TREATMENT OF TYPE 2 DIABETES: ADVANCES, CHALLENGES AND OPPORTUNITIES

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The prevalence of type 2 diabetes is increasing at an alarming rate throughout the world. The number of medications available to treat this condition has also increased over the past decade. Despite this the majority of people with type 2 diabetes are not achieving therapeutic goals for glucose control, and even fewer subjects achieve therapeutic goals for all cardiovascular risk factors. Use of newer medications to treat type 2 diabetes that have become available recently, if used appropriately, could facilitate achievement of therapeutic goals in many patients. These medications include incretin mimetics, such as exenatide and sitagliptin, which lower HbA1c concentrations by up to 1%. These agents primarily lower postprandial glucose but longer acting forms of GLP receptor analogues improve fasting glucose concentrations, and reduce HbA1c by more than 1.5%. Ultimately many patients with type 2 diabetes will require insulin, since the disorder is characterised by progressive beta cell dysfunction. Addition of basal insulin to subjects taking oral medications helps many subjects improve glycaemic control, but prandial insulin is also often required. Various insulin regimens can be employed to treat patients to target and achieve glucose levels that reduce the risk for the long-term complications of the disease. The opportunity to treat more patients to goal is easier today than it has been for many years; the challenge for the practitioner is how to use the newer medications, including insulin, to achieve these objectives.

THE EMERGING IMPORTANCE OF POSTPRANDIAL GLUCOSE

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Much of our 24-hour day is spent in a postprandial or postabsorptive state. In type 2 diabetes insulin resistance, increased hepatic gluconeogenesis and impaired insulin secretion contribute to postprandial elevations in glucose. As HbA1c concentrations approach normal, the postprandial glucose contributes more than the fasting glucose to the HbA1c. The epidemiological association between postprandial glucose excursion and mortality is well established – numerous studies have demonstrated increased mortality, particularly cardiovascular mortality, in individuals with impaired glucose tolerance. Higher glucose concentrations post meals are associated with increased oxidative stress and endothelial dysfunction. In individuals with IGT, acarbose use is associated with a reduction in new onset hypertension and reduced cardiovascular morbidity. In type 2 diabetes, there are specific therapies that lower postprandial glucose. In some studies lowering postprandial glucose reduces oxidative stress and improves endothelial function. The extent to which this may abrogate the long-term complications of the disease or improve outcomes is yet to be determined.

BLOOD PRESSURE CONTROL AND HYPERTENSION TREATMENT IN DIABETIC PATIENTS OVER A 3-YEAR PERIOD

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Objective: To assess the response of doctors working in the diabetes clinic of Kalafong Hospital to blood pressure measurements.

Methods: The clinical records of 175 patients attending the diabetes clinic were audited. Blood pressure measurements were assessed as well as the attending doctor’s response. Patients visit the clinic 4 times per year and blood pressure is measured at each visit. In total 1 527 patient visits was evaluated, stretching over a period of 3 years.

Results: Doctors responded in only 13.7% of patient visits if the systolic blood pressure was between 130 and 140 mmHg, this increased to 20.4% in patients with systolic blood pressure above 180 mmHg. The most frequent response was to add a drug: 13.5% if systolic BP > 180 mmHg, 6.4% if 159 - 180 mmHg and 4.6% if 139 - 160 mmHg. The second most frequent response was to increase the dosage of antihypertensive drugs: 13% if systolic BP > 180 mmHg, 6.4% if 159 - 180 mmHg and 3.7% if 139 - 160 mmHg. Doctors tend to respond in very similar ways if the diastolic blood pressure was elevated.

Conclusion: Hypertension control in diabetic patients is of the utmost importance to prevent complications. Currently doctors working in the diabetes clinic are reluctant to respond to elevated blood pressure measurements. Doctors will need to be trained and urged...
not to delay the initiation and increase in blood pressure treatment when the blood pressure is not sufficiently controlled.

AN AUDIT OF THE THYROID SCREENING PROGRAMME IN THE PENINSULA MATERNAL AND NEONATAL SERVICES (PMNS)
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Objective: To audit the cord blood thyroid screening programme in the PMNS from 01/01/00 to 31/12/04.

Method: All babies born in the PMNS from 01/01/00 to 31/12/04 were included in the audit. The medical records of all babies recalled following an abnormal screen were examined. 140 507 babies were born in the PMNS during the audit period, while 130 389 primary TSH screens were done. 2 207 of the screened babies had abnormal results requiring review.

Results: 13 cases of congenital hypothyroidism (CH) were detected out of the 751 abnormal screened individuals that were reviewed. The corrected incidence is calculated at 1: 3 448, which compares with the published general population. The cost of the programme was R22.02 per screened baby, or R221 552.96 per actual detected case of CH.

Conclusion: The current screening programme reveals major problems in the recall success, with only 34% of abnormal screens returning for review, and a default rate of 31% in those detected as having congenital hypothyroidism. The greatest contributing factor is that there is no education, neither population nor maternal, about the screening programme and/or hypothyroidism.

Despite these problems, this audit identified an incidence that emphasises the importance of this screening programme; and reflects its financial viability.

AN AFRICAN STORY: GENDER ASSIGNMENT GONE WRONG
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South Africa has the nickname ‘The Rainbow Nation’ as it has multiple cultures and ethnic origins, reflected in the fact that there are 11 official languages.

Each culture holds different roles for girls and boys, men and women. Modern cities, new technologies, and urbanisation contrast with ancestral worship, traditional magic and remote locations. This results in varying responses to intersexed individuals.

This case report illustrates the difficulties of imposing Western medical doctrines upon individuals in the African setting, as well as the disabilities encountered when the assigned gender has been surgically affirmed, and proven the wrong choice.

The case describes a Xhosa child labelled a boy at birth, assigned the female gender in infancy once the diagnosis of congenital adrenal hyperplasia was made, and then surgically feminised. The child had inconsistent adherence to medical therapy, and consequently virilised further and had rapid advancement of bone age with resulting short stature. At 14 years, the child insisted on the male gender role, and he had a surgical and hormonal sex change.

There is psychiatric, sexual, social and cultural morbidity as a result of his condition and the manner in which it was managed.

DYSGLYCAEMIA IN PATIENTS PRESENTING WITH AN ACUTE STROKE
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Background: Although diabetes is a risk factor for acute stroke, a number of recent studies have highlighted the high prevalence of previously undiagnosed hyperglycaemia in the setting of an acute stroke. However, it is often uncertain whether this hyperglycaemia is reactive or due to a previously unrecongnised abnormality of glucose metabolism. Vancheri et al reported that at 3 months after an acute stroke dyglycaemia persisted in two-thirds of their patients. As dyglycaemia correlates with a worse outcome and in view of the dearth of data from Africa, it was decided to evaluate the prevalence of persistent dyglycaemia in a cohort of South African patients admitted with an acute stroke to two teaching hospitals in Cape Town, South Africa.

Design: Prospective observational study.

Methods: Over a 2-year period patients over 40 years old who were admitted with an acute stroke and had no previous history of diabetes were enrolled. Patients were evaluated with serial fasting glucose measurements, HbA1C and a 75 g oral glucose tolerance test (OGTT) on day 4 or 5 of the acute admission. The OGTT was repeated at 3 months after discharge.

Results: 115 patients were enrolled, of whom 85 (74%) were of mixed ancestry. There were 61 males (53%) and 54 females (47%) with a mean age of 61 ± 12 years. Twenty-seven patients (23.5%) had diabetes, 38 patients (33%) had impaired glucose tolerance (IGT), and 5 patients (4.3%) had impaired fasting glucose (IFG). At 3 months 18 patients had died (8 patients with diabetes, 4 patients with IGT, 1 patient with IFG and 5 patients with normal glucose metabolism) and preliminary analysis of 65 of the remaining 97 patients showed that the majority of those with dysglycaemia had reverted to normoglycaemia [5 of 9 patients with diabetes (55.5%), 19 of 23 patients with IGT (82.6%) and 2 of 2 patients with IFG (100%)].
Conclusion: In contrast to studies from Europe (1,2) this preliminary analysis suggests that dysglycemia present in patients presenting with an acute stroke in Cape Town, South Africa is transient and that by 3 months the majority of patients are normoglycemic.

References: (1) Vancheri F et al., Q J Med 2005; 98:871-878; (2) Katz M et al., Diabetes Care 2006; 29:792-797; (3) Linberg PJ et al., Stroke 2004; 35:363-364; (4) Kernan WN et al., Arch Intern Med 2005; 165:227-233; (5) Baard TA et al., Stroke 2003; 34:2208-2214.

EXECUTIVE COGNITIVE IMPAIRMENT DETECTED BY SIMPLE BEDSIDE TESTING IS ASSOCIATED WITH POOR GLYCAEMIC CONTROL IN PEOPLE WITH TYPE 2 DIABETES

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Aims: Cognitive impairment in people with type 2 diabetes is a barrier to successful disease management. We sought to determine whether a battery of simple bedside cognitive tests of executive function was associated with impaired glycaemic control.

Methods: People with type 2 diabetes attending a tertiary referral diabetic clinic who consented to study participation underwent a brief battery of cognitive testing (the Bedside Executive Screening Test) designed to detecting executive function impairment. Glycaemic control was determined using blood glycated haemoglobin levels (HBA1C).

Results: Of the 98 study participants executive function impairment was detected in 51 (52%). The presence of executive function impairment was significantly associated with poor glycaemic control (HBA1C < 7%) with an odds ratio of 4.9 (95% CI = 1.3 - 18.8), p = 0.019. There were no significant differences between patients with and without executive function impairment with respect to age, education level, medications (insulin, metformin, sulphonylurea, aspirin and statin), target organ damage, and patient reported adherence.

Conclusions: Executive function impairment is common in a difficult to manage population of people with type 2 diabetes. The presence of executive impairment is significantly associated with poor glycaemic control.

DIABETES INTERVENTION IN RURAL SOUTH AFRICA: LONG-TERM RESULTS FROM THE HLABISA DIABETES PROJECT

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In 2000, we introduced a structured diabetes delivery service to Hlabisa District in KwaZulu-Natal, South Africa. Hlabisa is a scattered rural area with high levels of HIV/AIDS and socio-economic deprivation. A clinical algorithm for oral agent adjustment was introduced, as well as regular empowerment-based education. Care was delivered to primary health clinics (PHCs) rather than in the central hospital. Many hundreds of patients have now entered the service, but we report here detailed glycaemic control data on 80 type 2 patients who have been continuously followed for 4 years. At baseline, their age was 56 ± 11 years (mean ± SD), diabetes duration 7 ± 8 years, body mass index (BMI) 31.5 ± 7.2, and HbA1c 10.8 ± 4.0%. Follow-up HbA1c levels were 8.1 ± 2.2% at 6 months (p < 0.001), 7.5 ± 2.0% at 18 months, 8.4 ± 2.3% at 2 years, and 9.7 ± 2.2% at 4 years (p = 0.015 from baseline). BMI at 4 years was 32.2 ± 8.3 (pNS from start). The results demonstrate marked ‘glycaemic slippage’ after 18 months from intervention, but at 4 years HbA1c was still significantly better than at baseline. In addition, data from the UKPDS (United Kingdom Prospective Diabetes Study) would predict a 0.7% deterioration of HbA1c between diabetes duration 7 to 11 years (as in our cohort). We conclude that diabetes intervention programmes in Africa are highly beneficial, but that short to medium term HbA1c benefits are decline after 18 months. This partly relates to the natural history of type 2 diabetes, and intervention should still be regarded as highly worthwhile.

PHAECHROMOCYTOMA IN PREGNANCY

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Aim: To describe the clinical presentation and outcome of phaeochromocytoma in pregnancy.

Methods: The case records of patients presenting to the CHBH Endocrine Unit with phaeochromocytoma in pregnancy between 1985 and 2006 were reviewed.

Results: 6 patients were seen over a 21-year period. The age range was 20 - 32 years. The gestational age at presentation ranged between 8 and 33 weeks. All patients were found to be hypertensive. 5 patients presented with at least one of the triad of headache, palpitations and sweating. 3 patients were found to have gestational diabetes. Biochemical confirmation of phaeochromocytoma was made in all the cases. Antepartum tumour localisation was possible in 5. Alpha-blockade was used in all cases to control the blood pressure pre-operatively. In addition 3 patients were on a beta-blocker and 3 on a calcium channel blocker. All the patients were delivered by caesarean section (2 emergency, 4 elective). Tumour excision was carried out as follows: during the antepartum period (1 case), immediately post-caesarean section (3 cases; 2 at 35 weeks, 1 at 37 weeks); postpartum (2 cases). All were benign adrenal tumours. 2 patients remained hypertensive post-surgery. One baby died.

Conclusion: Vigilant management of phaeochromocytoma in pregnancy leads to improved maternal and fetal outcome.
NEW-ONSET DIABETES MELLITUS POST RENAL TRANSPLANTATION

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Aims: To determine 1) the incidence of new-onset diabetes in patients post renal transplantation, and 2) the association between new onset diabetes with particular immunosuppressive regimens and ethnicity; and 3) to assess outcomes in terms of morbidity and mortality.

Study design: 384 patient files from transplant period 30/06/1994 to 30/06/2004 were assessed. Data consisting of race, date of onset of diabetes, immunosuppressive regimens, infections and cardiovascular and overall morbidity and mortality were recorded.

Results: The incidence of new-onset diabetes was 15% with a mean time to onset of 13.8 months. 20% blacks, \( p = 0.0006 \), OR = 2.61; 8% whites, 20% Asians; 13% Indians and 10% coloured patients developed diabetes. Treatment with CyA had an incidence of diabetes of 14%; tacrolimus 23%, \( p = 0.038 \), OR = 1.96; Rapamune 7% \( p = 0.049 \); MMF 12%, \( p = 0.140 \). Infection rate was 18% in the diabetics, \( p = 0.003 \), OR = 8.88. Cardiovascular morbidity was 16%, \( p = 0.831 \). Overall mortality was 26%, \( p = 0.001 \), OR = 3.2.

Conclusions: The incidence of new-onset DM is significant as it confers a higher risk for infections and overall mortality. Blacks appear to be more affected, with an increased risk for those treated with tacrolimus.

HYPOGLYCAEMIA

Simon Heller

Hypoglycaemia is arguably the main reason that individuals with insulin-treated diabetes fail to reach and maintain the level of glycaemic control necessary to prevent diabetic complications. The main cause is current insulin delivery, which produces inappropriately high insulin concentrations between meals and at night plus a failure in physiological protection. The clinical relevance of hypoglycaemia is due to dependence of the CNS on a continuous supply of glucose. Interruption of glucose delivery causes impaired cerebral function, and eventually coma.

People with type 1 diabetes using standard treatment have around a 10% risk of one severe hypoglycaemic attack in a year, which increases to around 30% during intensive insulin therapy in the DCCT. Rates for those with type 2 diabetes are usually around 10 times less although as duration of insulin therapy in type 2 diabetes increases, so do the risks of hypoglycaemia.

The major physiological protective response to acute hypoglycaemia is a rise in glucagon and adrenaline, which limit the suppression of hepatic glucose output induced by insulin. Adrenaline release reflects activation of the autonomic nervous system and the generation of symptoms such as tremor, palpitations or sweating. Autonomic symptoms develop at a glucose level of around 3.2 mmol/l and cognitive function starts to deteriorate at around 3 mmol/l. Activation of the sympathoadrenal system in those who retain awareness of hypoglycaemia occurs before they develop significant cerebral dysfunction and alerts them while they still retain sufficient cognitive ability to take appropriate action.

Hypoglycaemic-induced cerebral dysfunction causes symptoms (neuroglycopenic) such as loss of concentration or coma. As duration increases, the intensity of autonomic symptoms diminishes and patients learn to rely on those caused by neuroglycopenia.

Patients with unawareness demonstrate sympathoadrenal activation at lower glucose concentrations than those unaffected and at a lower level than that for cognitive impairment. Progressive deterioration in cognitive ability as glucose falls, prevents affected individuals from both recognising peripheral symptoms indicating hypoglycaemia and taking the appropriate remedial action.

Hypoglycaemia unawareness is a major clinical problem in the management of those with insulin-treated diabetes and affects around 25% of those with type 1 diabetes of long duration. The risk of a severe episode increases 6- to 7-fold in those affected.

The two main causes of hypoglycaemia unawareness are increased diabetes duration and tight glycaemic control. During periods of intensive glucose control, antecedent hypoglycaemia leads to defective responses during hypoglycaemia and a downward vicious spiral of progressively impaired physiological responses, increasing clusters of hypoglycaemic episodes and the development of hypoglycaemia unawareness.

Hypoglycaemia unawareness can be reversed, at least in part, by strict avoidance of all episodes of hypoglycaemia for at least 4 weeks. Clinical approaches that may reduce hypoglycaemia during intensive insulin therapy include skills training in insulin dose adjustment, the use of insulin analogues and CSII. An HbA1c target of between 6 and 7% during insulin therapy may represent the best compromise between the risk of severe hypoglycaemia and impaired physiological protective responses and the risk of microvascular complications.

ENABLING EFFECTIVE SELF-MANAGEMENT OF TYPE 1 AND TYPE 2 DIABETES

Simon Heller

Type 1 and type 2 diabetes are common long-term conditions affecting around 5% of the population and consuming a disproportionate amount of health services resources (around 10%) each year. In developing countries, type 2 diabetes now affects up to 20% of the population and is destined to increase further in the coming years. In both conditions, the rise in blood glucose leads to damage to small blood vessels causing blindness, kidney damage, foot ulceration and amputation. In type 2 diabetes the combination
of raised glucose and additional risk factors including hypertension, abnormal blood lipids and abdominal obesity confer a high risk of death and morbidity due to stroke, myocardial infarction and peripheral vascular disease. Although there is proof that tight control of blood glucose reduces the risk of complications, few patients with either condition maintain tight glucose targets or cooperate with treatment and morbidity and mortality are high.

A prominent feature of conventional treatment is a failure to acknowledge the importance of patient involvement, with professionals failing to ensure that those with diabetes are systematically educated or encouraged to participate in their own management.

In the last few years, we have developed structured educational approaches to the management of both types of diabetes to see if we can improve outcomes in our patients. Using a framework published by the MRC we have developed and evaluated complex interventions that have been adopted by many centres in the UK who also feel that traditional approaches to diabetes management are often ineffective despite the provision of new therapies.

In type 1 diabetes we have developed the DAFNE (Dose Adjustment For Normal Eating) course from the successful 5-day structured training structured training programme in intensive insulin therapy and self-management pioneered in Düsseldorf. The underlying principle is that patients should acquire the skills to manage their condition entirely independently and be able to eat with the same dietary freedom as those without diabetes. Our trial published in the BMJ demonstrated improved glycaemic control and quality of life. The publication of the trial generated considerable interest, and over 60 centres in the UK and Ireland are now providing DAFNE training.

In type 2 diabetes we have evaluated a 6-hour training programme, DESMOND (Diabetes Education In Self Management, Ongoing And Newly Diagnosed) for newly diagnosed patients delivered in the community by primary care teams. The full results are still to be published, but pilot data suggest improved glycaemic control and psychological outcomes. Around a third of practices across the country are now referring their patients for DESMOND training. However, there are many barriers (including lack of resources and professional scepticism) that must be overcome if high quality training in patient self-management in type 1 diabetes is to become mainstream.

**INTERFERENCES IN ENDOCRINE ASSAYS**

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Endocrinology was revolutionised in the 1960s by the introduction of hormone measurements based on immunoassay, and for quantitative analysis of proteins and peptides there are still as yet few viable alternatives. Immunoassays are based on recognition of molecules by antibodies. Immunoassay methods can show such high specificity that there is a sense of security in the value of laboratory results. There are, however, instances where one or more results make no sense in terms of the patient presentation or overall clinical/endocrine picture. These unusual results are largely due to interferences from sample constituents (endogenous factors) and many such phenomena are recognised. These factors can be detected and eliminated, but they vary from patient to patient and also over time in one patient. Results higher than real are recorded due to a lack of antibody specificity although with changes in the formulation of some assays, particularly from manual techniques to highly automated procedures, one can now also encounter negative effects. Clinicians must be alert to the fact that immunoassays do not always produce correct results. A test request seeks to refute or confirm a clinical differential and any discrepancies in patient data should be reported to the laboratory so that appropriate investigations may be carried out.

**HOW GOOD ARE ENDOCRINE TESTS? – MEET THE EXPERT SESSION**

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Endocrine tests based on old and new strategies will be examined to challenge dogma in endocrinology. Patterns of hormone secretions are pulsatile, cyclical and age and gender dependent. The timings of blood samples for testosterone measurements through male puberty for example are critical to the assessment of this dynamic process. Stimulation tests with adrenocorticotropic hormone (ACTH 1-24 Synacthen) were introduced to test adrenal reserve. The response of plasma cortisol to an injection of 250 micrograms of Synacthen is followed over 30 or 60 minutes. A normal response with colorimetric assays is still applied even though cortisol is now measured more specifically. Lower doses have been tested usually with blood samples at 0, 30 and 60 minutes without questioning the validity of the modified procedure. The responses of intermediates and aldosterone are different to cortisol itself. Cortisol is described as having a diurnal rhythm and tests for are often performed at 0800h and midnight. Repeated rapid sampling in individuals shows pulsatile patterns of cortisol that are not synchronous. Suppression of cortisol secretion by inhaled corticosteroids is judged by loss of diurnal rhythm, suppression of urine free cortisol and poor response to ACTH but these may not give optimal information about the activity of the HPA axis. Reference ranges for steroid hormones vary considerably between methods and laboratories, making interpretation and comparison of data very difficult. In the diagnosis of polycystic ovary syndrome there are differing views of the condition. Endocrine assays, assessments of the severity of the condition, and ultrasound measurements...
Male Wistar rats were rendered type 1 diabetic

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Body weights of DIO animals were significantly diabetic than non-diabetic patients. According to

Diabetes mellitus is much greater among

patients still raise exciting challenges for the clinician and the laboratory.

**DIAGNOSIS OF DISORDERS OF THE ADRENAL CORTEX**

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Disorders of the adrenal cortex arise from abnormal development, defects in steroidogenesis, receptors, dysregulation and malignancy. Congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency (cytochrome p450 CYP21A2) is the commonest adrenal disorder affecting about 1 in 15 000 live births. Ambiguous genitalia and electrolyte imbalance are frequent. The mild mutations (non-classic) only present later with signs of androgen excess. Virilisation can be prevented in future pregnancies by dexamethasone treatment of affected girls. Defects of HSD3B2, CYP11B2, CYP17, CYP11A and steroidogenic acute regulatory protein (StAR) also cause CAH and rare forms present with hirsutism and amenorrhoea due to defects in electron transfer to steroidogenic enzymes. Hexose-6-phosphate dehydrogenase acts in the reduction of cortisone. Cytochrome P450 oxidoreductase provides electrons to CYP21 and CYP17. Smith-Lemli-Opitz syndrome has defective cholesterol and steroid synthesis. Gas chromatography of urinary steroids (profile analysis) is a versatile test for disorders of adrenal function. Inhaled and topical corticosteroids, herbal medicines can confuse diagnosis of Cushing’s syndrome. High aldosterone/renin ratios (ARR) are suggestive of primary aldosteronism and the test is now justified in patients with normokalaemia. Defects of ion channels also affect the renin-aldosterone axis. Human disorders and mouse models of an aberrant adrenal continue to provide clues for further factors in adrenal development and function.

**THE DISASTROUS EFFECTS OF 8 WEEKS OF OVERINDULGENCE**

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It is recognised that obesity and its associated complications, the metabolic syndrome, hypertension and cardiovascular disease, are escalating worldwide. In some of our population groups, the reported incidence of obesity is currently 60%. In recognition of this, untested remedies advertised as anti-diabetic agents are flooding the market. One such remedy is Diavite™. The producers of Diavite™ are seeking MCC registration for their product and therefore require solid scientific evidence of its effects. We set out to investigate the latter in rat models of both type 1 and type 2 diabetes.

**Methods:** Male Wistar rats were rendered type 1 diabetic by streptozotocin injection (65 mg/kg) and treated with Diavite™ (25 mg/kg/day) for 21 days. Zucker rats (Harlan, UK), as a type 2 diabetic model, were treated with a similar dose of Diavite™ for 8 weeks. At the end of this period, IVGTTs and a lipogram were performed. Adult ventricular myocytes were prepared from both normal rats and treated and untreated Zucker rats and tested for insulin stimulated glucose uptake.

We studied the effects of altered diet on myocardial function, using a rat model of hyperphagia (DIO = diet supplemented with sucrose and condensed milk for 8 weeks) compared with age-matched control animals. Afterwards, isolated perfused hearts were subjected to ischaemia/ reperfusion and infarct size determination by TTC staining. Fasting blood glucose, insulin and homocysteine levels and body weight were recorded.

**Results:** Body weights of DIO animals were significantly increased after 8 weeks on diet (396.1 ± 7.9 vs 358.2 ± 5.1 g, p = 0.0006, n = 12) and their fasting blood glucose levels significantly elevated (4.65 ± 0.2 vs 3.78 ± 0.1, p = 0.003, n = 8). Baseline mechanical function was identical in both groups. However post-ischaemic functional recovery was significantly lower in DIO animals than in controls (41.9% recovery vs 57.9%; p < 0.05, n = 7-11). Surprisingly, hearts from the DIO animals presented with significantly smaller infarct size (17.55 ± 1.8%, p = 0.005, n = 8) than controls (35.44 ± 6.5% of the area at risk, n = 7) after regional ischaemia.

**Conclusion:** 8 weeks of DIO resulted in weight gain and elevated blood glucose levels. In conjunction with this, hearts showed curtailed functional recovery after global ischaemia but smaller infarct size after regional ischaemia. They therefore show increased functional damage for smaller sized infarcted zone of the hearts.

**THE EFFECTS OF DIAVITE™ IN TWO DIFFERENT RAT MODELS OF DIABETES MELLITUS**

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Cardiovascular mortality is increased among persons with diabetes, and the incidence of heart failure, following a myocardial infarction is much greater among diabetic than non-diabetic patients. According to MRC predictions, the incidence of obesity is currently nearly 60% in some population groups in South Africa, foreshadowing an elevation in type 2 diabetes prevalence.
**Results:** (i) Diavite™ consistently lowered the fasting blood glucose of all normal, control animals and (ii) a watery extract of Diavite™ was able to dose dependently, stimulate glucose uptake by myocytes prepared these rats. (iii) The elevated triglyceride levels in the plasma from untreated type 1 diabetic rats were normalised by Diavite™ treatment, but not the blood glucose levels. (iv) Fasting blood glucose levels in the treated type 2 diabetic rats were significantly lower than untreated animals, but (v) no alterations on the lipid profile could be detected. (vi) Myocytes from treated type 2 diabetic rats were more insulin sensitive.

**Conclusion:** According to our results we conclude that Diavite™ has the ability to lower fasting blood glucose levels in both control and type 2 diabetic rats. It is also evident that, not only does Diavite™ contain something that can elicit glucose uptake by peripheral insulin sensitive cardiomyocytes, but treatment of diabetic animals with Diavite™ rendered these cells more insulin sensitive.

**THE SYNTHESIS OF LIPIDS FROM DIETARY GLUCOSE AND PALMITIC ACID**

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**Objective:** Little is known about the contribution of dietary derived glucose and free fatty acids to the synthesis of lipids in humans. The present study therefore used orally administered $^{13}$C-labelled glucose and palmitic acid to determine whether these molecules contribute carbon atoms for the synthesis of cholesterol and triglycerides.

**Method:** Fasting blood samples were obtained from 13 lean, 14 obese and 11 diabetic subjects. A 75 g oral glucose load spiked with $^{13}$C-glucose was administered and bloods drawn at 30 minutes and 2, 4 and 7 hours. Similarly, at a later date, a lipid emulsion spiked with $^{13}$C-palmitate was given and bloods drawn at 30 minutes and 2, 4 and 7 hours. Cholesterol, cholesterol esters (CE), triglyceride (TG) and free fatty acid (FFA) fractions were isolated from the serum using thin-layer chromatography and analysed for $^{13}$C content via mass spectrometry.

**Results:** No significant differences of $^{13}$C incorporation into lipids were observed between lean, obese and diabetic subjects. The groups were thus combined and analysed together. $^{13}$C incorporation from labelled glucose into serum TG, CE, cholesterol or FFA, was not significant. Following $^{13}$C-palmitate ingestion, $^{13}$C content of serum lipids showed the following at the 5-hour time point: (i) CE increased from baseline by $1.81 \pm 3.88\%$ ($p < 0.05$ vs. baseline); (ii) cholesterol increased by $1.66 \pm 3.15\%$ ($p < 0.005$); (iii) FFA increased by $5.10 \pm 6.51\%$ ($p < 0.0001$) and (iv) TG increased by $20.8 \pm 14.4\%$ ($p < 0.0001$).

**Conclusion:** Acute dietary glucose intake does not make a meaningful contribution to the carbon content of lipids, whereas dietary palmitic acid contributes predominantly to TG synthesis and, to a lesser degree, cholesterol synthesis.

**SAFETY, EFFICACY AND ACCEPTABILITY OF BIPHASIC INSULIN ASPART 30 AMONG SOUTH AFRICAN PATIENTS WITH TYPE 2 DIABETES: RESULTS FROM THE PRESENT STUDY**

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**Objectives:** To assess the safety, efficacy and acceptability of biphasic insulin aspart 30 (BIAsp30), NovoMix® 30) among South African patients with type 2 diabetes in actual clinical practice, this large-scale clinical experience programme – known as PRESENT (Physicians’ Routine Evaluation of Safety & Efficacy of NovoMix® 30 Therapy) – was conducted across 247 sites in South Africa.

**Methods:** This was a 6-month, prospective, open-labelled study. No study-specific interventions were involved except the collection of data. All patients with type 2 diabetes not adequately controlled on their previous therapy, and who were then prescribed BIAsp30 as monotherapy, or in combination with OHA, in accordance with the approved local labelling, were eligible for the study.

**Results:** A total of 1510 patients were enrolled, of which 1473 were included in the analysis, with the remaining 37 patients excluded due to a lack of baseline data. At baseline, the mean (± SD) age, duration of diabetes and BMI of patients was $51.90 \pm 12.05$ years, $7.44 \pm 6.58$ years and $30.43 \pm 6.51$ kg/m$^2$, respectively. The mean baseline HbA$_1c$, FPG, PPPG was $10.72 \pm 2.60\%$, $13.37 \pm 5.69$ mmol/l and $17.10 \pm 6.35$ mmol/l, respectively. At six months, the mean reductions in HbA$_1c$, FPG and post-prandial plasma glucose (PPPG) were $2.07 \pm 2.83\%$, $4.24 \pm 5.64$ mmol/l and $5.84 \pm 6.74$ mmol/l, respectively. The proportion of patients reporting hypoglycaemia increased from $10.5\%$ at baseline to $17.6\%$ at 6 months, but importantly, the majority of hypoglycaemic episodes at 6 months continued to be minor in nature, as at baseline, and there was no increase in the proportion of subjects reporting major hypoglycaemic episodes between baseline and 6 months (1.5%). The proportion of subjects reporting adverse drug reactions was low at $1.0\%$ at 3 months and $0.3\%$ at 6 months. As compared to their previous treatment, $92\%$ of patients were rated as being either ‘very satisfied’ or ‘satisfied’ with BIAsp30 treatment.

Physicians were asked to assess their satisfaction with BIAsp30 treatment, 92% of patients were rated as being either ‘very satisfied’ or ‘satisfied’ with BIAsp30 treatment. Physicians were asked to assess their satisfaction with BIAsp30 treatment in individual patients, and $92\%$ of responses were either ‘very satisfied’ or ‘satisfied’.

**Conclusion:** BIAsp30 therapy in South African patients with poorly controlled type 2 diabetes improves glycaemic control and is well tolerated among these patients. In addition, treatment satisfaction appears to be very high.
COMPREHENSIVE MANAGEMENT OF TYPE 2 DIABETES MELLITUS PATIENTS STUDY 2006
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Aim: To ‘revisit’ our diabetes clinics to ascertain how many diabetic patients are reaching the glycaemic, weight, blood pressure and lipid goals as recommended by SEMDSA guidelines and if there has been any improvement since a previous study conducted in 1996.

Study design: 150 patients (98 F, 52 M) from three academic hospitals were studied. Measurements included: blood pressure, weight, height, waist circumference, fasting lipograms and HBA1c. Patients from all ethnic groups age 35 years and older were included and were on diet, oral agents, insulin (Protaphane) or combination thereof.

Results: Black patients constituted 68%, white 12.7%. Indian 10.7% and coloured 8.7%. Mean age was 59 years. Mean HbA1c was 8.72% with HbA1c > 8% in 83 patients (55%). 37.3% of the subjects were obese, class I (BMI 30 - 34.9) in 22%, class II (35 - 39.9) in 10% and class III (BMI > 40) in 5.3%. Hypercholesterolemia (TC > 5.0 mmol/l) was present in 29.3% and hypertriglyceridaemia (TGs > 1.5 mmol/l) in 45.3%. Waist circumference was greater than 94 cm in 69% of males and greater than 80 cm in 98% of females. Hypertension was present in 84.67% with 78.74% having a SBP >/= 130 mmHg and 59.84% having a DBP >/= 80 mmHg. 43% of patients did not exercise, 6% smoked and 51% were on aspirin.

Conclusion: These findings show little improvement since the 1996 study and indicate that diabetic management is still largely confined to glycaemic control.

HYPERTHYROIDISM ASSOCIATED WITH ANAPLASTIC CARCINOMA OF THE THYROID
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Introduction: Thyroid storm is a life-threatening condition. We describe four cases of thyroid storm, all due to Graves’ disease, who achieved diagnostic scores exceeding 45, as proposed by Wartofsky and Burch in 1993. The mean score was 86. There were 2 males and 2 females. Ages ranged from 21 to 59 years.

Clinical characteristics: The commonest symptoms were sweating, palpitations, weight loss and hypermetabolism. Common to all, at presentation, were the presence of hyperthermia, life-threatening tachycardia, profound myopathy and changes in mental status. Jaundice was evident in one subject but biochemical elevations of bilirubin were present in three of the four patients. Only one patient had clinically evident ophthalmopathy. A precipitating factor was present in each patient and included diabetic ketoacidosis and non-compliance.

Thyroid function tests revealed severe hyperthyroidism with the average FT4 level exceeding 100 pmol/l. Anti-thyroid antibodies were positive in all but one patient. All patients were managed in a high care setting with one patient requiring admission to the ICU. Three patients required assisted ventilation, and one inotropic support. Pharmacological management included carbimazole, Lugol’s iodine, intravenous steroids and beta-blockade. Three out of the four patients managed had satisfactory outcomes, but one demised from cardio-respiratory arrest. Definitive therapy consisted of radioiodine ablation.

Of interest was the very rapid fall in FT4 levels documented in two of our subjects at 48 hours of approximately 60%, followed by further substantial and rapid reductions. This phenomenon is compatible with the decreased half-life of T4 demonstrated in patients with thyroid storm.
Conclusion: We report the clinical and biochemical features, and response to therapy in four patients with thyroid storm.

ASSOCIATIONS BETWEEN MEASURES OF BODY COMPOSITION AND INFLAMMATORY MARKERS AND GROWTH FACTORS IN BLACK TOWNSHIP ADOLESCENTS RESIDING IN THE NORTH-WEST PROVINCE (THE PLAY STUDY)

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Objective: To assess the association between various measures of body composition and markers of inflammation as well as growth factors.

Methods: The study consisted of 181 township adolescents (70 boys and 111 girls) recruited from two schools. Weight, height, BMI, waist circumference, hip circumference, WHR and percent body fat were measured as well as inflammatory markers (IL-6, TNF-α and CRP). In addition IGFBP-3, IGF-1 and leptin were measured. Insulin resistance and β-cell function (Homeostatic Model Assessment) were also calculated. Associations between variables were examined by using regression analysis.

Results: Backward regression analysis weighted for age revealed that Leptin and IGFBP-3 were positive predictors of BMI in boys, and leptin and TNF-α in girls. Waist circumference in boys was positively predicted by leptin while in girls it was leptin, IL-6 and TNF-α. IL-6 and TNF-α were predictors of waist/hip ratio in girls. Percent body fat in boys was positively predicted by leptin and insulin and negatively by glucose and β-cell function, while in girls positive predictors were leptin and glucose and negative predictors were IGFBP-3 and IGF-1.

Conclusion: Inflammatory markers and growth factors explained 42 - 54% of the variation in body composition measures in boys and 16 - 54% of the variation in girls, which suggests that even though there are gender differences in associations between the measured parameters in both boys and girls different body composition measures indicating overweight are associated with factors indicating low grade inflammation.

METASTATIC FOLLICULAR CARCINOMA IN A CHILD WITH CONGENITAL HYPOTHYROIDISM DUE TO IODIDE TRAPPING DEFECT: A MANAGEMENT DILEMMA

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The patient was diagnosed with congenital hypothyroidism as part of the neonatal screening programme. Thyroid scintigraphy showed ‘no functioning thyroid tissue in the neck’. On this basis a diagnosis of thyroid agenesis was made. Salivary gland uptake was not commented upon. He was treated with levothyroxine and then lost to follow-up. He presented 10 years later with a goitre and was clinically and biochemically hypothyroid. A repeat To-99 pertechnetate scan showed no uptake. An ultrasound scan revealed several large, echogenic, well defined masses in the distribution of the thyroid gland. A diagnosis of an iodine trapping defect was subsequently made.

He underwent excision biopsy and found to have a follicular carcinoma of the thyroid and underwent thyroidectomy.

Once again he was lost to follow-up and reappeared at age 18 with enlarged lymph nodes in the neck, which were shown on biopsy to be consistent metastatic follicular carcinoma of the thyroid.

The management dilemma of follicular carcinoma in the face of an iodide trapping defect is discussed.

HYPERTHYROIDISM AND RELATED COMORBIDITIES IN NINETY-SIX CONSECUTIVE PATIENTS FROM CENTRAL SOUTH AFRICA ADMITTED TO UNIVERSITAS ACADEMIC HOSPITAL

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Aim: The aim of the study was to describe the clinical features and co-morbidities of patients diagnosed with hyperthyroidism from central South Africa.

Methods: After obtaining ethics committee approval, all patients with a diagnosis of hyperthyroidism referred to Universitas Academic Hospital during a 1-year period (2005) were requested to participate in the study. After informed consent patients were evaluated according to a standardized protocol.

Main findings: 96 patients participated in the study (80 women; mean age 41.5 years (16 - 81), mean BMI 25.3 ± 5.7 kg/m², mean T4 80.4 ± 46.1 pmol/l, mean T3 21.9 ± 8.8 pmol/l; 16 men (mean age 42.7 years (16 - 83), mean BMI 20.1 ± 2.6 kg/m², mean T4 85.6 ± 47.3 pmol/l, T3 23.6 ± 7.8 pmol/l); 57 African, 12 Coloured, 1 Indian and 26 Caucasian). 81.8% suffered from Graves’ disease while multinodular disease and single nodules were the cause of hyperthyroidism in 13.6% and 4.6% respectively. Thyroid eye disease and dermopathy was present in 27 and 3 patients respectively. TSH-receptor antibodies were positive in 60 patients, thyroid antimicrosomal antibodies in 48 and antithyroglobulin antibodies in 28. Four patients fulfilled the criteria for impending thyroid storm. Atrial fibrillation (ECG) was present in 2 patients. The mean LVEF was 62.2 ± 5.8% and was < 52% in 2 patients and > 75% in 1. The mean plasma pro-BNP was
1007.8 ± 1429.3 pg/ml while the median plasma pro-BNP was 411 pg/ml. The total hip BMD T-score was ≤ -2.5 SD in 8 patients; > -2.5 SD but ≤ -1.0 SD in 45 while BMD was normal in 33. The total lumbar spine BMD T-score was ≤ -2.5 SD in 30 patients; > -2.5 SD but ≤ -1.0 SD in 36 while BMD was normal in 20. The urinary free deoxypyridinoline/creatinine ratio was elevated in 52/54 patients. Hypoaalbuminaemia was present in 49 patients and mild transaminitis in 23. Anaemia (mostly normochromic normocytic) was present in 71 patients.

Conclusion: The aetiology, clinical manifestations and co-morbidities of hyperthyroidism in this group of patients were very similar to those previously reported. A surprising finding, however, was the high proportion of patients (mainly black) with low BMD, especially of the lumbar spine. Furthermore, internationally accepted cut-points for plasma pro-BNP values to diagnose LV dysfunction did not apply to this group of patients with hyperthyroidism.

THE PREVALENCE OF OVERWEIGHT AND OBESITY AND ASSOCIATED RISK FACTORS IN A RURAL SOUTH AFRICAN COMMUNITY OF ZULU DESCENT

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The prevalence of overweight (OW) and obesity (OB) and associated risk factors was evaluated in a rural South African community of Zulu descent, in the Umthombo district of KwaZulu-Natal, selected by systematic cluster sampling of adults > 15 years. All subjects had demographic, anthropometric and biochemical measurements including a modified 75 g oral glucose tolerance test (OGTT). The 2000 WHO classification of OW and OB based on body mass index (BMI) (kg/m2) and the 1988 WHO criteria for disorders of glycaemia were used.

A total of 1 017 subjects (M:F 208:809) were studied. The crude prevalence of OW (preobese + OB) (BMI > 25) was 42.0% (M:F 22.1 vs. 47.2%), of preobese (PreOB) (BMI 25.0 - 29.99) 22.2% (M:F 13.5 vs. 24.5 %) and of obese (OB) (BMI > 30) 19.8% (M:F 8.7 vs. 22.6%); 58.1% (M: F 77.9 vs. 52.4%) were not overweight (‘normal’) (N) (BMI < 25.0). The prevalence of OW, PreOB and OB was higher in women. The prevalence of PreOB and OB increased with age, both in men and women, with peak prevalence in the 35 - 54-year age group.

When compared with the ‘normal’ (N) BMI group, subjects with preOB and OB were older (p < 0.001), had higher weight (p < 0.01), height (p < 0.001), waist (WC) (p < 0.001) and hip circumference (p < 0.001), waist-hip ratio (WHR) (p < 0.001), blood pressure (p < 0.01), fasting (FPG) (p < 0.001) and 2-hour post load (2PG) (p < 0.001) plasma glucose and serum total triglyceride (p < 0.001) and lower serum HDL cholesterol (p < 0.01). The prevalence of upper body obesity [increased WC (p < 0.001) and WHR (p < 0.001)], hypertension (p < 0.01), glycaemic disorders (p < 0.001) and components of the metabolic syndrome (p < 0.001) increased with higher BMI. In multivariate analysis significant risk factors associated with OW (PreOB + OB) (BMI > 25) included the following: history of hypertension (p = 0.04; OR 1.9, CI: 0 - 3.4), female sex (p = 0.0; OR 3.7; CI 1.9 - 7.2), age (p = 0.01; OR 0.99; CI 0.97-0.99); waist (p = 0.00; OR 1.1; CI 1.1 - 1.2) and hip circumference (p = 0.00; OR 1.2; CI 1.2 - 1.3) and serum triglyceride (p = 0.09; OR 1.3, CI 0.9 - 1.8).

This study has highlighted the high prevalence of abnormally increased BMI in a rural South African Black community, especially in women, and with significant association with potentially preventable and modifiable risk factors.

GLUCOSE AND LIPID METABOLISM AND PREVALENCE OF LIPODYSTROPHY IN RWANDAN HIV-POSITIVE PATIENTS RECEIVING ANTIRETROVIRAL THERAPY

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Little is known about highly active antiretroviral therapy (HAART)-associated lipodystrophy in African populations. This study measured the prevalence of lipodystrophy in HIV-infected African subjects receiving HAART and analysed lipid and glucose metabolism in subjects with lipodystrophy. The prevalence was measured in 571 (305 urban, 266 rural) Rwandans receiving HAART (81.6% of subjects received nevirapine/lamivudine/stavudine) for ≤ 6 months. Metabolic variables were measured in 100 HIV-positive adults with lipodystrophy (HIV+Lipo), 50 HIV-positive, non-lipodystrophic adults (HIV+NoLipo) and 50 HIV-negative volunteers (controls). Lipodystrophy was observed in 34% (48.5% in urban and 17.3% in rural groups) of the HIV-infected population with a prevalence of 69.6% in those receiving HAART for longer than 72 weeks. HIV+Lipo had significantly higher WHR (0.99 ± 0.05 versus 0.84 ± 0.03; p < 0.0005) than HIV+NoLipo. Total cholesterol concentrations (expressed as median [interquartile range]) were significantly higher in the HIV+Lipo (3.60 [1.38] mmol/l) than the HIV+NoLipo (3.19 [0.65] mmol/l; p < 0.005) and control (3.13 [0.70] mmol/l; p < 0.0005) groups. Impaired fasting glucose (glucose > 5.6 mmol/l) was observed in 18% of HIV+Lipo, 16% of HIV+NoLipo and 2% of the control group. Lipodystrophy in African subjects receiving HAART is characterised by increased WHR and elevated blood glucose and cholesterol concentrations. Glucose levels are also elevated in non-lipodystrophic, HIV-positive subjects suggesting that factors other than body fat re-distribution contribute to glucose intolerance in HAART-treated HIV-positive African patients.
EFFECTS OF ONCE-DAILY BIPHASIC INSULIN ASPART 30 WITH METFORMIN VERSUS TWICE-DAILY BIPHASIC INSULIN ASPART 30 IN SOUTH AFRICAN TYPE 2 DIABETES SUBJECTS

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Objective: To assess whether once-daily BIAsp30 at dinner plus metformin (BIAsp30+Met) was as efficacious as twice-daily BIAsp30 alone (BIAsp30).

Methods: This 24-week, multicentre, open-labelled, parallel, randomised (1:1) trial comprised 140 South African type 2 diabetes (T2DM) subjects poorly controlled on one or two oral antidiabetic drugs (OADs). OADs were discontinued and subjects randomised to BIAsp30+Met or BIAsp30 (mean diabetes duration 9.7 vs 8.2 years, HbA1c 10.1 vs 10.2%, BMI 28.8 vs 29.5 kg/m², respectively). Efficacy measures were HbA1c, prandial plasma glucose (PG) increment and plasma lipids. HbA1c was analysed using ANOVA with adjustment to baseline; comparison between treatments was performed using a predefined non-inferiority criterion of 0.6%. Safety variables included hypoglycaemic episodes and adverse events.

Results: After 24 weeks, HbA1c was improved in both BIAsp30+Met (-1.90 ± 1.44%) and BIAsp30 (-1.62 ± 1.74%). Non-inferiority between treatments was confirmed (difference -0.31%; 95% CI [-0.752; 0.129], p = 0.164). Change from baseline in average prandial (breakfast, lunch and dinner) PG improved in BIAsp30+Met (-1.18 ± 2.47 mmol/L, p = 0.0183) and BIAsp30 (-0.86 ± 2.41 mmol/L, p = 0.0054). Total cholesterol decreased in BIAsp30+Met (-0.12 ± 1.02 mmol/L) and increased in BIAsp30 (0.21 ± 0.88 mmol/L), difference -0.34 mmol/L, 95% CI [-0.678; -0.004]. LDL and HDL cholesterol and triglyceride were comparable in both treatments. Mean total daily BIAsp30 dose was 0.36U/kg in BIAsp30+Met (with daily metformin dose of 2 324 mg) and 0.65 U/kg in BIAsp30. The majority of hypoglycaemic episodes in BIAsp30+Met (94 episodes, 28 subjects) and BIAsp30 (147 episodes, 30 subjects) were minor/symptomatic, with one major hypoglycaemic episode in BIAsp30+Met. Adverse events were similar between treatments.

Conclusions: In treating T2DM subjects poorly controlled on OADs, once-daily BIAsp30+Met is as efficacious and safe as twice-daily BIAsp30.

ETNIC DIFFERENCES IN THE PREVALENCE OF POLYMORPHISMS IN THE APO CIII GENE

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Studies have demonstrated that serum triglyceride (TG) levels are higher in Indian and white than black South African subjects. Polymorphisms in the Apo CIII gene have been associated with raised TG levels. This study investigated the prevalence of Apo CIII polymorphisms and their effect on TG levels in three South African population groups and in subjects with mixed hyperlipidaemia (MH). Two Apo CIII polymorphic sites (T455C and C482T) were studied in 73 white, 24 Indian and 24 black subjects using RFLP analysis. Each ethnic group included MH and non-MH patients. Although TG levels were much higher in the MH subjects, no significant differences were noted between the groups for allele or genotype frequencies at either Apo CIII locus. Furthermore, at neither locus was there an association between the genotype and serum TG levels. The MH and non-MH subjects were therefore combined and ethnic differences in allele frequencies were investigated.

The black subjects had a higher frequency (0.79) of the unfavourable C allele at position 455 than both Indian (0.56, p = 0.02) and white (0.41, p < 0.0001) subjects. Furthermore, African subjects had a higher frequency (0.77) of the unfavourable T allele at locus 462 than Indian (0.44, p = 0.00) and white (0.36, p < 0.0001) subjects despite TG levels being lower in the African (0.77 ± 0.40 mM) than White (0.99 ± 0.30 mM, p = 0.01) non-MH subjects. These results suggest that the Apo CIII polymorphisms studied do not contribute to the raised TG levels observed in MH and do not influence serum TG levels in non-MH subjects. Furthermore, although the African population has lower TG levels than White and Indian groups, the prevalence of the ‘unfavourable’ Apo CIII alleles is higher in the former population.

INCREASING BMI BUT NOT INSULIN RESISTANCE ENHANCES THE RISK OF THE METABOLIC SYNDROME

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There is controversy regarding the role of insulin resistance in the aetiology of the metabolic syndrome (MS). Therefore, the present study investigated the relationship between insulin resistance, as measured using HOMA and the prevalence of the MS in a large South African cohort. All parameters of the MS were measured in 426 non-diabetic, urban South African adults and MS was diagnosed using the NCEP ATP III guidelines. The relationship between risk of MS and increasing HOMA was analysed by dividing subjects into octiles of HOMA for use in logistic regression. The prevalence of MS was found to be 14.8%. Logistic regression showed that the odds ratio (OR) for MS increased from 6.2 (95% CI: 0.7 - 57, p = 0.10) in octile 6 of HOMA to 21 (2.6 - 178, p = 0.004) in octile 7 and remained elevated in octile 8 (18 [2.2 - 152], p = 0.007). However, if BMI was introduced in to the model, all the significant ORs were attenuated to non-significant levels with the OR for BMI being very significant (1.2 [1.1 - 1.3], p < 0.0001). If a logistic regression was performed between MS and octiles of BMI and including HOMA only the top 2 octiles of BMI were significant (12.4 [2.6 - 60, p = 0.002 and 14.4 [2.8 - 73], p = 0.001, respectively)
The primary objective of the study was to reassure the patient that since he or she does not meet criteria. Such a paradox could result in a false sense of not having the metabolic syndrome based on current disease notwithstanding the fact that he or she does not be classified as having the metabolic syndrome. Yet this individual is already at a high risk for cardiovascular disease and diabetes. Of relevance is that evidence that the presence of the metabolic syndrome is that none of the current guidelines take into account major shortcomings. Thus a diabetic patient may have abnormalities, which he termed syndrome X. He described hypertension, glucose intolerance, elevated triglyceride and low HDL levels as part of the syndrome for which the underlying pathophysiology was insulin resistance. Although he did not include obesity in his list of disorders he did acknowledge its role in insulin resistance and hyperinsulinaemia. Since Reaven's first description several other metabolic abnormalities have been noted as part of the syndrome including central obesity, coagulation abnormalities, microalbuminuria, gout and polycystic ovarian disease. The WHO attempted to define the syndrome, as did the NCEP-ATP III, based on clinical criteria. Moreover the International Diabetes Federation has also come up with its own definition proposing different criteria depending on the ethnic groups studied. The significance of the metabolic syndrome lies in the fact that it confers these individuals with an increased risk for subsequent development of cardiovascular disease and diabetes. Of relevance is that the individual components of this syndrome themselves are cardiovascular risk factors. Therefore recently the value of defining the metabolic syndrome using specific criteria has been questioned. Certainly there is no evidence that the presence of the metabolic syndrome confers any additional risk compared to the sum of its components. Moreover the presence of diabetes or other degrees of glucose intolerance appears to be the critical factor conferring the increase in cardiovascular risk associated with this syndrome. A confounding factor is that none of the current guidelines take into account other important risk factors e.g. age, smoking. Therefore attempts to define this syndrome by the NCEP-ATP III guidelines as well as that of the IDF guidelines have major shortcomings. Thus a diabetic patient may have abnormal lipids but no other abnormality and yet would not be classified as having the metabolic syndrome. Yet this individual is already at a high risk for cardiovascular disease notwithstanding the fact that he or she does not have the metabolic syndrome based on current criteria. Such a paradox could result in a false sense of security on the part of the attending physician who might reassure the patient that since he or she does not meet the criteria for the metabolic syndrome, treatment need not be aggressive. However it is an established practice based on evidence that all diabetic patients should be aggressively treated in terms of glycaemic control as well as other risk factors.

**THE METABOLIC SYNDROME: DO WE NEED DIAGNOSTIC CRITERIA?**

**M A K Omar**

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As long ago as 1923 Kylin described the clustering of hypertension, hyperglycaemia and gout. However, it was only in 1988 that Gerald Reaven in his seminal Banting lecture put a name to these constellations of abnormalities, which he termed syndrome X. He described hypertension, glucose intolerance, elevated triglyceride and low HDL levels as part of the syndrome for which the underlying pathophysiology was insulin resistance. Although he did not include obesity in his list of disorders he did acknowledge its role in insulin resistance and hyperinsulinaemia. Since Reaven’s first description several other metabolic abnormalities have been noted as part of the syndrome including central obesity, coagulation abnormalities, microalbuminuria, gout and polycystic ovarian disease. The WHO attempted to define the syndrome, as did the NCEP-ATP III, based on clinical criteria. More recently the International Diabetes Federation has also come up with its own definition proposing different criteria depending on the ethnic groups studied. The significance of the metabolic syndrome lies in the fact that it confers these individuals with an increased risk for subsequent development of cardiovascular disease and diabetes. Of relevance is that the individual components of this syndrome themselves are cardiovascular risk factors. Therefore recently the value of defining the metabolic syndrome using specific criteria has been questioned. Certainly there is no evidence that the presence of the metabolic syndrome confers any additional risk compared to the sum of its components. Moreover the presence of diabetes or other degrees of glucose intolerance appears to be the critical factor conferring the increase in cardiovascular risk associated with this syndrome. A confounding factor is that none of the current guidelines take into account other important risk factors e.g. age, smoking. Therefore attempts to define this syndrome by the NCEP-ATP III guidelines as well as that of the IDF guidelines have major shortcomings. Thus a diabetic patient may have abnormal lipids but no other abnormality and yet would not be classified as having the metabolic syndrome. Yet this individual is already at a high risk for cardiovascular disease notwithstanding the fact that he or she does not have the metabolic syndrome based on current criteria. Such a paradox could result in a false sense of security on the part of the attending physician who might reassure the patient that since he or she does not meet...
INSULIN DETEMIR IS SAFE IN SUBJECTS WITH DIABETES: PREDICTIVE STUDY

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Aim: To assess the safety (incidence of serious adverse reaction) of insulin detemir (IDet) in subjects with diabetes in an observational study during routine clinical practice (PREDICTIVE study).

Methods: Subjects were enrolled after informed consent was obtained and a decision to change the current regimen to IDet was deemed necessary. Data were collected at baseline, 3 and 6 months. We present the results for South African cohort, which consists of 464 subjects.

Results: In subjects with type 1, which represents 46% of the efficacy analysis set (EAS) (57% female; mean age 34 yrs; mean duration of diabetes 12 yrs; mean BMI 25 kg/m²), overall hypoglycaemic episodes in the last 4 weeks were significantly reduced from 4.5 to 2.7 (p < 0.001). There was also significant reduction of major and nocturnal hypoglycaemic episodes (p < 0.001). There was no significant reduction in HbA1c (9.11% vs 9.03%) and no weight gain was observed during the study. In subjects with type 2, representing 54% of the EAS (59% male; mean age 54 yrs; mean duration of diabetes 10 yrs; mean BMI 32 kg/m²), overall hypoglycaemic episodes were not significantly reduced but there was significant reduction in major hypoglycaemic episodes (p < 0.01). There was also significant improvement in glycaemic control (HbA1c 9.26% vs 8.60%, p < 0.001). There was no significant weight change in type 2 subjects. Ten subjects (incidence of 2.2%) reported 17 serious adverse drug reactions during the study; the most common events was diabetic ketoacidosis (6), hypoglycaemia (4) and hypoglycaemic coma (3). Six subjects reported 7 different ADR.

Conclusions: Insulin detemir is safe to use in subjects with diabetes as part of routine clinical practice and appears to be weight neutral. In type 1 subjects, insulin detemir significantly reduced the risk of both major and nocturnal hypoglycaemia. Glycaemia was improved with once daily insulin detemir in type 2 subjects without increasing the risk of hypoglycaemia.

DIABETES AND RENAL CYSTS DUE TO A HETEROZYGOUS WHOLE GENE MUTATION OF HNF-1BETA (MODYS)

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Case report: A 13-year-old boy presented with a short history of dystonic movements due to non-ketotic severe hyperglycaemia (blood glucose 71 mmol/l). He had no family history of diabetes. Of note is that he was born with a small, non-functioning right kidney with cysts and required a pyeloplasty for left midureteric obstruction.

On examination he was lean (BMI 17.3 kg/m²), with chronic renal insufficiency with a measured GFR of 25.5 ml/min without proteinuria. The basal c-peptide was low (0.6 ug/l) with no response to glucagon stimulation. Antibodies to glutamate dehydrogenase and IA-2 were negative.

The association of non-ketotic diabetes with a predominant beta-cell defect, renal cysts, and urogenital anomalies prompted us to suspect that our patient has an HNF-1β mutation. The molecular genetic analysis of the HNF-1β gene by sequencing failed to detect a mutation. Therefore, a multiplex ligation-dependent probe amplification assay was performed that revealed a heterozygous deletion of the entire HNF-1β gene, thus confirming the diagnosis of MODY 5 (the Renal Cysts and Diabetes Syndrome).

We present this case to highlight several points:
1. Diabetes in the young requires an aetiological diagnosis.
2. MODY is a monogenic disorder and phenotypic diagnoses require genotypic confirmation.

AETIOLOGY OF ADDISON’S DISEASE IN SOUTH AFRICA: A RETROSPECTIVE STUDY

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Background: Although autoimmunity is the most common cause of Addison’s disease in industrialised countries, there are little data in Africa, apart from a single study suggesting that the aetiology was predominantly idiopathic. The aim of this study was to review the aetiology of Addison’s disease in a South African cohort.

Methods: We compiled a registry of patients with Addison’s disease in South Africa by contacting all academic and district hospitals as well as physicians, endocrinologists, general practitioners and paediatricians. Informed consent, clinical and therapeutic data were obtained. Serum samples were drawn for the measurement of 21 hydroxylase (measured by immunoprecipitation assay) and adrenocortical auto-antibodies (measured by indirect immunofluorescence). All male patients had plasma taken for very long chain fatty acids to exclude adrenoleukodystrophy.

Results: 149 patients were enrolled (58 males and 91 females). Mean age at enrolment was 46 ± 19.2 (SD)
years, while the mean age at diagnosis of Addison’s disease was 33.0 ± 18.3 years. Mean duration of disease was 13.3 ± 12.3 years (range 0.03 - 50 years). 53.8% of patients had a least one co-existent clinical autoimmune endocrinopathy, the majority of which were hypothyroidism, type 1 diabetes mellitus and premature ovarian failure. Antibodies to 21 hydroxylase were positive in 82% compared to 29.9% for adrenocortical auto-antibodies of 78 patients with clinical autoimmune disease. 7.4% had a history of tuberculosis. 4.1% had biochemically confirmed adrenoleukodystrophy and the clinical diagnosis of X-linked adrenal hypoplasia was made in 6.1%. 1.36% were classified as having ACTH resistance syndrome and 27.2% were considered to have idiopathic Addison’s disease.

Conclusions: Despite measurement long after diagnosis, autoimmune Addison’s disease is the predominant cause of Addison’s disease in South Africa. 21 hydroxylase auto-antibodies identified twice as many autoimmune Addison’s disease than adrenocortical auto-antibodies and therefore appear more sensitive markers in patients with longstanding disease.

MACROPROLACTINAEMIA ASSOCIATED WITH A PITUITARY MICROADENOMA – A CASE STUDY

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We report the case of a 41-year-old P2G2 female patient who presented with galactorrhoea in 1999. She was otherwise well and not on any medication. An MRI scan demonstrated a 4 mm by 4 mm hypodense lesion in the pituitary gland. In view of the radiological picture and biochemical hyperprolactinaemia, the diagnosis of a prolactin secreting pituitary microadenoma was made. She was treated with a dopamine agonist, to which she responded well with disappearance of her galactorrhoea. Upon cessation of therapy the galactorrhoea returned.

After implementing routine macroprolactin screening in our laboratory in 2006 it was discovered that her increased total prolactin consisted almost exclusively of macroprolactin and that the monomeric prolactin component was within the reference range. This has been confirmed with gel filtration chromatography.

Conclusion: As macroprolactin screening has been widely implemented in clinical laboratories health care professionals should take care not to dismiss all cases of macroprolactinaemia as a benign cause of hyperprolactinaemia. High levels of macroprolactin should still alert us to the possibility of underlying pathology especially in view of appropriate symptomatology. To the best of our knowledge only one other case of a patient with a symptomatic pituitary adenoma, normal monomeric prolactin and macroprolactinaemia has been published.

A CHILD WITH 46XY PARTIAL GONADAL DYSGENESIS

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We present a child who was born with ambiguous genitalia and initially reared as a boy. He was evaluated at 4 mo., when karyotype, sonar findings and the hormonal profile were consistent with a diagnosis of 46XY disorder of sex development with partial gonadal dysgenesis. At this time, the report of a structure consistent with a uterus and vagina in the pelvis led the family to change the gender of rearing to a girl.

At 8 mo., further testing confirmed the previous findings, but no uterus was seen on sonar. A laparoscopy confirmed this, and revealed the presence of both Müllerian and Wolffian remnants. A fibrosed gonad was removed.

After discussion of the diagnosis with the child’s mother, she elected to return to the original decision to rear him as a boy.

Partial gonadal dysgenesis and issues regarding gender of rearing in these children are reviewed.

A REVIEW OF THE GENITAL DISORDERS CLINIC AT RED CROSS CHILDREN’S HOSPITAL

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There are few recent reports of disorders of sex development (DSD) in Africa. Studies have examined series of patients with a particular condition, such as gonadal dysgenesis or 5α-reductase deficiency, in a defined population group. Previous reports have noted the relatively high incidence of ovotesticular DSD in southern Africa.

Aim: Review the local experience with disorders of sex development.

Method: Folder review 1980 - 2006.

Results:

• 216 records reviewed.

• 30% 46XX
  • 43% congenital adrenal hyperplasia, 53% 46XX ovotesticular DSD, 4% 46XX testicular DSD.
  • 40% 46XY
  • 55% hypospadias without specific diagnosis, 17% androgen insensitivity syndromes, 3% gonadal dysgenesis, 11% undescended testes, 4% micropenis, 8% other.
SOUTH AFRICA – A CHANGING SOCIETY: CHALLENGES AND BARRIERS FOR DIABETES EDUCATORS

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South Africa became a democracy in 1994 and in the last decade the changing society has produced many challenges in health care. There are 9 provinces each with its own government, 11 official languages and many diverse cultures.

Primary health care has received the bulk of the health budget and this has resulted in problems for the treatment of type 1 diabetes in some centers, as the cost of monitoring equipment is perceived as unnecessary and too expensive. Shortages of adequately trained staff and poor remuneration have added to the challenges. Diabetes educators are constantly seeking innovative and creative methods to ensure that patient care is not compromised.

The Diabetes Therapeutic Education and Care centre at Red Cross Children’s Hospital in Cape Town has been recognised as a centre of excellence where children from the poorest and wealthiest socio-economic groups are integrated and all receive the same education and care.

This presentation will outline the barriers, challenges and some of the solutions.

SUSTAINED WEIGHT LOSS AFTER AN 18-MONTH PERIOD OF INTENSIVE OBESITY INTERVENTION AND THE SUCCESSFUL USE OF PRO-BNP TO EXCLUDE CARDIAC DISEASE

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Aims: 1. Assessing the long-term efficacy of an 18-month intervention trial with pharmacotherapy (Topiramate) and lifestyle modification on sustained weight loss after 3 years. 2. Determining whether pro-BNP can be used to exclude cardiac risk in the obese patient population.

Materials and methods: 50 patients (2001) with a mean weight of 104.8 kg ± 1.2 (mean ± SEM), without cardiovascular disease, (ECG and echocardiograms). Anthropometric measurements were recorded and re-done 3 years later (2004).

Results: A sustained weight loss of 7.3 kg was observed 3 years after the intervention trial. Various indices (2004) correlated with pro-BNP (Immune assay N-terminal Roche Elecsys and MODULAR ANALYTICS) (67.6 pg/ml ± 0.3: normal range < 150): age (47 yrs, p < 0.02), weight (97.5 kg ± 1.1 p < 0.05), waist circumference (110 cm ± 0.8, p < 0.01) and height (166 cm ± p < 0.04), but pro-BNP remained within the normal range. Pro-BNP also correlated (linear regression) with the mean blood pressure and biochemical variables observed in 2001 (p < 0.004).

Conclusion: Education on lifestyle management combined with pharmacotherapy (Topiramate) resulted in a sustained weight loss of 7.3 kg after 3 years. Pro-BNP is a reliable assay to exclude cardiac risk in the obese patient, despite observations that it may be decreased in the obese population.

Conflict of interest:
1. The first and the third author were trialists for J & J.
2. Financial support was given by Roche South Africa towards the Pro BNP kit.

AUDIT OF THE INPATIENT MANAGEMENT OF DIABETES AND A SURVEY OF THE KNOWLEDGE AND ATTITUDES OF STAFF CARING FOR DIABETIC INPATIENTS

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Objective: To evaluate the current practices in the care of diabetic inpatients as well as the knowledge and attitudes of nursing and medical caregivers at a large secondary hospital.

Design and methods: An audit of clinical records of adult diabetic patients admitted to hospital for any reason over a period of 8 months. This was done to evaluate the monitoring and treatment schedules utilised by physicians and nurses as well as to assess the level of glycaemic control achieved in diabetic inpatients. A survey of doctors and nurses taking care of diabetic inpatients was done to assess their knowledge of diabetes inpatient management and their attitudes towards diabetic patients. This was done with the use of the diabetes knowledge questionnaire (O’Brien) and the DAS 3 scale.

Results: The hospital records of 164 diabetic patients were audited. With regards to glucose monitoring 60.8% of patients had irregular and erratic glucose monitoring, 37.2% had regular (either 4- or 6-hourly) monitoring and only 2% were monitored related to meals. Of the
A total of 52 patients (52% male) representing α₁c Health care workers (doctors and nurses) Evidence of decreased insulin sensitivity α₁α To determine if the adipokines TNFα and adiponectin are significant determinants of insulin sensitivity in critically ill patients.

**Methods:** A prospective observational study was performed. Forty sequential admissions to the Chris Hani Baragwanath ICU were recruited. Adiponectin, TNFα and IL-6 levels were measured on admission, day 3, day 7 and on discharge from the ICU. Severity of illness using the APACHE II score was calculated on admission. Blood glucose was measured 2 - 4-hourly, and a mean concentration calculated over the 24 hours. Insulin infusions were started when the blood glucose values exceeded 6.0 mmol/l, and adjusted according to a fixed sliding scale. Other factors related to insulin sensitivity such as cortisol, cholesterol and triglycerides were also measured.

**Results:** Although there was no statistically significant change in the mean 24-hour glucose concentration throughout the duration in ICU, the amount of administered insulin required to maintain normoglycaemia changed dramatically. To correct for this, a ratio of the administered insulin: mean plasma glucose was calculated and used as a measure of insulin sensitivity.

Adiponectin levels increased significantly from admission to discharge. IL-6 levels decreased significantly. TNFα levels did not change significantly. No statistically significant correlations were found between the levels of adiponectin, TNFα or IL-6 and insulin sensitivity. There was no significant correlation between APACHE II score and insulin sensitivity. Serum triglycerides and total cholesterol showed significant differences from admission to discharge, with values increasing from admission levels. This was inversely related to serum cortisol and IL-6 levels, and directly related with adiponectin levels.

**Conclusions:** Evidence of decreased insulin sensitivity during the stay in ICU was demonstrated. However, there was no statistically significant association between the adipokines adiponectin, TNFα or IL-6 and insulin sensitivity. Furthermore, other factors which may influence insulin sensitivity such as cortisol, cholesterol and triglycerides did not appear to play a significant role. Insulin sensitivity is affected by multiple factors, and further research into its aetiology is required.
SCREENING FOR ADRENAL SUPPRESSION IN SCHOOL-AGE CHILDREN AT THE ALLERGY UNIT OF RED CROSS CHILDREN’S HOSPITAL: A PILOT STUDY

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Background: It is impractical to test all asthmatic children on inhaled corticosteroids (ICS) for hypothalamic pituitary adrenal axis suppression (HPAS). A screening test would hence be useful.

Objective: To establish which clinical/biochemical parameter is a useful screening test for HPAS in asthmatic children.

Methods: 26 asthmatic children, 5 - 18 years, on ICS were recruited. Height velocity (HV), weight velocity (WV), height standard deviation score (SDS), weight SDS, change systolic blood pressure from supine to standing (∆SBP) were recorded. Early morning urinary free cortisol (UFC) and cortisol metabolites (UCM), plasma cortisol and ACTH were collected. The 1-day metyrapone test was performed. Spearman correlations (r) were calculated between the post-metyrapone ACTH and each screening variable. Diagnostic statistics were calculated for the most promising test.

From the ROC curve an ACTH of 11.7 pg/ml was the optimal cut-point. Its performance: sensitivity 89 (57 - 98)%, specificity 77 (53 - 90)%, positive predictive value (PV) 67 (39 - 86%), negative PV 93 (69 - 99)%, accuracy 81 (61 - 94)%, positive likelihood ratio (LR) 3.8 (1.1 - 6.4), negative LR 0.2 (0.1 - 2.3).

Conclusion: ACTH is most useful. A larger study will refine its precision.

THE PREVALENCE OF ADRENAL SUPPRESSION IN SCHOOL-AGE CHILDREN AT THE ALLERGY UNIT OF RED CROSS CHILDREN’S HOSPITAL: A PILOT STUDY

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Background: Hypothalamic pituitary adrenal axis suppression (HPAS) when treating asthmatic children with inhaled corticosteroids (ICS) or nasal steroids (NS) is thought to be rare.

Objectives: To determine the frequency of HPAS in asthmatic children treated with ICS & NS in the allergy unit of Red Cross Children’s Hospital.

Methods: 26 asthmatic children, 5 - 18 years old, on ICS, not treated with oral or topical steroids in the last year were recruited. Clinical features compatible with HPAS were documented. Daily and cumulative steroid dose, compliance, symptom control and lung functions were recorded. The 1-day metyrapone test was performed and HPAS prevalence estimated using 100 pg/ml post-metyrapone cut-off. Spearman correlations coefficients (r) were calculated between the post-metyrapone ACTH and each variable.

Results: Prevalence of HPAS = 35 (17 - 56) % (8/9 on NS). Of these, height velocity was < 25th percentile in 5/9, weight velocity < -2 SDS in 1/9, orthostatic hypotension in 1/9, symptoms in 1/9. *p<0.05.

19/26 were on budesonide (BUD) Hfa MDI, 7/26 on BUD CFC MDI, 23/26 used spacers, 22/26 on NS, 20/26 on nasal beclomethasone.

Conclusions: Every third asthmatic child on ICS & NS may have HPAS. Clinical signs are unhelpful. Level of asthma control is not predictive. Cumulative dose, body size and NS may contribute to HPAS.

Table I. Results

| Screening tests | Variable | r     |
|----------------|---------|-------|
|                | Height SDS | 0.02  |
|                | Weight SDS | 0.14  |
|                | HV SDS    | 0.08  |
|                | WV SDS    | -0.32 |
|                | ∆SBP      | -0.03 |
|                | Cortisol  | 0.33  |
|                | ACTH      | 0.68* |
|                | UFC (CMA) | 0.17  |
|                | UFC (GC/MS) | -0.01 |
|                | UFC (CMA) | 0.20  |
|                | UFC (GC/MS) | 0.01  |
|                | UCM       | -0.17 |
|                | UCM       | -0.03 |

1chemiluminescent assay 2gas chromatography/mass spectrometry 3creatinine *p<0.05.