEM)</td>
<td>23.83±1.98</td>
<td>28.1±3.1</td>
<td>20.0±2.5</td>
<td>0.041</td>
</tr>
<tr>
<td>S. FT4 (ng/dL, mean±SEM)</td>
<td>1.68±0.1</td>
<td>1.43±0.12</td>
<td>1.89±0.15</td>
<td>0.016</td>
</tr>
</tbody>
</table>

(within parentheses the percentage of the column total)
(p-value by Student’s t-test or Chi-square test as applicable)

The glycemic status of the study population is given in Table 2. 52.7% of the subjects had abnormal glucose tolerance (33.5% prediabetes and 19.3% diabetes). The frequency of NGT, prediabetes, and diabetes did not differ significantly among biochemically hypothyroid, hyperthyroid and euthyroid subjects with various thyroid disorders.
### Table 2: Glycemic status of the study population

<table>
<thead>
<tr>
<th>Glycemic Status</th>
<th>Total Subjects (N=400)</th>
<th>Hypothyroid Subjects (n=218)</th>
<th>Hyperthyroid Subjects (n=106)</th>
<th>Euthyroid Subjects (n=76)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>NGT</td>
<td>189 (47.3%)</td>
<td>115 (52.8%)</td>
<td>41 (38.7%)</td>
<td>33 (43.4%)</td>
<td>0.055</td>
</tr>
<tr>
<td>AGT</td>
<td>211 (52.7%)</td>
<td>103 (47.2%)</td>
<td>65 (61.3%)</td>
<td>43 (56.6%)</td>
<td></td>
</tr>
<tr>
<td>Prediabetes</td>
<td>134 (33.5%)</td>
<td>63 (28.9%)</td>
<td>48 (45.3%)</td>
<td>23 (30.3%)</td>
<td></td>
</tr>
<tr>
<td>IFG</td>
<td>22 (5.5%)</td>
<td>8 (3.7%)</td>
<td>11 (10.4%)</td>
<td>3 (4.0%)</td>
<td></td>
</tr>
<tr>
<td>IGT</td>
<td>86 (21.5%)</td>
<td>43 (19.7%)</td>
<td>29 (27.4%)</td>
<td>14 (18.4%)</td>
<td></td>
</tr>
<tr>
<td>Both IFG &amp; IGT</td>
<td>26 (6.5%)</td>
<td>12 (5.5%)</td>
<td>8 (7.5%)</td>
<td>6 (7.9%)</td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>77 (19.3%)</td>
<td>40 (18.3%)</td>
<td>17 (16.0%)</td>
<td>20 (26.3%)</td>
<td></td>
</tr>
</tbody>
</table>

(Within parentheses the percentage of the column total)

(p-value by Chi-square test)

The odds ratios calculated by binary logistic regression analysis of factors that may be related to abnormal glucose tolerance in the study population are given in table 3. Presence of family history of HTN and having abdominal obesity had the significant individual influence on the presence of dysglycaemia in the study population.

### Table 3: Binary logistic regression for the predictors of dysglycaemia in study population

<table>
<thead>
<tr>
<th>Variables</th>
<th>Subgroups</th>
<th>Odds Ratio (95% Confidence Interval)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age group</td>
<td>&lt;40 years</td>
<td>Reference</td>
<td>1.29 (0.784-1.924)</td>
</tr>
<tr>
<td></td>
<td>≥40 years</td>
<td>Reference</td>
<td>1.85 (0.942-3.634)</td>
</tr>
<tr>
<td>Gender</td>
<td>Female</td>
<td>Reference</td>
<td>1.01 (0.48-2.172)</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>Reference</td>
<td>0.93 (0.467-1.770)</td>
</tr>
<tr>
<td>Years of schooling</td>
<td>≥10 years</td>
<td>Reference</td>
<td>1.11 (0.641-1.909)</td>
</tr>
<tr>
<td></td>
<td>&lt;10 years</td>
<td>Reference</td>
<td>1.22 (0.763-1.937)</td>
</tr>
<tr>
<td>Smoking status</td>
<td>Non-smoker</td>
<td>Reference</td>
<td>0.51 (0.208-1.272)</td>
</tr>
<tr>
<td></td>
<td>Smoker</td>
<td>Reference</td>
<td>0.93 (0.467-1.770)</td>
</tr>
<tr>
<td>Family H/O thyroid disease</td>
<td>Absent</td>
<td>Reference</td>
<td>1.07 (0.588-1.932)</td>
</tr>
<tr>
<td></td>
<td>Present</td>
<td>Reference</td>
<td>1.07 (0.588-1.932)</td>
</tr>
<tr>
<td>Family H/O DM</td>
<td>Absent</td>
<td>Reference</td>
<td>1.66 (1.161-2.978)</td>
</tr>
<tr>
<td></td>
<td>Present</td>
<td>Reference</td>
<td>1.66 (1.161-2.978)</td>
</tr>
<tr>
<td>Family H/O HTN</td>
<td>Absent</td>
<td>Reference</td>
<td>2.21 (1.302-3.746)</td>
</tr>
<tr>
<td></td>
<td>Present</td>
<td>Reference</td>
<td>2.21 (1.302-3.746)</td>
</tr>
<tr>
<td>G1+T+er</td>
<td>Absent</td>
<td>Reference</td>
<td>1.07 (0.588-1.932)</td>
</tr>
<tr>
<td></td>
<td>Present</td>
<td>Reference</td>
<td>1.07 (0.588-1.932)</td>
</tr>
<tr>
<td>HTN</td>
<td>Absent</td>
<td>Reference</td>
<td>1.07 (0.588-1.932)</td>
</tr>
<tr>
<td></td>
<td>Present</td>
<td>Reference</td>
<td>1.07 (0.588-1.932)</td>
</tr>
<tr>
<td>BMI</td>
<td>&lt;23</td>
<td>Reference</td>
<td>0.92 (0.472-1.775)</td>
</tr>
<tr>
<td></td>
<td>≥23</td>
<td>Reference</td>
<td>0.92 (0.472-1.775)</td>
</tr>
<tr>
<td>Abdominal obesity</td>
<td>Absent</td>
<td>Reference</td>
<td>2.52 (1.285-4.930)</td>
</tr>
<tr>
<td></td>
<td>Present</td>
<td>Reference</td>
<td>2.52 (1.285-4.930)</td>
</tr>
<tr>
<td>Thyroid functional status</td>
<td>Euthyroid</td>
<td>Reference</td>
<td>1.83 (0.914-3.642)</td>
</tr>
<tr>
<td></td>
<td>Thyrotoxic</td>
<td>Reference</td>
<td>1.83 (0.914-3.642)</td>
</tr>
<tr>
<td></td>
<td>Hypothyroid</td>
<td>Reference</td>
<td>0.62 (0.344-1.135)</td>
</tr>
</tbody>
</table>
Discussion

DM and thyroid disease are closely linked. An array of complex intertwining biochemical, genetic, and hormonal malfunctions have been evidenced by many investigators mirroring this pathophysiological association (17). The observed frequency of dysglycemia in this study among the patients with thyroid disorders was 52.7%; of which 19.3% had DM and another 33.5% had prediabetes.

Several mechanisms have been described for dysglycemia in hyperthyroidism; the most important ones are, a) accelerated gastric emptying, enhanced intestinal glucose absorption and an increase in portal venous blood flow, b) increased insulin clearance, c) beta cell dysfunction resulting in reduced pancreatic insulin content, poor insulin response to glucose and decreased rate of insulin secretion, d) increased endogenous glucose production not responding to the suppressive effect of insulin, and e) exaggerated effects of glucagon and adrenaline on liver cells (2, 18, 19). Although hypothyroidism predisposes to hypoglycemia, it may also cause insulin resistance (1). A higher degree of insulin resistance mainly at the peripheral muscles has been observed in overt and subclinical hypothyroidism in various in vitro and preclinical studies (5, 6, 7, 17). In contrast to this hypothesis of insulin resistance, some studies clearly demonstrated diminished early insulin secretory response to intravenous glucose in hypothyroid patients (8). These findings indicate that thyroid diseases play a role in the development of abnormal glucose tolerance.

Moreover, diabetes and hypothyroidism also meet each other through various common clinical characteristics; both are independently associated with changes in body weight, dyslipidemia, hypertension, and depression (1).

In the present study, the overall frequency of diabetes and prediabetes in patients with thyroidal illness were 19.3% and 33.5% respectively. These frequencies are higher than the national prevalence of diabetes (9.7%) and prediabetes (23%) of our country (21).

The frequency of diabetes in hypothyroid subjects in our study was 18.3% and that of prediabetes was 28.9%. In our scenario, the previous study done by Ashrafuzzaman et al. found a lower frequency of diabetes (7.01%) and prediabetes (21.2%, 12.6% IGT and 8.6 IFG) than us (22). The frequency of diabetes in hyperthyroid subjects in our study was 16% and that of prediabetes was 45.3%; in total 61.5% had dysglycemia. Paul et al. in their study found 72.3% of hyperthyroid patients to have glucose intolerance, which is higher than the frequency observed by us (23). Roubsanthisuk et al. found 39.4% (7.9% DM, 31.5% prediabetes) of Thai patients with hyperthyroidism to have dysglycemia (24). The higher frequencies of abnormal glucose tolerance in hypothyroidism in the current study may be due to small sample size, relatively higher mean age of study subjects and presence of other contributing factors such as increased waist circumference, and family history of diabetes.

The frequency of diabetes and prediabetes in our euthyroid subjects were 26.3% and 30.3% respectively. These patients had some forms of structural thyroid abnormality. There are very limited data regarding glucose intolerance in patients with simple diffuse or nontoxic nodular goiter and thyroid malignancy though some studies have found the relation between euthyroid goiter and insulin resistance (23, 26). Higher frequency of glucose intolerance in thyroid malignancy also has been reported by some authors (27).

Age is well-established risk factor glucose intolerance. Subjects with dysglycemia had higher age than those with NGT in our study although higher age (≥40 years) itself was not found to be a significant risk factor of dysglycemia in our study subjects. In contrast, Roubsanthisuk et al. found no significant different the mean age between the subjects with NGT and AGT (24).

Subjects with AGT had a higher frequency of family history of hypertension and had higher systolic BP in our study. Roubsanthisuk et al. had similar observations (24). Presence of family history of HTN and was associated with significantly higher odds of AGT; being hypertensive was also associated with higher risk of AGT though it was not statistically significant.

Though subjects with AGT had higher mean BMI, higher BMI (≥23 kg/m2) was not an individual risk factor of AGT in our study population. Roubsanthisuk et al. found no difference in BMI between AGT and NGT subjects in their study (24) Subjects with AGT had higher waist circumference and abdominal obesity imparted higher odds of AGT in them. Abdominal obesity is a marker of insulin resistance and thyroid dysfunctions are associated with insulin resistance.

Having hypothyroidism or hyperthyroidism was not associated with higher risks of AGT than euthyroid subjects in our study subjects though subjects with AGT had lower TSH and higher FT4 than subjects with NGT. Roubsanthisuk et al. found higher T4 in AGT subjects and Paul et al. observed a significant positive correlation between FT4 and plasma glucose in Graves’ disease patients (23, 24).

Limitations of the study: The main limitation of this study is that had no healthy control group. It was a tertiary hospital-based single center study and the sample may not be representative to whole country. We did not measure HbAlc in our study subjects.

Conclusion

This study highlights the high frequencies of diabetes and prediabetes among the newly detected subjects with thyroid disorders. There is no definitive guideline regarding screening of glucose intolerance for the patients with thyroid disorders. Findings of this study have evidenced the intricate bond between glucose intolerance and thyroid pathology. As South Asian ethnicity is an independent risk factor for type 2 diabetes mellitus, the additional presence of thyroid diseases should prompt the screening for glucose intolerance in our setting.
References


Factors affecting cardiovascular risk in patients with type 2 diabetes mellitus; a clinic based study

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1District General Hospital Matara, 2Primary Medical Care Unit, Devinuwara 3Faculty of Medicine, Ruhuna 4Matara Nursing Home, Mataura

Introduction

World health organization estimated that 347 million people worldwide were having diabetes mellitus in 2013. The aging population and increasing prevalence of obesity and sedentary life habits among people increase the prevalence of diabetes (1). Prevalence of diabetes mellitus globally was 8.3% in 2011 and for the South East Asia it was 8.3% (2). Prevalence of diabetes in Sri Lanka was 10.3% in 2008, which has steeply increased from values of 2.01% in 1988. Sri Lanka diabetes and cardiovascular study (SLDCS) which was done in 2008 has revealed a diabetes female prevalence of 10.9% amongst females, compared to 9.8% in males (3). Among the Sri Lankan urban population the prevalence was 16.4% compared to the rural population which was 11.5% (3). Prevalence of diabetes mellitus in Southern province of Sri Lanka was 12.2% (4). Hospital admissions due to diabetes mellitus have increased from 86/100,000 to 226/100,000 over the last two decades (5, 6).

This study was conducted in Devinuwara which is a semi urban area in Matara district along the southern coast of Sri Lanka. Majority of people are engaged in the fishing industry. Devinuwara primary medical care unit (PMCU) caters to a population of 8000 -10,000. Our study population was selected from the diabetic patients who visited the medical clinic. Diabetic patients are more prone to develop cardiovascular diseases due to prevalence of risk factors which should be assessed at different stages to minimize complications. Risk of mortality from coronary heart disease and ischemic strokes is raised two to four folds in patients with type 2 diabetes (7). Number of studies have been conducted to assess the cardiovascular disease risk among normal people and selected people in different locations in Sri Lanka. Studies or audits on cardiovascular risk factors among type 2 diabetes mellitus patients who are followed up in the clinics were limited. Thus it is important to ascertain the risk factors for cardiovascular disease among patients with type 2 diabetes mellitus and to assess the risk reduction by interventions in local settings. Further, it will help to minimize the complications of diabetes and persuade life style changes of the affected patient.

Methodology

This was a descriptive cross sectional study. Convenient sampling method was used to select patients attending the medical clinic with type 2 diabetes mellitus. Patients with type I diabetes mellitus, mentally unfit patients, patients unable to or unwilling to give consent, patients with missing data, and patients with gestational diabetes were excluded from this study. Study was carried out during a period of one year starting from 25th November 2014. An interviewer administered questionnaire was used to collect relevant data. Procedure of the study and benefits to the patient were explained verbally and using a written information sheet. Risk factors assessed were age, menopausal state, and family history of cardiovascular disease (CVD), smoking, alcohol consumption, obesity, physical activity, hypertension, peripheral vascular disease, hyperglycemia, dyslipidemia, and microalbuminuria.

A questionnaire was formulated using World health organization (WHO) non-communicable disease (NCD) risk factor surveillance (STEPS) instrument for NCD risk factor screening. Initial part of the questionnaire included the questions regarding general information of the patient, tobacco use and alcohol consumption. International physical activity questionnaire short version (IPAQ) was used to assess the level of physical activity of the patient (8). Physical activities were categorized into two groups: vigorous and moderate. IPAQ has been validated in Sri Lanka. Sedentary behaviour refers to any walking activity characterized by energy expenditure ≤ 1.5 metabolic equivalents and a sitting or reclining posture. Resting for more than 52 hours per week was considered as highly sedentary, between 34 to 51 hours per week was considered as moderately sedentary and less than 33 hours per week was considered as not sedentary (8,9).

At the time of clinical assessment, a stethoscope weighing scale was used for weighing the patient without shoes to the nearest 500g. The height was measured using a stadiometer to the nearest 0.5 cm with the participant standing upright with the heel, buttock and upper back in the same vertical line. Body mass index (BMI) was calculated by dividing weight in kilograms by the square of the height in meters. Waist circumference was measured using a non-stretchable measuring tape. Measurement was taken at a point midway between the lowest rib and iliac crest. Cut off point was taken as 80cm (32 inches) for females and 90cm (36inches) for males, according to cut-off values recommended for Asians by the international diabetes federation (10). Peripheral pulse was detected by palpation of dorsalis pedis
artery on foot. Readings of blood pressures were recorded before and after antihypertensive treatment. Values of the lipid profile were recorded before and after the treatment for dyslipidaemia. Readings of blood pressure and lipid profile values prior to starting treatment were obtained from the patients’ record books. Glycosylated haemoglobin (HbA1c) and microalbuminuria were measured at the time of clinical assessment. Ethical approval for this study was granted by the National Institute of health sciences at Kalutara on 15th October 2014 under the reference number NIHS/ERC/14/09/R.

Results

Out of the total 136 patients in this study, majority were females -112 (82.35%), and males were 24 (17.64%). Amongst the female patients 82.14% (92) were in menopausal state. Age group of this sample varied from 30 to 90 years (mean = 61, SD±10.6).

Family history revealed that sixty four (47.05%) had history of cardiovascular disease in the family and 72(52.94%) had no cardiovascular disease in the family. Duration of the illness was divided into three categories. Period less than five years was found in 78 (57%) patients, between 6 to 10 years in 41(30%) patients and more than 10 years in 17 (12.4%) patients.

None of the female patients consumed alcohol or smoked cigarettes. However, out of the 24 male patients, 12 (50%) were smokers and 12(50%) were consuming alcohol. Data related to exercise and resting time was collected according to IPAQ (short version) (8). It is shown in table 2.

<table>
<thead>
<tr>
<th>Age group in years</th>
<th>Age distribution in number and percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>21-30</td>
<td>2(1.47%)</td>
</tr>
<tr>
<td>31-40</td>
<td>1(0.74)</td>
</tr>
<tr>
<td>41-50</td>
<td>20(14.7%)</td>
</tr>
<tr>
<td>51-60</td>
<td>38(27.94%)</td>
</tr>
<tr>
<td>61-70</td>
<td>54(39.7%)</td>
</tr>
<tr>
<td>71-80</td>
<td>14(10.29%)</td>
</tr>
<tr>
<td>&gt;80</td>
<td>7(5.14%)</td>
</tr>
<tr>
<td></td>
<td>136</td>
</tr>
</tbody>
</table>
When the Body Mass Index was analyzed 76 (55.88%) had BMI above 25kg/m² and were obese (24). Twenty three (16.91%) had BMI between 23 – 24.9 kg / m² and were overweight. Twenty seven (19.85%) had BMI between 18.5 – 22.9 kg / m² and were in the normal range and 10 (7.36%) were under weight (<18.4). Waist circumference of the study sample was categorized according to cut off points. Out of 24 males 14 (10.29%) had waist circumference below 90cm while 10 (7.3%) had above 90cm. Among the female only 7 (5.14%) had less than 80cm waist circumference while 165(77.2%) had more than 80cm.

<table>
<thead>
<tr>
<th>Type of exercise</th>
<th>Vigorous exercise</th>
<th>Moderate exercise</th>
<th>Type of resting period</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Minutes per week</td>
<td>Minutes per week</td>
<td>Hours per week</td>
</tr>
<tr>
<td></td>
<td>Number (%)</td>
<td>Number (%)</td>
<td>Number (%)</td>
</tr>
<tr>
<td>&lt;75</td>
<td>49 (36.02)</td>
<td>&lt;150</td>
<td>&lt;33</td>
</tr>
<tr>
<td>&gt;75</td>
<td>51 (37.5)</td>
<td>&gt;150</td>
<td>34-51</td>
</tr>
<tr>
<td>Zero</td>
<td>36 (26.47)</td>
<td>Zero</td>
<td>&gt;52</td>
</tr>
<tr>
<td>Total</td>
<td>136</td>
<td>136</td>
<td>136</td>
</tr>
</tbody>
</table>

**Table 3: Blood pressure at the initial stage of disease and after antihypertensive treatment to appropriate patients and percentages**

<table>
<thead>
<tr>
<th>Blood pressure range in mmHg</th>
<th>Before treatment</th>
<th>After treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number (%)</td>
<td>Number (%)</td>
</tr>
<tr>
<td>&lt;130/80</td>
<td>45 (33)</td>
<td>116 (85.29)</td>
</tr>
<tr>
<td>131/81 -140/90</td>
<td>23 (17)</td>
<td>14 (10.29)</td>
</tr>
<tr>
<td>&gt;141/91</td>
<td>68 (50)</td>
<td>6 (4.41)</td>
</tr>
<tr>
<td>Total</td>
<td>136</td>
<td>136</td>
</tr>
</tbody>
</table>
Forty five patients had normal blood pressure and 91 (67%) had elevated blood pressure. Antihypertensive therapy helped to reduce the blood pressure to normal in 71 (52%) of the patients while 20 (14.7%) had elevated blood pressure even after therapy. This study sample showed a mean value of systolic blood pressure 142mmHg (SD±17, 139-145mmHg) at the initial stage of attending the clinic and after starting antihypertensive drugs mean value was changed to 127mmHg (SD±10, 125-128mmHg, P=0.0001).

Mean value of total cholesterol was 224mg/dl (SD±32, 218-229mg/dl) before treatment and this was reduced to statistically significant mean value of 168mg/dl (SD±31,162-173mg/dl , p=0.001).Mean value of the low density lipoprotein was 147mg/dl (SD ±31, 141-152mg/dl) at the initial state and it was reduced significantly to mean value of 101 mg/dl (SD± 21, 97-104mg/dl, p=0.001) with the lipid lowering drugs. Mean value of high density lipoprotein was 42mg/dl (SD± 6.7, 41-43mg/dl) before lipid lowering therapy and it was raised significantly to a mean value of 44 mg/dl (SD ± 3.6, 43-44mg/dl p=0.001) after lipid lowering therapy. However, correlational studies of HDL did not show any association between vigorous, moderate or mild exercise.

When the HbA1c was analyzed, 59 (43.38%) had HbA1c less than 6% and 71 (52.21%) had HbA1c between 6.8%. Six people (4.41%) had more than 8%. Measurements of albuminuria level of the study sample showed less than 30mg/dl in 9 (6.7%) patients, between 31-299mg/dl in 103 (70.7%) patients and more than 300mg/dl in 24 (17.6%) patients. Peripheral pulse of the dorsalis pedis was palpable in 123 (90.44%) and was not felt in 13 (9.55%).

<table>
<thead>
<tr>
<th>Type of lipid</th>
<th>Blood levels</th>
<th>Number before treatment with lipid lowering drugs</th>
<th>Number after treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cholesterol</td>
<td>&lt;200</td>
<td>27 (19.85%)</td>
<td>120 (88.23%)</td>
</tr>
<tr>
<td></td>
<td>&gt;200</td>
<td>109 (80.14%)</td>
<td>16 (11.76%)</td>
</tr>
<tr>
<td>Low density lipoproteins</td>
<td>&lt;100</td>
<td>9 (6.61%)</td>
<td>66 (48.52%)</td>
</tr>
<tr>
<td></td>
<td>100-150</td>
<td>66 (48.52%)</td>
<td>69 (50.73%)</td>
</tr>
<tr>
<td></td>
<td>&gt;150</td>
<td>61 (44.85%)</td>
<td>1 (0.73%)</td>
</tr>
<tr>
<td>High density lipoprotein</td>
<td>&gt;35</td>
<td>121 (88.97%)</td>
<td>136 (100%)</td>
</tr>
<tr>
<td></td>
<td>&lt;35</td>
<td>15 (11.02%)</td>
<td>0</td>
</tr>
</tbody>
</table>
Discussion

This study has revealed cardiovascular risk factors as follows: hypertension in 67%, dyslipidemia in 80%, smoking in 8%, consumption of alcohol in 8%, over weight in 17%, obesity in 56% and family history of cardiovascular disease in 47%. A substantial number of patients had benefited by anti-hypertensive drugs and lipid lowering drugs.

A similar study which was done in North Catalonia in 2009, reported a prevalence rate of risk factors among type 2 diabetes patients as follows: hypertension in 74.5%, dyslipidemia in 77.7%, smoking in 14.9%, obesity in 44.9% and family history of cardiovascular disease in 38.4% (11). Compared to this study our population indicates higher percentage of obesity and family history of cardiovascular disease (CVD).

This study sample was based on diabetic patients who pursued to obtain treatment from PCMCU, Devinuwara and had a majority of females and minority of males. This may not represent the true gender variation of diabetes in the local population. Employment could be one of the main reasons which may have restricted people, mostly males, attending government hospital clinic held during working hours. In addition, overcrowding of the clinics and certain delays may have contributed for not seeking care from these clinics. Out of the females, majority were in their menopause. It has been found that females experience myocardial infarction later than men due to their protective effect of oestrogen (12,13). State of menopause has made the females of the study sample at high risk for cardiovascular disease. The incidence of myocardial infarction is higher in men than females in general population. In diabetes the incidence ratio is narrower (14). Family history of CVD was considered as an independent risk factor (15). In this sample half of the population had family history of CVD. A study has compared incidence of CVD in diabetes patient with family history of CVD and without, and has shown 50% higher incidence with first degree relatives who had CVD (16). Furthermore, it has shown 14.3% incidence of CVD among postmenopausal women.

A study conducted in Sri Lanka has found that the prevalence of diabetes was highest in the age group of 55 to 64 years (3). But in this study, majority belonged to the age group of 61 to 70 years. This slight deviation could be due to the gender variation in the sample. Younger age of onset for diabetes and duration of the illness for more than 10 years are considered to be high risk for CVD according to the guidelines issued by the American Heart association and American College of Cardiology (AHA/ACC). They further indicate that age below 40 years with shorter duration of illness have less CVD risk (17). In this study, majority belonged to the onset of diabetes less than 5 years category.

Out of the minority of males, twelve (50%) had a history of smoking. WHO–Sri Lanka NCD country profile 2011 has recorded a prevalence of smoking among males as 21.4% (18). Studies have revealed that the smoking increases the risk of heart disease in diabetic patients (19). Prevalence of smoking among males in this sample was much higher, exposing them to the risk of cardiovascular disease. Twelve (50%) out of the males in this study had given a history of alcohol consumption. As alcohol consumption alone is a risk factor for cardiovascular disease (20), our study sample male population is at high risk of cardiovascular disease.

When vigorous exercise was considered, only 37% had achieved the recommended level of more than 75 minutes of vigorous exercise per week. Twenty eight percent of the study group had shown engaging in moderate exercise up to the recommended level which is 150 minutes per week. Eighty percent of the study population had a sitting time less than 33 hours per week which is the recommended level. This may reduce their cardiovascular risk. It has been found that an ambulatory movement every 60 minutes of the day can reduce the risk of premature mortality of all causes by 13% in adults with diabetes (21).

In this study population majority was either obese or overweight. It has been found that BMI was an independent risk factor for cardiovascular disease and risk is increased by 13% for 5 unit increase of BMI (22). Further, similar proportion had shown higher waist circumference among females and males. Inappropriate dietetic habits, lack of knowledge, own social values and ignorance may have contributed to the diabetic status.

Blood pressure was more than 141/91 mm Hg in 50% of the study sample before starting antihypertensive treatment. After antihypertensive treatment, 85% of the people had blood pressure below 130/80 mm Hg. A meta-analysis which was done in 2015 revealed lowering of blood pressure by 10mmHg was significantly lowered the cardiovascular events (23). American Diabetes association (ADA) recommends a goal of systolic pressure of 140mmHg and diastolic pressure of 90mmHg for treating diabetics with hypertension (24). This is an achievable target in a clinic.

In 80% of the study sample, total cholesterol was more than 200mg/dl initially before starting lipid lowering therapy. 93% had LDL cholesterol more than 100mg/dl, indicating high risk for cardiovascular disease. With lipid lowering therapy 88% had total cholesterol less than 200mg/dl. But reduction of LDL cholesterol level below 100mg/dl, which is the recommended level, was achieved only by 48% of the study population. The 2013 AHA/ACC guidelines suggest adjusting the statins according to the LDL levels and ability of the patient’s tolerance (25). Lipid lowering therapy helped to reduce the risk level of cardiovascular disease in this study group. When HDL cholesterol level is considered, only 11% had HDL cholesterol less than 35mg/dl initially. After lipid lowering therapy 100% of the study sample had achieved HDL cholesterol level above 35mg/dl.

HbA1c level is the indicator of glycemic control. A Taiwan study conducted in year 2002 revealed that elevated HbA1c significantly associated with cardiovascular disease risk.
In this study population, only 5% had HbA1c above 8% and the majority had a good glycaemic control.

In this study sample, 16% had urine microalbumin more than 300mg/L. Several studies document an almost linear association between the level of microalbuminuria and risk of cardiovascular event (27). This study sample shows low risk in this aspect.

This study has few limitations. Female preponderance of the sample is a limitation but it signifies the pattern of treatment seeking behaviour in this area. Accelerometer and inclinometers are not used to measure the sedentary hours that was assessed during the interview process. Nonuse of Doppler ultrasonic equipment to assess the peripheral pulse is a limiting factor in our study.

**Conclusion**

Though the medication modifiable CVD risk factors like hyperglycaemia, hypertension, and dyslipidaemia have been reduced significantly, behavioural risk factors like alcoholism, smoking and obesity remained to be high among diabetic patient. Analysis of individual dietary pattern and annual risk factor assessment could help reduce the cardiovascular disease risk among diabetic patients.

**References**


Remission strategy in type 2 diabetes mellitus - a paradigm shift in the management of newly diagnosed patients

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Introduction

Type 2 diabetes (T2DM) is a chronic, complex metabolic disease characterized by two main pathophysiological defects namely; insulin resistance and beta cell dysfunction which does not occur at once (1). Insulin resistance is defined as target cell resistance to the activity of insulin and beta cell dysfunction indicates insufficient secretion of insulin by the pancreatic beta cells to maintain normoglycaemia. The natural history of T2DM is characterised by progressive deterioration of beta cell function overtime. This pathological process is considered to be unabated by the life style and existing pharmacological interventions informed by the standard existing clinical guidelines (2).

Because of the progressive nature, the management of T2DM requires continuous medical care with increasingly complex therapeutic regimens. Current standards of care acknowledge that management of this inevitably progressive disease involve sequential addition of oral hypoglycaemic agent’s overtime, followed by insulin therapy when the glycaemic control cannot be achieved without exogenous insulin supplementation due to near complete failure of pancreatic beta cell function.

The aforementioned practice of management of diabetes is characterized by ‘treatment for failure’ approach which is distinct from management of most of the other diseases, of which goals of management is cure. However, researchers in the field have not yet given up the uphill battle of defeating diabetes completely ie ‘finding a cure’. There is an emerging evidence regarding the possibility of reversal or regression of diabetes in a majority of patients with T2DM especially the new onset.

Current understanding of pathophysiology of type 2 diabetes

As mentioned above, the natural history of T2DM shows inexorable progression despite diet, exercise and medical therapy. In the UKPDS study, among 4075 patients newly diagnosed as having type 2 diabetes who were managed with monotherapy of diet, metformin, sulfonylureas or insulin showed majority had progressive deterioration of glycaemic control with only 25% achieving the glycaemic control at 9 years with monotherapy (2). Similar findings were shown with sulfonylureas in ADOPT trial (3).

The two major pathological factors causing type 2 diabetes namely, insulin resistance and beta cell dysfunction are recognised to have different time courses rather than occurring simultaneously according to the current understanding (1). Insulin signalling defects (4), glucose transporter defects (5) and lipotoxicity (6) may be driving insulin resistance in skeletal muscles, liver and pancreas, whereas amyloid deposition in the islets (7), oxidative stress (8), excess fatty acid (9), or dysfunction of incretin effect (10) are attributed as causes of beta cell dysfunction.

Insulin resistance in muscles

Insulin resistance in skeletal muscles is the earliest abnormality detected in T2DM which is the main contributing factor for whole body insulin resistance (11). Despite several genetic and acquired defects of insulin action at receptor levels being studied in research, exact pathophysiology of muscle insulin resistance is yet to be identified. However when separation of the contributions of muscle and liver were studied, early improvement in the control of fasting plasma glucose level was shown to be associated predominantly with the improvement of liver insulin sensitivity (12, 13).

Additionally many individuals are observed to maintain normal blood glucose levels despite having similar levels of muscle insulin resistance to those with type 2 diabetes (14). Nevertheless, it has been recognised that longstanding muscle insulin resistance causes increase plasma insulin levels accelerating the accumulation of fat in the liver by stimulating de novo lipogenesis. Thus pathophysiological importance of muscle insulin resistance operates over a period of many years (1).

Insulin resistance in the liver

When daily caloric intake exceeds expenditure, storage of liver fat occurs increasing the metabolic stress to
hepatocytes. Within the hepatocyte, fatty acids can be derived from de novo lipogenesis, uptake of non-esterified fatty acids and low density lipoproteins (LDL) or lipolysis of intracellular triacylglycerol. This fatty acid pool may be oxidized for energy production or may be combined with glycerol to form mono-, di-, or triacylglycerols (15). Chronic hyperinsulinaemia associated with long standing muscle insulin resistance accelerates de novo lipogenesis and production of malonyl-CoA which inhibits transport of fatty acids into mitochondria for oxidation. Thus newly synthesized triacylglycerol is preferentially directed towards storage or export, thereby increasing the hepatic fat content and plasma VLDL triacylglycerol levels (15). Furthermore, excess diacylglycerol profoundly affects the signalling pathway from insulin receptor to insulin receptor substrate 1 (IRS-1) which is the first post receptor step in intracellular insulin action causing insulin resistance (16). Additionally, excess fatty acids promote ceramide synthesis which in turn increases gluconeogenic enzymes leading to increased hepatic glucose production (17). Thus, under circumstances of chronic energy excess, a raised level of intracellular diacylglycerol specifically prevents normal insulin action, and hepatic glucose production fails to be suppressed leading to increased fasting plasma glucose (1). Nevertheless, despite the above mentioned close relationship between raised liver fat content and insulin resistance, high levels of liver fat are not inevitably associated with hepatic insulin resistance in all individuals due to yet unidentified mechanisms (1).

Beta cell dysfunction

A population-based survey conducted in Mexico involving 2279 adults studied whether conversion of normoglycaemia to hyperglycaemia occurs gradually overtime or in a stepwise manner when diabetes develops. Very often the onset of diabetes was observed to be rapid, rather than gradual and it was in part explained by a fall in glucose-stimulated acute insulin response which plays a major role in determining glucose tolerance status over time (18). Furthermore, the progressive decrease in beta cell insulin secretion particularly in the first phase (acute insulin response) is likely the most critical functional defect in the development of T2DM according to physiological studies (19,20). Moreover, subsequent studies revealed younger age and weight gain were more associated with diabetes progression from the onset (21) and around 50% experienced loss of glycaemic control while on medications indicating unabated deterioration of beta cell function despite therapy (2).

Pathophysiology of beta cell dysfunction

In a background of long standing insulin resistance, pancreatic beta cells increase the output of insulin from each cell and/or increase its cell mass, to maintain normoglycaemia (22). Over a period of time inadequate compensation featured by inadequate insulin secretion from each cell or an inadequate beta cell mass for the levels of prevailing insulin sensitivity would lead to development of diabetes. The beta cell dysfunction is progressive and is usually considered to be about 50% by the time a person’s plasma glucose level is in diabetic range. (22). Moreover it continues to worsen even after the development of diabetes.

Glucotoxicity and lipotoxicity are two acquired defects hypothesized to be associated with impaired insulin secretion. In glucotoxicity, chronic hyperglycaemia depletes insulin secretory granules from beta cells impairing the amount of insulin available for secretion. Furthermore, lowering of glucose levels has shown to improve acute beta cell insulin response (22). Lipotoxicity is characterised by reduced beta cell capacity due to chronic exposure to high level of fatty acids (22, 23). In a state of increased fatty acid levels beta cells avidly import them in to cells through CD 36 transporters and excess is stored as triglycerol. The energy surplus state prevents the increase in ATP production from the glucose oxidation which is a requirement for insulin secretion in response to glycaemic load. Additionally, increased fatty acid availability inhibits pyruvate cycling and the major rate-limiting enzyme of glucose oxidation the pyruvate dehydrogenase activity. Furthermore, in vitro studies have shown that excess fatty acids prevent beta cell proliferation by induction of cell cycle inhibitors P16 and P18, which is further worsened by high glucose concentration (22, 24, 25, and 26).

There is approximately 50% reduction in the number of beta cells in T2DM patients when compared to normoglycaemic subjects indicating reduction of total possible insulin response (22). Beta cell loss via apoptosis appears to increase as the duration of diabetes increases. The apoptosis is thought to be increased by chronic exposure to high concentration of fatty acid metabolites and products synthesised from fatty acids, such as ceramide (27, 28).

Low grade beta cell inflammation is hypothesised to be a possible contributory factor in the development of T2DM. Pancreatic islets from T2DM patients are known to have amyloid deposits, fibrosis, and increased cell death, associated with an inflammatory response. Glucotoxicity is a likely inducer of this inflammatory reaction (23). However, the onset and expression of hyperglycaemia is not uniform even in the presence of above mentioned pathological abnormalities indicating that individual susceptibility factors determine the onset of the condition, and both genetic and epigenetic factors may contribute (1,22).
The twin cycle hypothesis of type 2 diabetes

Evidence coming from bariatric surgery and hypocaloric diet has led to development of twin cycle hypothesis for aetiology of diabetes. Positive caloric balance is the primary influence of the whole process which leads to accumulation of liver fat and secondarily in the pancreas. These self-reinforcing cycles interact to bring about T2DM. Fatty liver leads to impaired fasting glucose metabolism and increases export of VLDL triacylglycerol, which increases fat delivery to all tissues, including the islets of pancreas. The liver and pancreas cycles drive forward even after onset of diabetes with steady decrease in beta cell function (1, 29).

Is reversal of type 2 diabetes possible?

Numerous studies conducted in the field of diabetes in search of a cure have revealed promising evidence on the possibility of reversal or remission of T2DM. Out of all the strategies used, most beneficial results were found with use of bariatric surgery and hypocaloric diet (1).

Bariatric surgery

Early indications of the possibility of T2DM being a fully reversible disease in some patients emerged from the outcomes of bariatric surgery (30-32). Bariatric surgery leads to remission of diabetes in up to 95% of patients. A randomised controlled trial (RCT) of 60 people comparing gastric bypass or bili-pancreatic diversion and medical treatment revealed a remission rates of diabetes in 37% and 63% of patients respectively at 5 years, where none of the medically managed patients achieved remission (30). Adjustable gastric banding in diabetic patients diagnosed within 2 years with BMI between 30 - 40kg/m², showed a remission rate of 73% at 2 years (31). Roux-en-Y gastric bypass (RYGB) was found to be more potent in achieving partial or complete remission of diabetes at 1 year, compared to adjustable gastric banding (32). The effect of normalization of blood glucose was persistent in almost 90% of patients even after 10 years of surgery (32).

Dietary intervention

The unforeseen observation of normalisation of blood glucose within days of bariatric surgery even before substantial loss of weight occur directed towards the possibility of acute profound decrease in caloric intake in reversing diabetes. There are several types of diet regimes studied in this purpose.

Low caloric diet

Studies have shown that remission of diabetes is achievable with low caloric diet. A study by Lim et al, where a 600 kcal/day diet comprising of liquid formulas and non-starchy vegetables for 8 weeks was given to 11 participants with a diabetes duration less than 4 years, shown significant reduction in FBS, along with improved insulin sensitivity in the liver, reduced liver and pancreatic fat content and improved beta cell function at 8 weeks (33).

An almost similar method was used by Steven et al, where very low caloric diet (624kcal/day) was given for 8 weeks, to patients with diabetes duration less than 8 years, followed by 2 week of isocaloric food reintroduction and followed up for 6 months of weight maintenance. 43% had remission of
diabetes at the end of 6 months, and the remission negatively correlated with the duration of diabetes, baseline FBS and HbA1c, but no association was found with the baseline BMI (34).

**Intensive life style intervention**

In the Look AHEAD study involving around 5000, overweight adults with T2DM, where intensive lifestyle intervention (ILI) was compared to diabetes support and education programme (DSE), a frequent, weekly individual counselling was offered to the ILI group for the first 6 months followed by 3 per month for second 6 months and twice monthly for next 2 years. The ILI aimed to reduce total caloric intake to 1200 to 1800kcal/d through reductions in total and saturated fat intake and by increasing physical activity levels to a goal of 175 min/wk. The remission rate was higher in ILI compared to DSE group, but however even in the ILI group the prevalence of remission was found to be low. Mean reduction of body weight of about 9% after one year in the intensive lifestyle intervention arm, was associated with a complete remission of only 1.3% of participants (35).

A retrospective study among 88 participants included in the Why WAIT, a 12 week multidisciplinary intensive weight management programme involving intensive and interactive medication adjustments, structured modified dietary intervention, graded exercise and cognitive behavioural programme, marked improvement in glycemic control was seen in 19, with partial and complete remission in 2.3% each (36).

Recently, an open label, cluster -randomised trial- DIRECT, showed that remission of T2DM is a practical target in primary care with intensive weight management. All anti-diabetic and anti-hypertensive medications were withdrawn in the intervention group at the beginning of the study, and a total diet replacement of nearly 850 kcal/day was given followed by a stepped food reintroduction and weight management programme, targeting a weight loss of 15kg. The weight loss of 15kg was achieved in 24% of the intervention group, 48% of intervention group achieved remission at 1 year (37).

**Mediterranean diet**

A randomized control trial, comparing a low carbohydrate Mediterranean diet (MED) to a low fat diet, in newly diagnosed patients with diabetes with BMI greater than 25, showed that MED diet was associated with lower HbA1c and FBS, and lower need for initiation of drug treatment (38).

**Pharmacological interventions**

Oral hypoglycaemic agents and insulin alone, or in combination were studied with regard to their potential in reversing diabetes. Early intensive insulin therapy appears to be promising when compared to oral hypoglycaemic agents in achieving diabetes remission.

**Oral hypoglycaemic agents**

Gliclazide MR 60 mg was studied vs 16 u of premixed insulin, in newly diagnosed drug naïve diabetes patients with FBS >200 mgs, along with medical nutrition therapy. Although blood glucose levels normalised in both groups in 2-6 weeks, the drug free remission with oral gliclazide was only 5% at 6 months, whereas in the insulin treated group it was 80% (39).

Oral hypoglycaemic agents (OHA) (glibenpiptide and/or metformin) vs. insulin glargine alone or in combination with above OHAs is used to achieve a FBS target of 6.1mmol/l, and 2-hr post meal glucose of 8mmol/l, which was maintained for 3 months, and after which the treatment was stopped. The remission rate was higher in the combination group (insulin + OHA) rather than OHA group at 1 year (40).

When taking everything into account, oral hypoglycaemic agents alone, has poor capacity to induce remission of diabetes when compared to insulin regimes.

**Insulin**

It was 30 years ago, a group of researchers showed that insulin treatment in NIDDM appears to have a beneficial effect by lowering insulin resistance, and resulted in remission of diabetes (41).

When insulin was given as a continuous subcutaneous infusion, in a physiological dose (0.6u/kg) for 2 weeks, to achieve normoglycaemia in a group of newly diagnosed diabetic patients who failed to achieve normoglycaemia with diet and exercise, remission of diabetes was noted in 9 out 13 patients at 6 months (42).

Similarly Li et al demonstrated remission of diabetes along with the improvement in beta cell function in a group of newly diagnosed diabetes patients in a Chinese population treated with continuous subcutaneous insulin infusion for 2 weeks (43).

**Combination of interventions**

**Combined diet and pharmacotherapy**

Forty-two per cent of newly diagnosed, unslected African Americans with Type 2 diabetes, presenting with severe hyperglycaemia, treated intensively using pharmacological agents, education and diet developed near-norm glycaemic remission at 1 year (44).

**Combined pharmacotherapy and lifestyle interventions**

In a pilot study carried out among patients with diabetes diagnosed within 3 years and with a HbA1c of less than 8.5 while not on oral drugs or less than 7.5 in one or two OHA, a combination of lifestyle, OHAs (acarbose and metformin) or insulin glargine, either alone or in combination with OHAs was used for 8 weeks, and 16 weeks to achieve a target FBS of 4 – 5.3 mmol/l after which treatment was tilted off to zero over 3 days. Twelve weeks after completion of the intervention, 21.4% of the 8week intervention group and 40.7 % of the 16 week group met the HbA1c criteria for partial or complete diabetes remission (45).
Theories behind reversal of type 2 diabetes; what remission studies say?

The degree of weight loss stems the remission of diabetes in studies involving bariatric surgery. Since surgery is more effective in achieving weight loss, surgical procedures showed the most benefit when compared to non-surgical methods (30). Surgery induced specific changes mediated through incretin hormone secretion was thought to be the cause for immediate normalisation of blood sugar initially (46). But later on, acute profound reduction in calorie intake at the time of surgery was thought to be the more likely cause. This precipitous reversal of traffic in to fat stores brings about profound change in intracellular concentration of fat metabolites and other products synthesised from fatty acids (1).

Furthermore, in a state of negative caloric balance induced by surgery or diet, fat is mobilized first from the liver and other ectopic sites rather than from visceral or subcutaneous fat stores which ultimately leads to reduction of liver fat and improvement of hepatic insulin sensitivity (47). Thus fasting plasma glucose normalises within 7 days of the intervention (46). Moreover, normalisation of acute insulin response as well as the maximal insulin response can occur with substantial reduction of calorie intake over 8 weeks from similar interventions (11). Gradual and steady reduction of pancreatic fat content was compatible with the time course of the increase in both first phase and total insulin secretion in these studies.

According to the aforementioned understanding about beta cell apoptosis and rates of turnover during adult life, it is conceivable that removal of adverse factors such as glucotoxicity and lipotoxicity could result in restoration of normal beta cell number. Plasticity of lineage and transdifferentiation of human adult beta cells could possibly be contributing (48). All inclusively, it is clear that at least a critical mass of beta cells is not permanently damaged but merely metabolically stunned at the onset of T2DM. Thus induction of long lasting remission or reversal of T2DM is possible in some patients with right interventions more likely at the early period of the disease.

Paradigm shift in management of newly diagnosed patients with type 2 diabetes

Upcoming evidence on possibility of T2DM will change the face of the disease which was long known to have the nature of inevitable progression despite treatment. This evidence will give new hope to clinicians as well as patients who were labelled as having chronic illness which will ultimately cost their life span.

Though the approaches used to induce remission of type 2 diabetes look strenuous and laborious, the ultimate outcome will save a lifetime to the patient and a huge economical gain to the health care system if successful, by eliminating the long-term cost of medications and diabetic care.

Moreover even if the reversal is not achieved or not sustainable, the role of intensive glycemic control early in the course of the disease in preventing microvascular complications in the long run, is a well-established phenomenon. This concept is based on the hypothesis that microvascular complications are related to the degree and length of exposure to hyperglycaemia. This was described as “metabolic memory” by the DCCT/EDIC (49) investigators and as “legacy effect” by the UKPDS investigators (50).

Metabolic memory /legacy effect

Early achievement of glycaemic control translated into a long-term reduction of the risk of micro- and macro vascular complications in the UKPDS study. Despite an early loss of glycaemic differences between the conventional and intensive treatment group, a continued reduction in micro vascular risk and emergent risk reductions for myocardial infarction and death from any cause were observed during 10 years of post-trial follow-up (50). Similarly DCCT/EDIC follow-up study also demonstrated the legacy effect in type 1 diabetes in which the initial 2% HbA1c separation between the intensive or conventional control groups was lost during the follow up, when the two groups of participants returned to standard treatment but the initial intensively treated group continued to have lower rates of development of micro vascular and macro vascular complications. (49). The underlying mechanism behind the metabolic memory or legacy effect is still not clearly elucidated.

With the available evidence, it can be assumed, regardless of the reintroduction or escalation of medications after the intensive treatment phase, and glycaemic control after the cessation of intensive glycemic management, the long-term cardiovascular outcomes should be better in the intensively managed patients. However, long term follow up of the regression trials are necessary to study the phenomenon of metabolic memory or legacy effects in the study population treated with intensive glycemic control.

Limitations of the regression studies

Though there are multiple approaches to induce regression of T2DM, except for bariatric surgery and hypocaloric diet, other approaches were not uniformly studied. Furthermore those approaches are not comparable to each other because of the different study population with regard to BMI, duration of diabetes and baseline HbA1c. In addition, the definition of remission varies between trials. Most of the data available on the regression of diabetes is from overweight or obese subjects. Specifically in an Asian population where lean diabetes/ diabetes with a normal BMI is prevalent(51), due to the presence of high visceral adiposity, the applicability of the above principles remain unknown and need to be evaluated.

Quality of life is an important domain to be assessed when major changes in lifestyle have been made. However there was no significant difference in quality of life between the intensive life style intervention arm and the control arm in one study (45). But subsequently the DiRECT trial demonstrated significant improvement in the quality of life at 12 months as measured by the EuroQol 5 Dimensions visual analogue scale (37). Adhering to an intensive lifestyle modification with regard to diet and exercise is challenging and need continuous motivation and support. But the aforementioned trials have proved that it is a practical target even in primary care set up.
Cardiovascular disease remains the main cause of mortality in diabetes, and it is of no wonder, that treatment modalities of diabetes mellitus should address the cardiovascular outcomes. Long term follow up data regarding the sustenance of remission, cardiovascular outcomes and diabetic related complications is sparse in the regression trials. Most of the studies have been done with a short term follow-up of 6 months to 1 year. A Chinese follow-up study over 20 years, after an intensive life style intervention of 6 years failed to show significant cardiovascular benefit compared to the control group (52). An 8 year follow-up of LOOK AHEAD trial showed some optimism regarding the sustainability of weight loss over 8 years with I1L. Although the study showed benefits of the weight loss intervention on diverse outcomes, including chronic kidney disease, disability, depression, and sleep quality, no significant effect was demonstrated on CVD, raising the concerns regarding the benefits of life style interventions in long term (53).

The huge cost associated with above mentioned approaches is also an important issue when applying this concept in resource poor settings like in the Asian context, where 60% of world diabetic population live. Special dietary practices exercise programmes, medication cost and stringent monitoring during this process, add to the initial cost on management of the patient. Overcrowded health care centres and lack of experience regarding the above concept further pushes away the mission of achieving diabetes remission.

Conclusion

Remission of diabetes has become an achievable ambition using multiple approaches. The safety and sustainability of the interventions remains to be elucidated. Further multi centered studies with long term follow up are needed, comparing different approaches in achieving long-term remission of diabetes and evaluating cardiovascular outcomes and complications.

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Primary hyperaldosteronism presenting as hypokalaemic periodic paralysis

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Teaching hospital Karapitiya

Abstract

Hypokalaemic periodic paralysis is episodic painless muscle weakness associated with areflexia (1). Hypertension and hypokalaemia are the classic presentation of primary hyperaldosteronism though some patients can be normokalaemic (2). Hypokalaemic paralysis is occasionally seen in patients with hyperaldosteronism (1). This middle aged female presented with her 3rd episode of hypokalaemic periodic paralysis and later diagnosed to have primary hyperaldosteronism due to unilateral adrenal hyperplasia, cured after adrenalectomy.

Key words: primary hyperaldosteronism, periodic paralysis, hypokalaemia.

Case

A forty year old previously healthy female was admitted to the medical casualty with painless weakness of both lower limbs for 4 days duration. Weakness was more in proximal muscles and it was progressive over time. Bilateral upper limbs were involved by fourth day of illness. She did not feel numb over the muscles of weakness. She did not have diplopia, dysarthria or dysphagia and she did not feel breathless. Symptoms did not demonstrate a diurnal variation. Bladder and bowel habits were normal. There were no similar illnesses in the family.

She has had 2 similar, but less severe episodes about 1 and 3 months ago respectively. The weakness improved spontaneously without medical attention. She was well between episodes, without residual weakness. She was clinically euthyroid.

On examination, she was not pale. She was not dyspnoic and saturation on breathing ambient air was 100%. Her motor system examination revealed flaccid quadriparesis. Proximal muscles were weaker than the distal muscles. Tendon reflexes were diminished in both upper and lower limbs. Sensory and joint position sensations were intact with flexor plantar response. Cranial nerves, cerebellar functions and fundoscopy examination were normal. Her blood pressure on admission was 210/130mmHg, with a pulse rate of 90 beats per minute. Rest of the cardio vascular, abdomen and respiratory system examination were unremarkable.

Her basic investigations revealed hypokalaemia with metabolic alkalosis (table 1). ECG showed U waves from V2 to V5. Her complete blood analysis, liver functions and inflammatory markers were normal. Hypokalaemia was corrected with intravenous potassium chloride infusion with cardiac monitoring. Patient made a complete recovery.

Her thyroid enzyme profile was normal. Further investigations were performed to confirm the possibility of hyperaldosteronism. Calculated urine potassium to creatinine ratio was 16.52 mmol/mmol (normal value <2 mmol/mmol)(3). Serum aldosterone and renin levels in upright position demonstrated suppressed serum renin levels and a high serum aldosterone to renin ratio, suggestive of primary hyperaldosteronism (table 2). Low dose dexamethasone suppression test ruled out the possibility of associated Cushing’s syndrome. Renal artery duplex excluded renal artery stenosis. Contrast enhanced CT abdomen was also unable to show any evidence of adrenal abnormality.
### Table 1: Laboratory data – Basic investigations

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patient’s Value</th>
<th>Reference Range</th>
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<tbody>
<tr>
<td>pH</td>
<td>7.51</td>
<td>7.38-7.42</td>
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<tr>
<td>PaCO₂ (mmHg)</td>
<td>26</td>
<td>38-42</td>
</tr>
<tr>
<td>PaO₂ (mmHg)</td>
<td>100</td>
<td>94-100</td>
</tr>
<tr>
<td>HCO₃ (mmol/L)</td>
<td>27</td>
<td>22-28</td>
</tr>
<tr>
<td>S. Potassium (mmol/L)</td>
<td>1.9</td>
<td>3.5-5.1</td>
</tr>
<tr>
<td>S. Sodium (mmol/L)</td>
<td>141</td>
<td>136-142</td>
</tr>
<tr>
<td>S. Calcium (Albumin corrected µmol/L)</td>
<td>8.9</td>
<td>8.6-10.3</td>
</tr>
<tr>
<td>S. Magnesium (mg/dL)</td>
<td>2.11</td>
<td>1.9 - 2.5</td>
</tr>
<tr>
<td>Urine Sodium (mmol/L)</td>
<td>183</td>
<td>40-220</td>
</tr>
<tr>
<td>Urine Potassium (mmol/L)</td>
<td>21.6</td>
<td>13-62</td>
</tr>
<tr>
<td>Urine Potassium to Creatinine ratio (mmol/mmol)</td>
<td>16.52</td>
<td>&lt;2mmol/mmol</td>
</tr>
<tr>
<td>S. Creatinine (µmol/L)</td>
<td>58</td>
<td>58-96</td>
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<tr>
<td>Blood urea (mg/dL)</td>
<td>15</td>
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### Table 2: second line investigations

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<tr>
<th>Variable</th>
<th>Patient’s Value</th>
<th>Reference range</th>
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<tbody>
<tr>
<td>Serum Aldosterone – Upright (pg/mL)</td>
<td>201</td>
<td>34.7 -275</td>
</tr>
<tr>
<td>Serum Renin – Upright (pg/mL)</td>
<td>1.2</td>
<td>5.4-34.6</td>
</tr>
<tr>
<td>Serum Aldosterone/ Renin ratio</td>
<td>163</td>
<td>&lt;50</td>
</tr>
<tr>
<td>Low dose dexamethasone suppression test</td>
<td></td>
<td></td>
</tr>
<tr>
<td>basal 9am cortisol (µg/dL)</td>
<td>274</td>
<td>240- 620</td>
</tr>
<tr>
<td>cortisol at 48 hours</td>
<td>20.7</td>
<td>&lt;50</td>
</tr>
</tbody>
</table>
Primary hyperaldosteronism was confirmed by saline infusion test. In this test, 0.9% NaCl is infused intravenously, at a rate of 500ml per hour, for a duration of 4 hours. Serum Aldosterone levels are measured sequentially every hour, in the upright position (Table 3). Failure to suppress serum aldosterone levels over time confirms primary hyperaldosteronism.

Adrenal venous sampling was performed later to isolate the side of adrenal hyper secretion (Table 4).

Laterization of the test was interpreted in terms of lateralization index.

Lateralization index values greater than 3 to 5 are considered to define lateralized aldosterone production (4). Our patient had a lateralization index value of 12.9, left side adrenal gland being the dominant gland. After the diagnosis of hypersecretion of aldosterone from left adrenal gland, patient was referred to surgical team for left sided adrenalectomy. Adrenalectomy was performed and histology revealed a multiple foci of adrenal cortical hyperplasia.

### Table 3: Laboratory data – saline infusion test – serum Aldosterone levels after infusing 0.9% NaCl

<table>
<thead>
<tr>
<th>Serum aldosterone (ng/dl)</th>
<th>Reference value</th>
<th>Patient’s value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st hour</td>
<td>Expected fall in normal population &lt; 5</td>
<td>21.89</td>
</tr>
<tr>
<td>2nd hour</td>
<td>Suggestive of primary hyperaldosteronism &gt;10</td>
<td>20.09</td>
</tr>
<tr>
<td>3rd hour</td>
<td></td>
<td>20.84</td>
</tr>
<tr>
<td>4th hour</td>
<td></td>
<td>10.79</td>
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### Table 4: Laboratory data – Adrenal venous sampling

<table>
<thead>
<tr>
<th></th>
<th>Left adrenal vein</th>
<th>Right adrenal vein</th>
<th>IVC</th>
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<tr>
<td>Aldosterone (ng/dL)</td>
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<td>17.3</td>
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<tr>
<td>Aldosterone to cortisol ratio</td>
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<td>0.013</td>
<td>21.01</td>
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</table>
Discussion

Periodic paralysis is characterized by painless episodes of muscle paralysis (1). These attacks are typically sudden onset muscle weakness with preservation of consciousness. Bulbar muscles and respiratory muscles are occasionally involved.

Main differential diagnoses for hypokalaemic periodic paralysis are thyrotoxic periodic paralysis, myasthenia gravis, metabolic myopathies and secondary hypokalaemia due to gastrointestinal, renal and other losses (3). High urinary potassium to creatinine ratio, high trans-tubular potassium gradient and severe hypokalaemia indicate secondary causes (3).

Primary hyperaldosteronism is renin- independent hypersecretion of aldosterone from adrenal glands. The classical symptoms at presentation are hypertension and hypokalaemia (1). Though hypokalaemia is conventionally considered as a feature of primary hyperaldosteronism, hypokalaemia is not seen in around 20% of patients (2). Hypokalaemic periodic paralysis is occasionally associated with hyperaldosteronism (1). The percentage of patients with primary hyperaldosteronism, presenting with hypokalaemic periodic paralysis lies within a range of 1 to 49 in case series (8).

It is reported more frequently in East Asians (8).

Commonest causes of primary hyperaldosteronism are aldosterone producing adenomas and idiopathic hyperaldosteronism. Unilateral adrenal hyperplasia and adrenal carcinoma are not commonly seen. Inherited causes of primary hyperaldosteronism such as familial hyperaldosteronism account for less than 1% of all causes (6). Aldosterone to renin ratio is used to detect cases of suspected primary hyperaldosteronism. Several confirmatory tests such as oral sodium loading test, saline infusion test and frusemide upright test are used with varying sensitivity and specificity for diagnosis (7). The diagnosis was confirmed in our patient by saline infusion test as described above.

Adrenal venous sampling performed by an experienced interventional radiologist, isolates unilateral cases of hyperaldosteronism (4). CT imaging is helpful in detecting adrenal space occupying lesions, especially in patients with other co-morbidities, as it is a noninvasive procedure. Despite of its usefulness in diagnosis, it carries significant false positive and false negative rates. Idiopathic adrenal hyperplasia can be falsely interpreted as normal in CT. Also, non-functioning adrenal macro adenomas are common in the elderly, and can be misinterpreted as functioning tumours (7).

Surgical treatment is the treatment of choice for patient with unilateral adrenal hyperplasia, which cures the disease.

Acknowledgement

Dr. A. Thewarapperuma (Consultant Onco-surgeon), Dr. Anoma Perera (Consultant Histopathologist), Dr Manjula Dissanayake (Consultant chemical pathologist), Dr B.K.T.P. Dayanath (Consultant chemical pathologist)
References


Young male with heart failure and negative angiogram

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Key works- Paraganglioma, Negative angiogram

Abstract

A young previously well male presented with features of acute coronary syndrome and heart failure. ECG showed inferior ST elevations but his cardiac markers and angiogram was negative. He was found to have a large abdominal paraganglioma with normal adrenal glands. He had a successful excision of the tumor and is now under life-long surveillance. He is awaiting genetic testing.

Case

Mr. PW, a 32 year old previously well male, got admitted to the local hospital with sudden onset, severe tightening chest pain. Examination revealed decompensated congestive cardiac failure with no signs of pericarditis. An acute cardiac event was suspected. ECG showed ST segment elevations in the inferior leads. Interestingly, troponin I level was negative. Following stabilization, he was immediately transferred to the cardiology unit at Teaching Hospital Kurunegala.

PW was a young fit self-employed gentlemen with a good exercise tolerance. There was no significant family history of cardiovascular disease and he was a non-smoker. He was treated with Intravenous (IV) GTN infusion, IV Frusemide along with antiplatelets. Chest X-ray revealed evidence of pulmonary oedema without cardiomegaly. Echocardiogram revealed ejection fraction of 35% with marked hypokinesia of inferior and posterior walls. Once stabilized, an elective coronary angiogram was performed. During the procedure, his condition deteriorated again as the blood pressure shot up to 220/120 mmHg with ECG revealing a stain pattern. Surprisingly, the angiogram was negative with none of the coronary arteries demonstrating any blockage. His blood pressure remained elevated.

He was put on antihypertensives cautiously: beta-blockers had been avoided, and was transferred to the cardiology unit Colombo for further management. He was referred to the Endocrinology team to be evaluated as a young hypertensive patient.

On specific questioning, he revealed that he experienced episodes of short lasting palpitations, headache and excessive sweating over the last 6-7 months. These episodes occurred without a specific precipitating event. He did not have a history of anxiety disorder and was not on any drugs which could cause similar symptoms. There were no evidence of muscle weakness, easy bruising, factures or recent change in his appearance. He consumed alcohol occasionally. There was no family history of hormone disorders, high calcium, brain tumors, adrenal tumors or early onset hypertension. He was a father of one child and managed his own grocery shop.

On examination, he was thin built with a body mass index (BMI) of 20.5 kg/m2. His height was similar to his sibling and did not have any marfanoid body habitus, skin rashes or skin or mucosal tags/growths. He had a small, non-tender diffuse goiter without cervical lymphadenopathy. He had sinus tachycardia with a pulse rate of 110 beats/min and a blood pressure of 180/110 mmHg (lying and standing) without no difference in the arms. No masses were palpable in the abdomen and there were no abdominal or thoracic bruit. There was no cardiomegaly or chronic hypertensive retinopathy indicating an abrupt onset of hypertension. There were no cardiac murmurs. Further examination was also normal. PW did not have a family history of Pheochromocytoma and evidence for other endocrinopathies were not present. Features of Von Hippel Lindau syndrome, such as cerebellar hemangioblastoma, retinal angiomas, renal cell carcinoma, and
islet cell tumours were not clinically apparent in our patient, neither did he have neurofibromas or Café au lait patches.

Basic testing including renal functions and serum electrolytes were normal without any hypokalemia. Ultrasound scan of the abdomen with renal Doppler was normal without any renal, adrenal structural abnormalities or renal artery stenosis. Due to episodic spells and negative angiography, pheochromocytoma had to be excluded. Though urine fractionated metanephrines/plasma metanephrines could be regarded as the best test to investigate this, since it was not available in the government sector and because of the cost, the patient underwent urine 24 hour Vanillylmandelic Acid (VMA) testing.

VMA showed an elevated level of 27.2 ng/ml (1-11 ng/ml) which was confirmed by a second reading, at 39.6 ng/ml.

Localizing studies were done and CT scan of the abdomen showed normal bilateral adrenal glands. However, there was a 2.6 cm ×3.3 cm × 2.3 cm size, peripherally enhancing retroperitoneal paraganglioma mass on the right side of the aorta, at the level of the renal artery behind the head of the pancreas. It was anterior to the inferior vena cava (IVC) and appeared to be compressing the IVC. The mass was suggestive of an abdominal paraganglioma.

Figure 1: CT image showing an abdominal paraganglioma
Other associated endocrine diseases were sort. Since he had a goiter, a ultrasound scan of the thyroid was done, revealing a mild moderately enlarged gland without nodules or lymphadenopathy. The thyroid functions showed euthyroidism (TSH was 0.4 mIU/mL, Free T4 was 1.36 ng/dL).Fine needle aspiration cytology of the thyroid gland was Thy-2, benign cells. PW had a normal calcium and normal PTH.

Removal of the tumor was planned. Since it was in close proximity and causing compression of the IVC, he was evaluated by the vascular surgical team. Preoperative preparation was initiated to control the heart rate, the blood pressure and the circulatory volume to prevent hemodynamic instability during and after surgery. He was started on phenoxpybenzamine 10 mg nocte which was gradually increased to 20 mg twice a day. Postural drop in blood pressure and heart rate was monitored.

PW underwent open laparotomy under the supervision of the most experience Anesthetist available. He was give Intravenous magnesium sulphate (MgSO4) at induction of anesthesia. Mechanism of MgSO4 is by inhibiting catecholamine release, it is also a potential α receptor blocker and useful in controlling catecholamine induced arrhythmias (1). During surgery, endotracheal intubation and direct manipulation of a paraganglioma can precipitate catecholamine release, so continuous cardiac and blood pressure monitoring should be carried out.

During surgery, blood pressure increased which was managed with GTN infusion. Otherwise the surgery was uncomplicated and he recovered without major adverse events. Tumor mass was completely removed and there was no local invasion or spread to regional tissue. Hypotension and hypoglycemia are the most common immediate postoperative complications and should be anticipated (2).

Histology of the resected tumour demonstrated well-defined nests of cuboidal cells with moderately abundant, granular, basophilic cytoplasm separated by highly vascular fibrous septae. Mitotic activity was inconspicuous and the Ki-67 index was <1%. The tumour was completely removed along with the surrounding thin capsule. The cells showed cytoplasmic positivity for neuroendocrine markers; chromogranin, synaptophysin and S100, confirming that it was a paraganglioma.

One to two weeks after surgery urine/plasma fractionated Catecholamines and Metanephrine levels should be carried out, to confirm that the tumour is completely resected. In PW, urinary VMA was used as a marker and it became normal 2 weeks postoperatively.

PW was considered for genetic testing for SDH mutations and he is currently on surveillance for any recurrence. Postoperative surveillance is mandatory to detect metastatic and recurrent disease. According to the 2004 World Health Organization (WHO) criteria, malignant behavior in pheochromocytomas and paragangliomas can only be accurately distinguished by metastatic spread (3). Overall recurrence is high as 15% and is frequently due to appearance of metastasis (4).

Discussion

Pheochromocytomas are rare neuroendocrine tumors arising from chromaffin cells of adrenal medulla. It has an annual incidence of approximately 0.8 per 100,000 (3) and a prevalence that ranges from 0.1-0.6% (2). In an autopsy study, 50% were found to be asymptomatic (6). Paragangliomas are similar extra adrenal tumors that arise from sympathetic and parasympathetic ganglia. Out of chromaffin cell tumours, pheochromocytomas account for 80-85% cases and Paragangliomas account for 15-20%. Epinephrine is secreted exclusively from adrenal glands whereas norepinephrine is secreted from both adrenals and sympathetic ganglia (7).

The biochemical diagnosis of catecholamine excess is established by measuring levels of catecholamines (dopamine, norepinephrine, and epinephrine) or their metabolites (normetanephrine, metanephrines, VMA ) in the plasma or urine. Since catecholamines are metabolized inside the tumors to some degree the plasma levels can be falsely low. VMA also lacks sensitivity as it's only positive in about 60% of cases. In addition to that, certain foods and medications can cause false positive elevations.

Superiority of measurement of metanephrines over other tests has been clearly demonstrated (8). Urinary Metanephrine levels by mass spectrometry provide excellent sensitivity (97%) and specificity (91%) (9). Plasma metanephrines also have high sensitivity but is found to be less specific (10). Plasma metanephrines should be done fasting and following 30 min recumbence as when done in seated position false positive level can occur up to 3 folds(11).

After biochemical confirmation of Pheochromocytoma, localizing the site of the tumour is the next step. CT scan with contrast provides an excellent initial method of localization, with a sensitivity between 88 and 100% (12). On CT, Pheochromocytoma will be homogenous or heterogeneous, necrotic with some calcifications, solid or cystic. Although typically Pheochromocytoma have attenuation values more than 10 HU in non-contrast CT, some cases has been detected with lower attenuation values and contrast washout > 60 % due to high fat content (13).

Surgery in paraganglioma/pheochromocytoma should be well planned. Commencing α blockers should be done at least 7-14 days prior to surgery (8). Superiority of selective, irreversible and long acting non selective α blockage vs. short acting competitive α-1 blockage is not established. But in a small study done non-selective blockage was associated with better arterial pressure control (14). Nevertheless, it is linked to more postop hypotension. Reflex tachycardia is another adverse side effect of non-selective blockage which is due to lack of noradrenaline re-uptake from the presynaptic membrane with blockage of α2 receptors.
Once α-adrenergic blockade is established, β-blockers maybe added especially if tachycardia ensues. β-blockers should never be used alone, as unopposed α-stimulated vasoconstriction may precipitate a hypertensive crisis. The most commonly employed β-blocker is propranolol (β1 and β2 non selective). In PW we used metoprolol (β1 selective), due to presence of congestive cardiac failure.

Other drugs that are employed to control blood pressure and catecholamine excess are calcium channel blockers, tyrosine hydroxylase inhibitor (Metyrosine). Metyrosine inhibits tyrosine hydroxylase, the rate-limiting enzyme of catecholamine biosynthesis which converts tyrosine to DOPA. Metyrosine is generally reserved for patients with a large tumor burden preoperatively and prior to radiofrequency ablation of metastasis where other agents have been ineffective. It is also employed in the long term management of malignant Pheochromocytoma when surgery is contraindicated (15).

Most common adverse effect is sedation which is observed in more than 20%. Calcium channel blockers act by inhibiting catecholamine mediated calcium transport in to the vascular smooth muscle triggering vasoconstriction.

In the perioperative period, there is no consensus on the target blood pressure due to lack of randomized control trials. The endocrine society guidelines recommend the blood pressure of less than 130/80 mmHg, with standing systolic pressure greater than 90 mmHg. Heart rate target is 60-80 bpm (8).

Fluid and salt repletion is essential prior to surgery, as they are depleted as a result of excess Catecholamines, which once corrected following surgery, may lead to substantial hypovension.

Most pheochromocytomas are sporadic but nearly 30% is familial. The familial forms includes familial MEN syndromes (MEN IIA and IIB), neuroectodermal disorders like Von-Hippel Lindau syndrome (VHL) and neurofibromatosis type 1 and Succinate Dehydrogenase (SDH) mutations (8).)

Germ line mutations in SDH genes account for most (>80%) of the hereditary paraganglioma/ Pheochromocytoma syndrome (HPGL/PCC) and <10% of sporadic paragangliomas and pheochromocytomas (16). PW, is planned to have genetic testing for SDH mutations. The probable subtype with the clinical correlation is SDHB as it is the one associated with abdominal, pelvic and mediastinal paraganglioma.

The mean age of tumor presentation in SDHB mutations carriers is around 30 years but, there had been cases that were diagnosed before the age of 10 years suggesting that tumor screening of asymptomatic SDHB carriers should start as early as 10 years of age. SDHB mutations cause malignant HPGL/PCC in 40% or more cases (17).

SDHD mutations are associated with head and neck paragangliomas and occur exclusively when the mutation is transmitted from the father. Others mutations are characterized by autosomal dominant inheritance with variable penetrance. Penetrance by the age of 60 years is >80%.

Succinate Dehydrogenase (SDH) is an enzyme complex located in the inner mitochondrial membrane and contains four subunits encoded by four nuclear genes; SDHA, SDHB, SDHC and SDHD (figure2).

Figure 2: SDHA and SDHB as catalytic subunits, which protrude into the mitochondrial matrix and are anchored.
SDH complex leads to oxidation of succinate to fumarate as a part of the Krebs cycle and also causes electron transfer to ubiquinone to prevent formation of potentially dangerous Reactive Oxygen Species (ROS). Loss-of-function mutations of any of the SDH genes or Succinate Dehydrogenase Complex assembly factors (SDHAF2) are associated with a variable clinical presentations ranging from early-onset devastating encephalomyopathy, tumour susceptibility in adulthood and optic atrophy in the elderly (18). In addition to HPGL/PCC, SDHX mutations are also associated with gastrointestinal stromal tumours and renal tumors.

The underlying pathogenic mechanism is largely unknown, but it is clear that SDH genes act as classical tumor suppressor genes. Possible mechanisms postulated are the central function in cellular energy production, prevention of ROS formation and prevention of accumulation of succinate which may be a carcinogenic precipitant. Accumulation of succinate and the production of reactive oxygen species (ROS) may act independently or in a synergetic manner, leading to hypoxic response despite normoxic conditions (pseudo-hypoxia). In addition to pseudohypoxia, succinate might inhibit apoptosis of neuronal cells or cause dysregulation of the G-protein-coupled receptor (GPCRs). ROS accumulation may result in oxidative damage to DNA.

Figure 3: Mechanisms of tumorigenesis due to SDH inactivation mutations
A Case of Classical Galactosaemia presenting with Fanconi syndrome

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1 Faculty of Medicine, University of Ruhuna 2 Teaching Hospital Karapitiya 3 Lady Ridgeway Hospital

Abstract

Galactosaemia is a rare autosomal recessive metabolic disorder with the prevalence of 1:60000. Classical Galactosaemia (CG) is the most common variant of Galactosaemia and which is due to deficiency of Galactose-1-phosphate Uridyltransferase enzyme. Fanconi Syndrome (FS) is a rare presentation of CG. Here we present a baby girl with CG presenting with FS, which led to a diagnostic difficulty.

Introduction

Galactosaemia is a rare autosomal recessive metabolic disorder with the prevalence of 1:60000 (1). Classical Galactosaemia (CG), Galactokinase deficiency and Galactose Epimerase deficiency are the different types of Galactosaemia (2). In CG, there is a deficiency of Galactose-1-phosphate Uridyltransferase (GALT) enzyme (1). Fanconi Syndrome (FS) or proximal renal tubular dysfunction is a rare association of CG (2). Here we present a baby girl with CG presenting with FS.

Case Report

A 5 month old baby girl presented with recurrent vomiting since early neonatal period. She was the first baby born to second degree consanguineous parents following uncomplicated antenatal period, with a birth weight of 2.35kg. She was commenced on breast feeding within one hour of birth and discharged on day 3. The baby had unconjugated hyperbilirubinaemia since day 2 onwards and has received double phototherapy during the post-natal ward stay.

She was exclusively breast fed and there was a history of non-bilious vomiting following feeds since early neonatal period. There was no history of prolonged jaundice, pale stools or dark urine. Her weight gain was suboptimal and there was a global developmental delay.

On admission, she looked ill, tachypnoeic and dehydrated. There was no pallor or icterus. Her weight and length were 4.4kg (<-3SD) and 55 cm (<-3SD) respectively. There was 4cm hepatomegaly without splenomegaly. Her development age was 3 months. Rest of her physical examination was normal.

Her basic haematological parameters and inflammatory markers were normal. There were elevated liver enzymes with normal renal functions. She had normal anion gap metabolic acidosis and her both dinitest and clinicist tests were positive. Further investigations revealed proximal tubular dysfunction (Table 1). Her bone profile showed hypophosphataemia, hypocalcaemia and low vitamin D3 levels. Ophthalmological assessment didn’t show cataract. Dry blood spot for serum galactose level was well above the normal range. (67.55mg/dL).

Based on the clinical and biochemical findings, the diagnosis of CG complicated with FS was made and she was commenced on lactose free formula. For renal tubular acidosis, she was started on bicarbonate and potassium supplementation. Her symptoms were markedly improved with the treatment and subsequently there was a good weight gain.
Table 1: Investigation Summary

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Discussion

CG is the most common variant of Galactosaemia (3). In developed countries, Galactosaemia is diagnosed during neonatal period as a result of newborn screening programmes. However, in Sri Lanka, there is no screening programme to detect Galactosaemia.

In GALT deficiency, there is a failure of conversion of Galactose 1 phosphate to Glucose 1 phosphate and UDP galactose to UDP glucose resulting excess accumulation of galactose in the body. Excess amount of galactose damages the major organs such as brain, kidney, liver and eyes (3).

Clinical features of CG include vomiting, failure to thrive, feeding difficulties, prolonged jaundice, hepatomegaly, hypotonia and cataract (2). In this case, except for cholestatic jaundice and cataract most of the other clinical features were there. FS is a rare complication of CG and the presence of FS in CG might challenge the diagnosis of the underlying condition. In this case, the child had normal anion gap metabolic acidosis secondary proximal renal tubular dysfunction, however, CG alone would have presented with high anion gap metabolic acidosis (4).

In addition, the characteristic investigation finding of Galactosemia is the positive urine reducing substances (Clinistix) in the absence of glycosuria (Clinistix) (3). However, when there is coexisting FS together with CG, both Clinistix and Clinistix would become positive challenging the diagnosis. The confirmatory test to diagnose CG is the erythrocyte GALT enzyme assay (5). In this child the test was not performed due to lack of facilities. The mainstay of management of CG is the lifelong abstinence of lactose containing foods (5). In addition, associated complications such as liver failure, renal tubular dysfunctions and neurological manifestations needs to be addressed separately (5).

The prognosis of CG depends on the age at diagnosis. Those who were diagnosed through newborn screening programmes can have near normal life. However, they also can have mild degree of intellectual impairment and almost all females with CG develops primary ovarian failure (5).

References

Visual Vignette- Nelson’s syndrome: a Giant Pituitary

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Abstract

Nelson’s syndrome is an infrequent pituitary mass with an incidence of 8–43% in adults and 25–66% in children that develops following total bilateral adrenalectomy (TBA) for the treatment of Cushing’s disease. It is one of the most challenging of all endocrine conditions. The frequent aggressiveness of the underlying ACTH-secreting pituitary adenoma (corticotrophinoma) necessitates regular biochemical and radiological screening. Current evidence favours a lack of prophylactic neoadjuvant pituitary radiotherapy at the time of TBA and a rapid rise of ACTH levels in the year post TBA as factors that may predict the occurrence of Nelson’s syndrome. Though, computed tomography (CT)/magnetic resonance imaging (MRI) have led to the early diagnosis and improvement in management. Nelson’s related tumours are sometimes detected late, through clinical manifestations of invasion and compression of the surrounding structures. With this perspective in mind, we describe a 22 year old gentleman 10 years after TBA who presented with right sided hemiparesis due to a corticotrop adenoma.

Running Title: Nelson syndrome

Key terms: Nelson syndrome, radiotherapy, bilateral adrenalectomy

Introduction

Nelson’s syndrome is an infrequent pituitary mass that develops following total bilateral adrenalectomy (TBA) for the treatment of Cushing’s disease. It is one of the most challenging of all endocrine conditions. In 1958, Don Nelson described the first case in a 33-year-old woman who had undergone total bilateral adrenalectomy (TBA) for the treatment of refractory Cushing’s disease. With an incidence of 8–43% in adults and 25–66% in children, Nelson’s syndrome can develop up to 24 years post TBA (1, 2). The central pathological feature of Nelson’s syndrome is an underlying ACTH-secreting pituitary adenoma (corticotrophinoma). The frequent aggressiveness of the underlying corticotrophinoma justifiably necessitates close screening. Current evidence suggests risk factors that include a lack of prophylactic neoadjuvant pituitary radiotherapy at the time of TBA and a rapid rise of ACTH levels in the first year post TBA as factors that may predict the occurrence of Nelson’s syndrome. The current management is centered on surgery and radiotherapy. In recent times the alkylating agent, Temozolomide, holds promise as a novel and effective therapeutic agent in the treatment of associated aggressive corticotroph tumours.

Though computed tomography (CT) and magnetic resonance imaging (MRI) have led to an earlier diagnosis and improved management, Nelson’s tumours are sometimes detected late through clinical manifestations of invasion and compression of surrounding structures. With this background, we report a 22 year gentleman, 10 years after TBA who presented with right sided hemiparesis as a result of a corticotroph adenoma.

Case

In 2004, a 23 year old man was diagnosed to have adrenocorticotropic hormone (ACTH) dependent Cushing’s syndrome. The source of ACTH was not localized during the initial workup. His evaluation had revealed a normal pituitary gland on magnetic resonance imaging (MRI). (Fig.1a, b) and there wasn’t any evidence of an ectopic source of ACTH. In view of refractory hypokalemia and progressive symptoms, he underwent bilateral adrenalectomy. Preoperatively his ACTH value was 154pg/ml (normal< 40pg/ml). After surgery, he was well
on oral prednisolone and fluocortisone replacement therapy. Subsequent follow up after one year revealed progressive hyperpigmentation of the skin and mucous membranes with an ACTH level of 850pg/ml. Screening for the source of ACTH was negative. He was lost to follow up and returned for re evaluation after a period of 7 years, when he noticed weakness of the right upper and lower limb which had progressed over three weeks. He could not walk without support or write. Subsequently, he developed urinary incontinence, headache and recurrent vomiting. On examination, his GCS (Glasgow coma score) was 15/15 and vital signs were normal. He had generalized hyperpigmentation of the skin, old scars of surgery and the mucous membranes (Fig.2a, b). Systemic examination revealed right sided hemiparesis with facial nerve involvement. Perimetry revealed had bitemporal hemianopia. ACTH levels were > 1250pg/ml (normal < 46). MRI of the brain demonstrated a sellar mass with suprasellar extension into the third ventricle, causing hydrocephalus (Fig.3a, b). He underwent a biventricular peritoneal shunt for hydrocephalus and focused radiotherapy (5400 cGy in 30 fractions) was administered to the giant suprasellar mass. After a year, he was symptomatically better with resolution of hemiparesis. His subsequent MRI showed partial regression of the mass (Fig. 4a,b).

The present subject had persistently elevated ACTH levels with compressive symptoms due to a giant pituitary mass. He was subjected to radiotherapy alone, as surgery was not considered the appropriate primary choice in view of extentive invasion of the surrounding structures.

Transsphenoidal pituitary surgery is the first line of treatment for Cushing’s disease; though recurrence has been observed in about 20% of patients (3).

In 1958, Don Nelson et al were the first to report a corticosteroid macroadenoma in a 33 year old lady who had underwent total bilateral adrenalectomy (TBA) for refractory Cushing’s syndrome(4). TBA may be proposed in any patient with a non-localized pituitary source of ACTH or failure of pituitary surgery and those refractory to medical therapy. However, the major concern following adrenalectomy is the occurrence of Nelson’s syndrome (NS), a corticotroph adenoma with concomitantly high ACTH levels.

This syndrome does not occur infrequently and has an incidence of 8–43% in adults and 25–66% in children, with a time interval between adrenalectomy and NS diagnosis of 6 months to 24 years (4). The usual presentation involves progressive hyperpigmentation of the skin and mucous membranes with ACTH levels >500 pg/ml despite adequate corticosteroid supplementation. Visual field defects and cranial nerve palsies were additional presenting features due to the mass effects of the tumor invading adjacent structures as was seen in the present case, but are uncommon in recent years (4,5). Dopamine agonist like Cabergoline have been documented to induce remission and tumour reduction in some patients with NS (4). Selective somatostatin analogues (SSAs) like Octreotide may decrease plasma ACTH levels and reduce tumour volume in some patients with Nelson’s syndrome (5). In refractory cases newer somatostatin analogues like Pasireotide or the alkylating agent: Temozolomide hold promise as therapeutic agents in reducing plasma ACTH and causing regression of the tumor (2). Current evidence suggests that lack of prophylactic neoadjuvant pituitary radiotherapy at the time of TBA, a rapid rise of ACTH levels in a year post TBA , the presence of residual pituitary tumour on magnetic resonance imaging (MRI) and post transsphenoidal surgery (TSS) as common risk factors for NS. Pituitary surgery should be the first-line of treatment and in view of the aggressiveness of the underlying corticopherminoma in NS, adjuvant radiotherapy should be considered in most patients.

References

Figure 1a, Figure 1b: T1W sagittal and coronal MRI images showing normal pituitary gland.

Figure 2a: Hyperpigmentation of the scars over the back and Fig2b: Hyperpigmentation of knuckles of hands.
Figure 3a, b: T1W sagittal and coronal contrast MRI images showing 61 x 60 x 49 mm (Transverse x Coronal x Sagittal) sella-suprasellar mass extending into the suprasellar cistern and the third ventricle, causing obstruction of the 3rd ventricle and hydrocephalus, performed when the patient had symptoms in 2012.

Figure 4a, b: T1W sagittal and coronal contrast MRI images showing a giant pituitary adenoma in 2014 but with a reduction in size 42 x 41 x 30 mm (Transverse x Coronal x Transverse) 1 year after radiotherapy, when compared to the previous MRI done in 2012.
CASE REPORT

Hypoglycemia as a presenting manifestation of Sheehan’s syndrome

Mandeep Singla, Geetika Garg

Government Medical College and Hospital, Chandigar, India

Abstract

Sheehan’s syndrome is caused by ischemic necrosis of the pituitary gland from massive postpartum uterine bleeding. Despite advances in obstetric care, it is still an important cause of hypopituitarism in developing countries. Sheehan’s syndrome has an insidious course with variable presentation. Here, we present a case having recurrent hypoglycemia and was later found to have hypopituitarism due to Sheehan’s syndrome. Despite the presence of lactation failure and secondary amenorrhea following the delivery, she was diagnosed ten years later. Awareness of these clues and prompt evaluation for pan hypopituitarism can significantly reduce the morbidity and mortality in these patients.

Keywords: sheehan’s syndrome, hypoglycemia, hypopituitarism, empty sella

Introduction

Sheehan’s syndrome is caused by ischemic necrosis of the pituitary gland from massive postpartum uterine bleeding. It was first described by Sheehan in 1937(1). With advancements of obstetrical care, Sheehan’s syndrome has become uncommon in the western countries. However, it is still an important cause of hypopituitarism in developing countries. Sheehan’s syndrome has an insidious course with variable presentations. The majority of cases remain undiagnosed for many years after delivery. Here, we present a case of Sheehan’s syndrome with recurrent hypoglycemia as the presenting manifestation.

Case

A 40-year-old female presented to the emergency department in a state of altered mentation. She was confused and sweating profusely. Her blood glucose level was 37 mg/dl. She regained consciousness after the administration of dextrose infusion. She had episodes of palpitations, blurred vision, and confusion for the past four years, which were relieved on eating. She had weight loss of twelve kilograms during the same period. She was non-diabetic, not on any medication, and had no known malignancy. General physical examination revealed pallor, dry and coarse skin, facial wrinkling, absent axillary and pubic hair, and breast atrophy, suggestive of hypopituitarism. Her body mass index was 18.5 kg/m². On eliciting a detailed history, she had lactation failure and secondary amenorrhea since her last child birth ten years back. She had received six unit of blood due to postpartum haemorrhage. Biochemical investigations revealed low haemoglobin (9.7 g/dl) and hyponatraemia (124 meq/l). Hormonal profile revealed panhypopituitarism: freeT3 1.2 pg/ml (2.3-4.2), freeT4 0.6 ng/ml (0.89-1.76), thyroid-stimulating hormone(TSH) 8.8iu/l (0.35-5.5), follicle-stimulating hormone(FSH) 1.8 IU/l (2.5-10.2), luteinizing hormone(LH) <0.1 IU/l (1.9-12.5), prolactin 1.3ng/ml (4-25), insulin-like growth factor-1(IGF-1) 78.6 ng/ml (109-284), cortisol 68 nmol/l (100-550), and adrenocorticotropic hormone(ACTH) 2.3 ng/l (5-60). Magnetic resonance imaging of the brain revealed thinning of anterior pituitary gland with extension of suprasellar cistern CSF into sella (Figure 1 & 2), thus confirming the diagnosis of Sheehan’s syndrome. She was treated with oral hydrocortisone followed by levothyroxine supplementation. Hormone replacement therapy was instituted for gonadotropin deficiency. Following treatment, she started gaining weight and the hypoglycemic symptoms abated.

Discussion

Sheehan’s syndrome is defined as pituitary hormone deficiency due to ischemic necrosis of the pituitary gland from massive postpartum uterine bleeding. Enlargement of pituitary gland, small sellar size and disseminated intravascular coagulation are considered to play a role in its pathogenesis. Anti-pituitary antibodies have also been demonstrated in patients with Sheehan’s syndrome, suggesting an underlying autoimmune etiology (2). Extensive destruction of cells results in varying degrees of anterior pituitary dysfunction. It is one of the
common causes of hypopituitarism in developing countries. An epidemiological study from Kashmir valley of India reported the prevalence to be around 3% for women above 20 years of age, almost two-thirds of whom had delivered babies at home(3).

It can manifest in the postpartum period or after months to years following the inciting delivery. The majority of cases remain undiagnosed for many years after delivery. In a study of 60 patients, the mean duration between the inciting delivery and the diagnosis was 13 years (4). Characteristic manifestations include failure to lactate or to resume menstruation, genital and axillary hair loss, asthenia and weakness, dryness and wrinkling of the skin, signs of premature aging and hypopigmentation(5). Uncommonly, it can present acutely with circulatory collapse, hyponatraemia, diabetes insipidus, hypoglycemia, or psychosis. Hypoglycaemia in Sheehan’s syndrome is attributed to the deficiency of glucose counterregulatory hormones, including cortisol and growth hormone. Deficiency of these hormones results in glycogen depletion and impaired gluconeogenesis.

The characteristic radiological finding is the presence of an empty sella or partially empty sella. Treatment is aimed at replacing the deficient hormones and to reduce the mortality due to hypopituitarism. In patients with both secondary hypocortisolism and hypothyroidism, glucocorticoids should be replaced first followed by thyroid hormone supplementation. Gonadotropin deficiency should be treated with a hormone replacement therapy. Replacement of growth hormone should be considered in patients with GH deficiency to maintain insulin-like growth factor-1 levels within the age-appropriate range for the patient.

Conclusion

Sheehan’s syndrome is still an important cause of hypopituitarism in developing countries. This case highlights the diverse manifestations of Sheehan’s syndrome. History of postpartum hemorrhage, failure to lactate and cessation of menses are important clues to the diagnosis. Awareness of these clues and prompt evaluation for panhypopituitarism can significantly reduce the morbidity and mortality in these patients.

References

Figure 1, Figure 2: Sagittal and coronal sections of Magnetic resonance imaging of the brain showing thinning of anterior pituitary gland with extension of suprasellar cistern CSF into sella
A case series of Pyridoxine Resistant Classical Homocystinuria

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Abstract

Homocystinuria is an autosomal recessive disorder with the prevalence of 1:200000. It is due to the defect in the Methionine metabolism which results in accumulation of Homocysteine in the body. We report a series of patients with Homocystinuria followed up at university paediatric clinic, Teaching Hospital Karapitiya. There were four children with Homocystinuria from 7 to 18 years, of them, 2 were males. None of them were born to consanguineous parents and two were siblings. The age at diagnosis ranged between 6 to 17 years. All children had delayed cognitive development with the IQ level between 40-77. The condition was suspected with the onset of ophthalmic manifestations such as Ectopia lentis glaucoma and ptosis. Marfanoid body habitus (tall stature, high arch palate and arachnodactyly) and scoliosis were present in all four children. Three children had low bone mineral density and 2 of them had fractures. None of them had thromboembolic events. Serum Homocysteine and Methionine levels were high, ranged 145-373μmol/L (4.6-8.1) and 79-177 μmol/L (6-60) respectively. All had normal vitamin B12 levels between 150.0 and 216.0 pmol/L (140-650).

It is well known that early detection and initiation of treatment would prevent most of the complications in Homocystinuria. However, in this case series, all children were diagnosed later. Therefore, it is important to suspect the condition in children with intellectual impairment, visual defects and marfanoid body habitus.

Introduction

Homocystinuria is a rare, inherited metabolic disorder of the methionine metabolism (1). Accumulation of Homocysteine in, brain, blood vessels, bones and eyes, is responsible for the clinical phenotype(1). The worldwide prevalence of Homocystinuria varies between 1; 50,000 to 1; 200,000 (2). We report four children with homocystinuria who are being followed up at Teaching Hospital, Karapitiya. Though the first line treatment for Homocystinuria is Pyridoxine, all of them were resistant to the standard treatment.

Case 02

A 10 year old boy presents with poor academic performances and visual disturbances. He was the second child born to non-consanguineous parents with one affected elder sibling with homocystinuria. He had had a fracture radius at the age of 5 years following minor trauma. He was followed up at child psychiatry clinic for attention deficit hyperactive (ADHD) disorder since 7 years of age. His IQ score was 70. Examination didn’t reveal any marfanoid body habitus and his height was at 50th centile. Investigations showed high homocysteine and Methionine levels with normal B12 suggestive of CH. His DXA scan showed low BMD. Though, he was started on high dose Pyridoxine and...
methionine restricted diet, the expected biochemical response was not seen.

Case 03
An 11-year-old girl was referred by the ophthalmologist for further evaluation of glaucoma and ectopia lentis. She was tall for her age and had marfanoid body habitus. She had global developmental delay and she attends to a special school. Her IQ score was 54. Investigations revealed elevated Methionine and Homocystein with normal B12 levels suggestive of CH. Her DXA scan showed low BMD. There was no improvement in her serum Homocystein level following Pyridoxine treatment.

Case 04
A seven-year-old child who has had global developmental delay presents with impaired vision. He was found to have ectopia lentis, proptosis and marfanoid body habitus. He had a fracture tibia at the age of four years. He was behind his peers at school and the IQ score was 40. Investigation findings were compatible with a case of CH and BMD was low in DXA scan. He was commenced on high dose Pyridoxine therapy and methionine restricted diet, for which there was no biochemical improvement.

<table>
<thead>
<tr>
<th>Case</th>
<th>Homocystein (4.6-8.1 μmol/L)</th>
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Table 1: Biochemical values of Patients with Homocystinuria
Discussion

Homocysteine is produced by the Cystathionine beta- synthase (CBS) enzyme as an intermediate product of methionine metabolism. In the absence of CBS enzyme, homocysteine accumulates in different organs in the body such as brain, eye, blood vessels and bones resulting multisystem disease (1).

The clinical presentation of CH varies depends on the severity of the enzyme deficiency and milder forms might not present until they get thromboembolic events in adolescence (3). However, all these children had severe multisystem involvement since early childhood. In this case series the commonest reason to suspect the condition was ophthalmologic manifestations and marfanoid body habitus.

The ophthalmologic manifestations seen in CH are ectopia lentis, astigmatism Glaucoma, Cataract, Retinal detachment and Optic atrophy (4). In this case series all four children had ectopia lentis and the two of them had glaucoma. Moreover, all these patients had low IQ (40-77) and neuropsychiatric manifestations. All these children had low bone mineral density and two of them had fractures. Though, none of them had thromboembolic manifestations up to now they are at risk of developing such events in future.

The worldwide prevalence of pyridoxine responsiveness in CBS deficiency is 50%, however, all these patients were Pyridoxine resistant (3). For late-diagnosed patients the target homocysteine level should be <100 μmol/L and pyridoxine resistant patients need Betaine therapy, which is not available in Sri Lanka (5).

Conclusion

In the absence of new-born screening programme to detect Homocystinuria, in Sri Lanka, patients with homocystinuria have developed major complications at the time of diagnosis. However, it is important to consider Homocystinuria in children with marfanoid body habitus, neuro-psychiatric manifestations and fractures. Moreover, it is important to make Betaine available in Sri Lanka to treat these children with pyridoxine resistant Homocystinuria.

References