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1. Are sulphonylureas still relevant in an incretin world?
IW Campbell

Sulphonylureas (SUs) were first introduced into clinical practice in 1956, and have contributed to the management of type 2 diabetes mellitus for more than 50 years. SUs, which act quickly, were initially considered to be the most effective class of oral hypoglycaemic agents. Although the occurrence of hypoglycaemia is not negligible with SUs, severe episodes requiring third party intervention are uncommon. Mortality that is due to SU-induced hypoglycaemia is rare.

Adhering to the prescribing guidelines for SUs in the context of renal and hepatic impairment, especially patients over 70 years of age, minimises the risk of SU-induced hypoglycaemia, as does avoiding restricted carbohydrate intake at times of anorexia. To further reduce the risk of SU-induced hypoglycaemia, the concomitant use of potentiating drugs, such as salicylates and warfarin, should be considered.

Theoretical and animal data have raised the possibility of adverse cardiac events caused by some SUs, especially glibenclamide, through impairment of ischaemic pre-conditioning. However, no reliable clinical evidence associates SUs with an increased cardiovascular risk.

The long-term safety of multiple diabetes therapies has been shown in several prospective trials: United Kingdom Prospective Diabetes Study (UKPDS), A Diabetes Outcome Progression Trial (ADOPT), Action to Control Cardiovascular Risk in Diabetes (ACCORD) and Diabetes Mellitus Insulin-Glucose Infusion in Acute Myocardial Infarction 2 (DIGAMI 2), the four-year follow-up to DIGAMI. The possible side-effects of incretin-based therapies, such as immunosuppression on exocrine pancreatic pathology, thyroid C-cell hyperactivity and skin lesions, has still not been fully evaluated and therefore needs to be fully assessed.

The low cost of SUs, compared with incretins, such as glucagon-like peptide-1 (GLP-1) based therapies, plays an important role in keeping SUs in the prescribing guidelines for healthcare professionals in health services where resources are limited. Therefore, SUs should retain their position as second-line drugs of choice, after metformin, in the treatment of type 2 diabetes mellitus.

2. Effect of a multi-disciplinary approach in the treatment of type 2 diabetes mellitus
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Background: Management of type 2 diabetes mellitus is often suboptimal, possibly because of over-reliance on physician-driven care, which fails to address psycho-social and lifestyle factors that are necessary to improve control. We prospectively studied the effect of a multi-disciplinary team approach on several determinants of outcome in type 2 diabetes mellitus.

Method: Participants were recruited from a diabetic outpatient department and followed-up for five months. Of 18 participants initially recruited, 14 (77.8%) completed the study course. A multidisciplinary team consisting of a physician, nurse, physiotherapist, dietitian, podiatrist and social worker reviewed each participant on a monthly basis and provided specialty-based education and intervention. Body mass index (BMI), random hemo gluco test (HGT), and blood pressure (BP) were measured at the start of the intervention and on study completion. Change in parameters was analysed using the Wilcoxon matched pairs test. P-value < 0.05 was considered to be significant.

Results: Reduction in haemoglobin A$_1c$ (HbA$_1c$) was observed in 92% of participants. The change in HbA$_1c$ was statistically significant (p-value = 0.007). Possibly as a result of the short duration of this study, this reduction was below the CTID recommended target. Fifty-five per cent of participants showed nonstatistically significant improvement in random HGT (p-value = 0.51). Systolic BP improved nonsignificantly in 72% (p-value = 0.45). Diastolic BP improved nonsignificantly in 73%
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3. To compare control in a group of insulin-requiring patients with type 2 diabetes mellitus before and after the implementation of specialist supervised care

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**Objectives:** To measure the differences, if any, in parameters of control, i.e. HbA1c, total cholesterol (TC), BP and BMI in a single group of patients with type 2 diabetes mellitus before and after specialist supervised care. Secondly, to describe differences in the use of antiplatelet and statin therapy as primary cardiovascular prophylaxis.

**Method:** Patients were recruited from the diabetes clinic at Chris Hani Baragwanath Academic Hospital. The audits were conducted between two periods. The first recorded standard of care delivered by registrars from January 2005 to December 2007. The second recorded care by the specialist supervised clinic was from September 2009 to September 2012. The patients were all insulin-requiring and were seen for 24 months in both audit periods. The first recorded HbA1c in each period marked the start of the 24-month assessment period. It was necessary for 80% of parameters to be available for the patients to be included. This meant that of the 506 patients seen in 2005, 136 patients were assessed. The remainder of patients either had insufficient data, were lost to follow-up, or were transferred to local clinics.

**Results:** The average duration of diabetes was 14.7 years at the start of audit 1. Both periods showed a significant improvement in HbA1c but the second had a 2.17% drop in HbA1c (p-value = 0.0001). Between periods 1 and 2, HbA1c fell significantly from 9.59 ± 2.39% to 8.39 ± 1.3% (p-value = 0.0001), 30% vs. 17.6% of patients achieved a HbA1c < 7%. There was also a significant fall in systolic blood pressure (SBP), but not diastolic blood pressure (DBP). 29.7% vs. 21.3% achieved a SBP < 130 mmHg. TC and BMI did not change.

**Conclusion:** This study uncovered a difference in levels of care delivered by an endocrinologist-supervised clinic versus registrars, with the greatest benefit seen in HbA1c, and the percentage of patients achieving the guideline goals.

4. Understanding the numbers: limitations of assays

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The practice of clinical endocrinology is premised on the ability to accurately measure hormones as the criteria for diagnosis. The goals of therapy are frequently based on biochemistry. The improvement in outcomes in a plethora of conditions is a consequence of the improved performance of immunoassays that are employed. In parallel to the improvement in hormone measurement, there has also been a move towards practice driven by adherence to consensus guidelines, which implies the adoption into local practice of internationally defined consensus cut-off criteria. However, it must be recognised that all assays have limitations. A free thyroxine (T4) and thyroid-stimulating hormone (TSH) within the stated reference range does not exclude TSH deficiency, and a low serum cortisol does not automatically mean hypoadrenalism as corticosteroid-binding globulin deficiency can result in low-serum total cortisol, but normal free, biologically active, cortisol. In Cushings patients on metyrapone therapy, cross-reactivity of 11-deoxycortisol in conventional cortisol assays may result in spuriously high-serum cortisol and a failure to appreciate if a patient is overtreated and hypoadrenal. The performance of growth hormone (GH) assays have improved according to some criteria, but according to others, their clinical applicability has deteriorated: for example, the bias between different commercial assays has increased. In other words, the reported value for a given sample can vary greatly depending on the assay methodology, a factor rarely considered in consensus criteria published on the diagnosis of GH deficiency or goals of therapy for acromegaly, but may impact on an individuals eligibility for a treatment such as GH replacement therapy. The comparison of data between insulin-like growth factor-1 (IGF-I) assays, and therefore the use of consensus cut-offs, is greatly limited by the lack of a common reference material, and in some cases, the absence of well validated, age-related reference ranges. In summary, a clinical endocrinologist needs to combine clinical acumen, access to a good laboratory and a thorough understanding of the characteristics of the assays that are employed.

5. The determinants of non-alcoholic fatty liver disease in South African females

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**Objective:** Non-alcoholic fatty liver disease (NAFLD) is the most common hepatic pathology in industrialised countries. However, this disease has been little studied in Africa. Therefore, the aim of our study was to investigate the anthropometric and metabolic characteristics of African, Indian and European subjects, with varying levels of hepatic triglyceride (TG) deposition.

**Method:** Indian (46), African (29) and European (28) female volunteers were recruited. Fasting blood lipid, insulin and glucose levels were measured. Insulin resistance was quantified using the homeostatic model assessment (HOMA) method. Computed tomography (CT) scans were used to measure hepatic lipid deposition [using the liver-to-spleen attenuation ratio (LAR)] and visceral and subcutaneous fat volume. Subjects were divided into tertiles based on LAR. Physical activity was assessed using an activity monitor (Sensewear® PRO2, Bodymedia).

**Results:** Within the Indian cohort, 45.6% of subjects were in the lowest LAR tertile, compared to 20.7% of the African subjects (p-value < 0.05). None of the anthropometric or physical activity variables were significantly different across the LAR tertiles after adjustment for ethnicity. The only metabolic variable that showed significant changes across the tertiles were fasting insulin levels [median and interquartile range (IQR)], which increased from 29.3 (31.8) pmol/l in...
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4. Metabolism and the association with inflammatory gene expression

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Previously, we demonstrated that black South African women have a greater subcutaneous adipose tissue (SAT) inflammatory profile than white women. We hypothesise that this may be associated with the intake and metabolism of polyunsaturated fatty acids (PUFA), specifically the proinflammatory n-6 PUFA, arachidonic acid [AA], AA levels are dependent on dietary intake and metabolic processing of precursor linoleic acid (LA) by the activity of desaturase enzymes. The aim of the study was to compare serum fatty acid composition and desaturase enzymes between black and white South African women. Serum fatty acid composition and gluteral SAT inflammatory gene expression were measured in 60 black and white South African women. Although LA tended to be higher (57.7 ± 4.4 vs. 55.9 ± 3.7, p-value = 0.079) in black compared to white women, its metabolites, γ-linolenic acid [GLA] (GLA, 0.70 ± 0.29 vs. 0.89 ± 0.31, p-value = 0.015) and dihomo-γ-linolenic acid [DGLA] (DGLA, 0.67 ± 0.14 vs. 0.76 ± 0.15, p-value < 0.001) were lower, while AA (9.2 ± 1.8 vs. 7.9 ± 1.4, p-value = 0.004) was higher. These differences may be explained by lower δ6 desaturase (D6D, 0.012 ± 0.006 vs. 0.016 ± 0.006, p-value = 0.017), which catalyses the conversion of LA to GLA, and higher δ5D (δ5D, 0.14 ± 2.8 vs. 10.6 ± 2.9, p-value < 0.001), which catalyses the conversion of DGLA to AA, in black compared to white women. Lower LA, and higher DGLA and AA levels were associated with increased SAT expression of the inflammatory cytokine, tumour necrosis factor-α (TNF-α) (LA: r = -0.49, p-value = 0.007; DGLA: r = 0.51, p-value = 0.005; AA: r = 0.39, p-value = 0.03) in black, but not white women. In conclusion, we showed ethnic differences in the metabolism of n-6 PUFA, with increased conversion of LA to AA in black, compared to white women, that was associated with increased SAT inflammatory profile. These findings have implications for disease risk. It is suggested that ethnic-specific dietary recommendations are considered.

8. Longitudinal changes in body composition and its relation to metabolic outcomes in black South African women

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Objective: To investigate changes in body composition and regional fat distribution over a 5.5-year period and its association with metabolic outcomes in black South African women.

Method: Changes in body composition (dual-energy X-ray absorptiometry and computerised tomography), BP, fasting glucose, insulin, lipid levels and lifestyle factors, including socio-economic status, dietary intake and physical activity, were measured in 66 black South African women at baseline [27 ± 8 years] and after a 5.5-year period.

Results: Mean body weight (body weight, 61.1 ± 9.9 kg, p-value > 0.001) and fat mass (fat mass, 43.3 ± 6.9 kg, p-value > 0.001) increased over the 5.5-years, with the greatest increase in fat mass being in the central depot (2.7 ± 3.7kg, p-value < 0.001).Women who were younger and had a lower starting BMI at baseline gained the most weight and fat mass, relative to their starting weight (p-value < 0.001). Increases in central fat mass were associated with increases in plasma glucose and serum TGs (r = 0.40, p-value > 0.01 and r = 0.27, p-value < 0.05, respectively), while increases in gynoid fat mass were associated with reduced plasma glucose (r = -0.30, p-value < 0.05) and insulin levels (r = -0.35, p-value < 0.01). Changes in body composition did not correlate with baseline socio-economic status. However, women who gained more body weight had a significantly higher energy intake (52.8 vs. 34.5 kca/kg body weight, p-value < 0.001), irrespective of macronutrient distribution, compared to those who gained less body weight.
Conclusion: In a sample of black South African women, increases in central fat mass were associated with reduced insulin sensitivity, and may in part be due to excessive energy intake. Women who were younger and who had a lower BMI were at greater risk of gaining body weight. They should be the focus of future interventions.

9. Cardiovascular risk factors across body mass index categories in adults residing in Bellville South, South Africa

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Objective: To determine the distribution of obesity phenotypes and assess their association with subclinical cardiovascular disease (CVD) in mixed-ancestry South Africans.

Method: The study was conducted cross-sectionally in 339 adults (men 24.5%) recruited from the Bellville South community in Cape Town. Participants were stratified for BMI (in kg/m²) as normal weight (<25), overweight (25 to <30) and obese (≥30), and for metabolic status as healthy or abnormal in the presence of <2, or ≥2 of the following: BP ≥130/85 mmHg or known hypertension, diabetes mellitus or fasting blood glucose ≥5.6 mmol/l, TG >1.69 mmol/l or high-density lipoprotein (HDL) cholesterol <1.02 mmol/l in men or <1.29 in women. Subclinical vascular status was based on echocardiographical common carotid intima-media thickness (CIMT) and cardiac interventricular septum thickness (IVS).

Results: Within BMI subgroups, there was a less favourable CVD risk profile among metabolically abnormal versus healthy individuals. At least one diabetic individual was present in all subgroups, but the prevalence was the highest in metabolically abnormal obese individuals (43.6%). Similarly, hypertensive individuals were present in all BMI categories, with the highest prevalence (50.8%) observed in metabolically abnormal obese individuals. Metabolically abnormal, normal-weight individuals had the highest mean TC (>6.1 mmol/l) and low-density lipoprotein (LDL) cholesterol (>3 mmol/l). Median CIMT was higher in the metabolically abnormal, normal weight and overweight individuals (p-value = 0.003 and 0.014, respectively), while the IVS was higher only in the metabolically abnormal overweight individuals (p-value = 0.0001).

Conclusion: The clustering of cardiometabolic abnormalities was frequent across the BMI categories in this population, with only borderline effects on markers of subclinical CVD.

10. The Global Attitudes of Patients and Physicians 2™ (GAPP2™) survey finds that patients with type 2 diabetes mellitus using insulin analogue worry about self-treated hypoglycaemia in South Africa

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Background: The Global Attitudes of Patients and Physicians 2 (GAPP2™) survey investigated the insulin-taking behaviour of patients on basal analogue insulin. We report on the frequency and impact of self-treated hypoglycaemia in patients with type 2 diabetes mellitus from South Africa.

Method: South African data from 75 patients on insulin analogue and 100 prescribers were compared with data from 3 042 patients and 1 222 prescribers from six other GAPP2™ countries (USA, Canada, Japan, UK, Germany and Denmark).

Results: Of the South African patients, 37% had experienced hypoglycaemia, while one in ten (10%) recalled having hypoglycaemia in the preceding 30 days (versus 36% for other countries). Nineteen per cent had it at night. At least 40% of South African patients worried about experiencing hypoglycaemia on a daily basis, compared to 23% in other countries. However, South African prescribers reported lower levels of worry from their patients by at least 14 percentage points in given daily situations (Table I). Forty-one per cent of South African prescribers had not discussed hypoglycaemia with their patients in the last 30 days. More insulin analogue patients from South Africa have missed a basal insulin dose than those in other countries (35% vs. 5%, p-value ≤ 0.001) (when responding to the last episode of hypoglycaemia). In addition, 9% reported to have reduced a basal insulin dose and 35% to have increased the level of glucose monitoring.

Conclusion: Hypoglycaemia is less common in South African patients than it is in patients in other GAPP2™ countries, but worry and insulin-dose adjustments in response to hypoglycaemia warrant further discussion and education from prescribers in order to address these concerns. The GAPP2™ surveys were supported by a grant from Novo Nordisk.

Table I: Patient worry about hypoglycaemia and prescriber-reported patient worry

| Situation                     | Percentage of patients who were very or somewhat worried about hypoglycaemia | Prescribers (percentage of patients reporting worries about minor hypoglycaemia) |
|-------------------------------|------------------------------------------------------------------------------|------------------------------------------------------------------------------|
| When driving                  | 51%                                                                          | 29%                                                                          |
| When caring for children or grandchildren | 51%                                                                          | 15%                                                                          |
| Somewhere where there is no easy access to food or drink | 51%                                                                          | 22%                                                                          |
| When alone at home            | 49%                                                                          | 23%                                                                          |
| While sleeping                | 49%                                                                          | 35%                                                                          |
| At work                       | 43%                                                                          | 19%                                                                          |
| While out socialising         | 41%                                                                          | 18%                                                                          |
| During waking hours           | 40%                                                                          | 22%                                                                          |

11. The association between health-related quality of life and some indicators of severity and control in patients with type 2 diabetes mellitus

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Objectives: The purpose of this study was to determine whether there is an association between health-related quality of life and certain indicators of the severity and control of type 2 diabetes at the Diabetic Clinic at Helen Joseph Hospital.
The objectives were:

- To determine the health-related quality of life of a sample of patients with type 2 diabetes mellitus.
- To describe the demographics (age, gender, smoking pack history over the years and number of alcohol units consumed per week) of the population being studied.
- To document the following parameters which are important in determining the control and severity of type 2 diabetes: glycosylated HbA1c, the patient’s total amount of insulin required per day (if on insulin therapy), BMI and exercise compliance.
- To ascertain whether or not there is an association between any or all of the above parameters and the health-related quality of life of these patients.
- To determine the presence of any co-existing diseases and to compare health-related quality of life of patients with diabetes mellitus, with and without co-existing diseases, such as hypertension and dyslipidaemia.

Method: This was a prospective clinical audit, cross-sectional in nature, and a descriptive study of patients attending the Helen Joseph Hospital Diabetic Clinic from June to September 2012. The study population was a sample of 200 patients with type 2 diabetes mellitus who routinely attended the diabetic clinic. Each patient was given a Diabetes-39 questionnaire which was then analysed in conjunction with data from the patients’ files. No incentives were offered for participation. The patients were not discriminated against if they refused to participate. The questionnaire captured demographic variables such as age, gender, age of diagnosis, marital status, exercise regimen, employment status, living arrangements, smoking and alcohol habits, height, weight, as well as diabetes-specific variables, such as concurrent use of antihypertensive medication and/or cholesterol-lowering drugs. The patients’ files were then analysed and various diabetic parameters (HbA1c, lipogram, weight, height, number of insulin units used per day and whether or not there was any concurrent use of oral hypoglycaemic agents) were noted.

Results: Results have shown there to be an association between HbA1c and health-related quality of life. Furthermore, there was an association between health-related quality of life and hypertension and dyslipidaemia. No association was found between health-related quality of life and other clinical parameters, such as number of insulin units used per day, exercise, BMI, lipogram and the use of oral hypoglycaemic agents. Demographic parameters, including age, gender, age at diagnosis, employment status and living arrangements, were also shown to have no impact on health-related quality of life in this study. No association was found between health-related quality of life in patients who consumed alcohol and cigarettes and those who didn’t.

12. Eat less, move more: if it’s so simple to fight the obesity epidemic, why are we not winning?

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The WHO has classified obesity as one of the major threats to human health in the 21st century. Twelve per cent of the world’s population are now classified as obese, with 1.7 billion people at risk of weight-related illness. Increases are particularly remarkable in children and young adults, and in low- and middle-income countries. Globally, in 2010, the number of overweight children under the age of five was estimated to be over 42 million, with 35 million of these living in developing countries. So what causes obesity? In the simplest terms, healthy metabolism is maintained through a careful balance of consumed and expended calories. In reality, genetics, metabolism, behaviour, environment, culture and socio-economic status all play a role in the loss of that balance, which leads to obesity. While global guidelines on diet and exercise are reportedly well understood, implementation has met with mixed success. The ready availability of low-cost, high-fat, high-sugar foods and drinks continues to create a toxic metabolic environment. At the same time, physical inactivity is now identified as the fourth leading risk factor in global mortality: a staggering statistic. So how can the obesity epidemic be combated? Success may lie in multidisciplinary, culturally relevant approaches to diet, exercise and lifestyle. Individual responsibility can only have its full impact when people have access to all the tools, information and support that they need to make healthy choices. Eat less, move more; it sounds simple. We will explore why we are not currently winning the battle and will introduce emerging new strategies aimed at turning the tide.

13. Phenotypic and genotypic characterisation of type 1 diabetes mellitus in black South African patients

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The age at diagnosis of type 1 diabetes is higher in black, than white, South African subjects. Furthermore, in a previous study we showed that there are two subgroups of type 1 black patients with diabetes based on age at diagnosis. One group is diagnosed in their mid-teens and the second group in their early 20s. Therefore, we compared the genetic and phenotypic characteristics in black South African patients with type 1 diabetes mellitus with an early (≤ 20 years, n = 131, group 1) and late (> 20 years, n = 103, group 2) age of diagnosis. Anthropometric measurements were taken, glutamic acid decarboxylase (GAD) 65 and IA2 autoantibody titres measured and genotypes determined by PCR-restriction fragment length polymorphism analysis for five type 1 diabetes susceptibility genes (PTPN22, CTLA4, INS, E1B and GAD65). There was no significant difference in gender, duration of disease or family history between the two groups. However, there was a statistically significant difference in autoantibody positivity. Group 1 had a higher positivity rate for both autoantibodies [GAD65: 77.1% vs. 52.4% (p-value < 0.0001), IA2: 28.2% vs. 8.7% (p-value < 0.0002)]. No differences were found in the allelic frequencies of the type 1 diabetes susceptibility gene single-nucleotide polymorphisms that were studied. These data demonstrate that these two groups of patients with type 1 diabetes can be distinguished by differences in autoimmune components of the disease process. This warrants further research to fully characterise possible differences in disease aetiology.

14. Demographic and laboratory characteristics of children newly diagnosed with diabetes from 2005-2009 at Red Cross War Memorial Children’s Hospital

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Objective: To document the demographics and pattern of clinical and laboratory characteristics at the time of diagnosis for newly diagnosed diabetics younger than 14 years who were reviewed at the Red Cross War Memorial Children’s Hospital Diabetic Clinic between 2005 and 2009. Diabetes caused by medication or
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second to another illness, and neonatal diabetes was excluded.

**Method:** A retrospective folder review was carried out of newly diagnosed diabetic patients younger than 14 years old at the age of diagnosis. Two hundred and twenty-five patients were included for analysis.

**Results:** Fifty-eight per cent of the patients were female and most of the patients were diagnosed with type 1 diabetes. The average age at diagnosis was 9.1 years, with an average HbA1c of 11.3%. Sixty-eight per cent of the patients fell into the normal weight category. 8.4% of patients fell into the obese category. One hundred and forty-eight (65%) of the 225 patients presented with diabetic ketoacidosis. Fifty-three per cent of the Caucasian children were younger than four years old at diagnosis, while most of the children in the black and coloured group were diagnosed after the age of 10 years.

**Conclusion:** Almost a quarter of children with diabetes presented before the age of four years. Caucasian children presented earlier than those of other ethnicities. A large proportion of patients presented with diabetic ketoacidosis, which can be life-threatening. This calls for increased awareness among physicians and parents to recognise symptoms earlier.

**15. Predictors of glycaemic control in children and adolescents with type 1 diabetes, as indicated by haemoglobin A1c levels in a population of patients from the Red Cross Children’s Hospital Diabetes Clinic**

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**Objective:** This cross-sectional interpretive study aimed to determine the predictors of glycaemic control, as measured by glycated HbA1c, in children, adolescents and young adults with type 1 diabetes. It also aimed to assess whether the Diabetes Clinic at the Red Cross Children’s Hospital was achieving the treatment goal set by the International Society of Pediatric and Adolescent Diabetes (ISPAD) guidelines on HbA1c, viz. < 7.5%, and its own target HbA1c levels of < 8% for pre-schoolers and < 7% for schoolchildren.

**Method:** The clinical records of patients attending the Red Cross Children’s Hospital Diabetes Clinic for outpatients from 1 July 2011 to 30 June 2012 were reviewed. The following clinical and demographic parameters were recorded and analysed: HbA1c, gender, age, age at time of diagnosis, duration of diabetes, language, income class, residential postal code and number of clinic visits in the one-year period.

**Results:** In the analysed population (n = 250, 138 females and 112 males), the median age was 13 years (range of 10-15.75 years). The overall mean HbA1c level for the study sample was 9.6% (standard deviation (SD) = 1.74%) and the overall median HbA1c level was 9.2% (IQR: 8.50-10.69). Gender was not a predictor of glycaemic control and there was no a strong association between HbA1c and number of clinic attendances. However, there was a downward trend in HbA1c with increased number of visits. High mean HbA1c correlated significantly with older age, a longer duration of diabetes, lower income class, Xhosa speakers and further distance of residence from the hospital (p-value < 0.05).

**Conclusion:** Glycaemic control in youth with type 1 diabetes is affected by various patient-related and treatment-related factors. The Diabetes Clinic at the Red Cross Children’s Hospital is not achieving its HbA1c treatment goals. Changes in healthcare delivery, by means of targeting these influential factors, are required.

**16. Screening for hypothalamic-pituitary-adrenal axis suppression in children with asthma is not possible when employing clinical and biochemical parameters**

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**Objective:** It is impractical to test asthmatic children for hypothalamic-pituitary-adrenal axis suppression [HPAS] with dynamic adrenal function tests. To determine which parameter is the most useful screening test for HPAS.

**Method:** One hundred and forty-three children with asthma were recruited. Height velocity, weight velocity (WV), height SD score, weight SD score, and change in SBP from supine to standing, were recorded. Early morning urinary free cortisol (UFC), morning serum cortisol [C], adrenocorticotropic hormone [ACTH] and dehydroepiandrosterone sulphate [DHEAS] were collected. UFC was expressed as a ratio of creatinine excretion and as a ratio of body surface area. A metyrapone (MTP) test was performed if the 08h00 C was > 83 nmol/l. Spearman correlation coefficients (r) were calculated between the post-MTP ACTH, DHEAS, UFC, 11-deoxycorticisol (11DOC), 11DOC+C, and each variable. Diagnostic statistics were calculated.

**Results:** All screening variables correlated weakly with the three MTP outcomes. Only DHEAS and UFC (mmol/m²) were statistically significant. DHEAS for MTP, ACTH and 11DOC (r = 0.20, p-value = 0.025, r = 0.21, p-value = 0.017); UFC (nmol/m²) for MTP, 11DOC and 11DOC+C (r = 0.19, p-value = 0.033, r = 0.20, p-value = 0.022). The area under receiver operating characteristic (ROC) curve for DHEAS in the 5-9 year age group was 0.69 (CI: 0.47-0.92). At DHEAS cut-off of 0.2 mmol/l: sensitivity = 0.88, specificity = 0.61, positive predictive value = 0.37, negative predictive value = 0.95, accuracy = 0.67, positive likelihood ratio = 2.26 and negative likelihood ratio = 0.20.

**Conclusion:** No parameter is useful as a universal screening test. DHEAS may be suitable to exclude HPAS before adrenarche.

**17. Screening for thyroid disease in pregnancy: what’s the evidence and what to do**

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Implementation of a screening programme for any medical problem is predicated upon the occurrence of that disorder in the targeted population, availability of accurate diagnostic testing for the disorder, adverse outcomes associated with the disorder’s pathophysiology and evidence that an existing therapy ameliorates these outcomes. Thyroid disorders affect up to 4% of women during gestation. Subclinical hypothyroidism occurs most commonly in 1:50 pregnancies. Thyroid function tests identify affected women, but the trimester-specific upper-limit cut-offs for serum TSH may be higher than 2.5 mIU/l, as defined by recently published guidelines from the Endocrine...
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Society and the American Thyroid Association. Serum free T4 levels decrease throughout gestation and changes are assay-specific. Measurement of total T4 is more robust and reflects a 50% increase over the nonpregnant reference range.

In retrospective case series, overt maternal hypothyroidism has been associated with adverse maternal outcomes. Evidence-based Endocrine Society, American Thyroid Association and Cochrane guidelines recommend levothyroxine (LT4) treatment based upon standard practice. Six large, epidemiological, population-based observational studies have failed to confirm a consistent association with poor gestational outcomes as have been suggested by earlier retrospective small studies for subclinical hypothyroidism. Furthermore, two recent prospective randomised controlled studies evaluated screening for maternal thyroid dysfunction at the end of the first trimester and reported no effect on either obstetrical outcomes or the cognitive development of the offspring. The negative findings of these studies have been potentially attributed to late timing of the intervention and to a milder degree of maternal hypothyroidism in these cases, compared to those in the retrospective reports.

Based upon available data, universal screening for thyroid dysfunction cannot be recommended either before or during pregnancy by the Endocrine Society, American Thyroid Association or Cochrane. In addition, with the absence of prospective data that demonstrate the effectiveness of LT4 therapy for subclinical maternal hypothyroidism, treatment can only be recommended and justified based upon the low risk of therapy. Lastly, although all three guidelines recommend targeting case findings by measuring thyroid function in women at high risk of thyroid disease, they acknowledge that there are insufficient or low-quality data to support this recommendation.

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18. So we think we know how to treat Graves’ disease

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Of the three treatments of the hyperthyroidism of Graves’ disease: antithyroid drugs, iodine-131 and surgery, each is effective, but none is perfect. Increasingly radioiodine is regarded as the primary therapy of choice in people older than 20 years of age, accepting that permanent hypothyroidism is the outcome in the great majority. Thyroid surgeons now advocate total thyroidectomy to manage Graves’ disease. This radical approach is justified because it removes all coincidental microfoci of papillary carcinoma (not a common problem) and the desire to avoid recurrent hyperthyroidism (which it does not). It is unwise to advocate vigorous treatments with almost always result in thyroid failure when there is no consensus about the correct dose and form of thyroid hormone replacement. It is also incorrect to consider patients with Graves’ disease as cured when the outcome is the substitution of hyperthyroidism with hypothyroidism. Physicians have been reluctant to advise more than one course of antithyroid drugs, but for no obvious reason. If the drug is tolerated and the patient compliant, there is no contraindication to relatively long-term treatment, e.g. 5-10 years, if there is recurrence after the initial course of 12-18 months. At least with an antithyroid drug, the hypothalamic-pituitary-thyroid axis remains intact, and unlike the patient who is treated with iodine-131 or surgery, there are no anxieties about whether a suppressed serum TSH concentration is a sign of overtreatment with LT4, and a risk factor for atrial fibrillation and osteoporosis.

19. Biology or technology: stem cells, transplants and the artificial pancreas project

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Recent improvements in the success of islet transplantation therapy for the treatment of type 1 diabetes have provided critical proof of principle that cell replacement therapy can allow liberation from insulin injections and freedom from hypoglycaemia in patients with type 1 diabetes mellitus. However, while transplant protocols continue to improve, donor availability and the prospect of lifelong immunosuppression continue to drive the need for alternative sources of insulin-producing cells. Exciting advances in stem cell biology have recently been coupled with innovative three-dimensional tissue engineering strategies to generate functional insulin-producing cell clusters from naïve, starting cell populations. Do stem cells offer a realistic alternative to donor islet material in cell replacement therapy for type 1 diabetes mellitus? Or could technology alone provide an effective alternative treatment? The Artificial Pancreas Project aims to combine programmable insulin pumps with continuous glucose-monitoring systems to generate a closed-loop system that allows automated control of blood glucose levels in patients with type 1 diabetes. Since the publication of the Juvenile Diabetes Research Foundation Artificial pancreas roadmap in 2009, exciting progress has been made, with recent successful hospital studies now being expanded to diabetes camps and at-home trials. The ultimate aim of all the approaches discussed here is to provide safe and effective glucose-responsive insulin release, mimicking normal pancreatic beta-cell function as closely as possible and providing improved glycaemic control, free from the burden of daily insulin injections. Will biology or technology provide the answer?

20. Mechanism of exenatide-induced hypoglycaemic effect in an animal model of type 1 diabetes

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The dysfunction of pancreatic β cells leads to diabetes mellitus and hyperglycaemia, Exenatide (1 μg/kg body weight), a GLP-1 agonist, was administered intraperitoneally to normal and diabetic Wistar rats daily, for two-and-a-half months. Diabetes mellitus was induced by a single intraperitoneal injection of streptozotocin (60 mg/kg). A similar amount of phosphate buffered solution was given to control rats. Exenatide-immunoreactive cells were seen in the outer region of the islets of Langerhans of normal rats. However, exenatide-immunopositive cells were discerned in both the peripheral, as well as central, compartments of the pancreatic islets of diabetic rats. The number of exenatide-immunoreactive cells increased significantly after the onset of diabetes. Exenatide induced large and significant (p-value < 0.001) increases in the number of insulin, catalase- and glutathione-immunopositive cells in pancreatic islets. In conclusion, exenatide may contribute to increased pancreatic β-cell mass by enhancing endogenous pool of antioxidants, which may in turn help in the survival of pancreatic β cells after the onset of diabetes mellitus. The increased antioxidant pool may contribute to an exenatide-induced hypoglycaemic effect in experimental diabetes mellitus.

No conflict of interest is associated with this work.
21. Islet immunity and beta-cell reserve of black South African patients with ketoacidosis at the initial diagnosis of diabetes

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Objective: To classify patients with ketoacidosis at the initial diagnosis of diabetes using markers of islet immunity and β-cell reserve.

Method: A prospective study of black South African patients admitted into Nelson Mandela Academic Hospital, Mthatha, between 2010 and 2012, with ketoacidosis as the first manifestation of diabetes. Islet immunity was assessed using anti-glutamic acid decarboxylase 65 (AGAD 65) antibody, while β-cell reserve was assessed using the serum C-peptide response to intravenous injection of glucagon. Positive- and negative-serum AGAD 65 antibody levels were levels ≥ 5 units/l (A+) and < 5 units/l (A-) respectively. Replete (β+) and deplete (β-) β-cell reserve were serum C-peptide taken six minutes after an intravenous injection of 1 mg glucagon of ≥ 0.5 ng/ml and < 0.5 ng/ml, respectively. Patients were subsequently categorised into any one of the following diabetes classes: A+ β- and A+ β+ (type 1A), A- β+ (type 2) and A- β-.

Results: Seventy-one patients were studied, of whom 38 were males. The majority of patients (46.5%) were A- β-. Seventy-one patients were studied, of whom 38 were males. The majority of patients (46.5%) were A- β-. The A- β+ were 22.5% and 4.2% respectively, 26.8% of patients were A- β-. The A- β+ were older than older groups and also had higher proportions of patients with acanthosis nigricans, hypertension, increased waist circumference and obesity than the other groups.

Conclusion: The majority of our patients with ketoacidosis at the initial manifestation of diabetes had type 2 diabetes (A- β+).

22. Defensive active coping and neural fatigue in Africans and Caucasians with subclinical vascular disease risk: the Sympathetic Activity and Ambulatory Blood Pressure in Africans (SABPA) study

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Objective: Psychosocial stress and ethnic variations in coping responses have been associated with pathology. And so, in Africans (especially men), the defensive active coping response is a recognised cardiovascular risk. It is uncertain whether sympathetic dysfunction may be the underlying cause. Therefore, we investigated salivary 3-methoxy-4-hydroxyphenolglycol (MHPG), as an indicator of sympathetic neural activity, and the extent of subclinical vascular disease risk in defensive active coping Africans and Caucasians.

Method: The Coping Strategies Index questionnaire identified participants who preferentially utilised defensive active coping. Twenty-four-hour ambulatory BP measurements were obtained, together with blood samples and saliva samples (analysed for MHPG levels with high-performance liquid chromatography). CIMT was calculated from ultrasound images as an indicator of subclinical vascular disease risk.

Results: Defensive active coping Africans (n = 143) showed overall poorer health than Caucasians (n = 148), with higher self-reported stress, alcohol abuse, hypertension, and diabetes risk (p-value ≤ 0.05). African women revealed lower levels of MHPG compared to Caucasian women, although no differences were established in men. Furthermore, Africans demonstrated a trend of increased low-grade inflammation and glycated haemoglobin associated with increased CIMT. In African men at high risk of subclinical vascular disease (n = 30), an inverse association was revealed between MHPG and CIMT [β = -0.22 (-0.40, -0.03)].

Conclusion: Novel findings revealed that Africans utilising defensive active coping are more vulnerable to subclinical vascular disease, possibly resultant from neural fatigue and sympathetic hyperactivity (decreased MHPG). When defensive active coping fails, sympathetic hyperactivity may be followed by neural fatigue and sympatho-adrenal-medulatory desensitisation, resulting in pathology.

The authors declare no conflict of interest.

23. Reduced bioavailable insulin-like growth factor-1 is significantly linked to ambulatory blood pressure in African men: the the Sympathetic Activity and Ambulatory Blood Pressure in Africans (SABPA) study

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Objective: Insulin-like growth factor-1 (IGF-1) is regarded as a powerful vasoprotective agent because of its endothelial-protective, antiplatelet and antithrombotic activities. Reduced bioavailable IGF-1 concentrations, as a possible contributor to the high prevalence of hypertension in black populations, need to be thoroughly investigated. Therefore, we compared components of the IGF-1 axis of African and Caucasian men in terms of its association with ambulatory blood pressure and common carotid intima-media thickness (CIMT).

Design and method: We included African (n = 86) and Caucasian (n = 101) male school teachers and measured growth hormone (GH), total IGF-1, IGF binding protein-3 (IGFBP-3), and pregnancy-associated plasma protein-A (PAPP-A) levels.

Results: The ambulatory BP of African men was almost 10 mmHg higher than that of Caucasians (137/88 mmHg vs. 128/80 mmHg, p-value < 0.001), accompanied by a significantly unfavourable IGF-axis for all measured components (p-value < 0.001), including reduced bioavailable IGF-1 (IGF-1/IGFBP-3, p-value = 0.006) and tissue utilisation of IGF-1 represented by IGF-1/IGFBP-3 and PAPP-A (p-value < 0.001). Single, partial and multiple regression analyses confirmed a significant independent association between ambulatory SBP and bioavailable IGF-1 only in African men (R² = 0.23, p = 0.21, p-value = 0.042). CIMT was similar in both ethnic groups (p-value = 0.34), and was only associated with bioavailable IGF-1 in Caucasian men prior to adjustment for γ-glutamyl transferase.

Conclusion: The elevated ambulatory blood pressure of African men is significantly linked to reduced IGF-1 bioavailability. It is worthwhile considering recombinant IGF-1 administration as a potential pharmacological tool in cardiovascular medicine to curb the rising prevalence of CVD.
24. **The contribution of diabetes mellitus to lower extremity amputations in four public sector hospitals in Cape Town for 2009 and 2010**

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**Objective:** Globally, diabetes is the most common cause of nontraumatic lower-extremity amputations (LEAs), but there are sparse data from South Africa and Africa. The objective was to determine the contribution of diabetes to the burden of LEAs in the Cape Town metropole and describe the patients’ demographic characteristics, the causes and sites of LEAs, and length of hospitalisation.

**Method:** A retrospective analysis of LEAs was performed in four Cape Town public sector hospitals, from 1 January 2009 to 31 December 2010. Cases were identified from theatre registers and information was extracted from their clinical records using a data extraction form.

**Results:** There were 1 280 nontraumatic LEAs in 867 patients. 925 LEAs in 593 patients with diabetes (68.4%) and 355 LEAs in 274 non-diabetic patients (31.6%). The proportion of men and women in the diabetes group was similar (each 50%), but men were twice as common in the non-diabetes group (66 vs. 33%). Ulcers (25.3 vs. 15.3%) and infections (85.7 vs. 63.3%) were the dominant causes in the diabetic group, and ischaemia (23.7 vs. 49.3%) in the non-diabetic group (all p-value < 0.001). Duration of hospital stay was similar in the two groups (diabetes 10.6, 6.4 days; non-diabetes 10.7, 8.3 days, p-value = 0.7), but the diabetic group had more multiple admissions and multiple LEAs than the non-diabetic group (p-value < 0.005).

**Conclusion:** The rate of 8.9 LEA/week in people with diabetes is unacceptable. An integrated programme is urgently required to reduce the burden of this preventable complication of diabetes.

25. **Low-serum testosterone levels in an urban, tertiary diabetic population**

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**Background:** According to the literature, low-serum testosterone levels are associated with diabetes mellitus. No or minimal data exist for its prevalence or predictors in South Africa.

**Method:** An observational, cross-sectional study was performed in 150 consecutive male patients with diabetes over the age of 50 years in the diabetic clinic at the Steve Biko Academic Hospital. These patients were evaluated for diabetes control and complications, the presence of erectile dysfunction and hypogonadism symptoms. Early morning serum testosterone levels were assessed. Subjects with low testosterone levels were compared to those with normal testosterone levels.

**Results:** Some degree of erectile dysfunction was reported in 95.3% of the patients, while 51.3% reported serious erectile dysfunction. The prevalence of androgen deficiency symptoms was 94.7%. Fifty per cent of the men had low total testosterone levels, 40.7% had low calculated bioavailable testosterone levels, and 27.3% had both low total and low calculated bioavailable testosterone levels. Variables univariately associated with low total testosterone were found to be the BMI, the waist circumference and the presence of known CVD. Using multivariate logistic regression, the only significant factors were found to be waist circumference and known CVD. Univariate associations with a low calculated testosterone level were age, diabetes duration, BMI, waist circumference and known CVD. Following multivariate logistic regression, the remaining significant variables were found to be age, diabetes duration and BMI. Univariate associations for both low total and low calculated bioavailable testosterone levels were age, diabetes duration, hypertension duration, BMI, waist circumference and the presence of known CVD. After multivariate logistic regression, the significant factors were diabetes duration, BMI and known CVD.

**Conclusion:** This study confirms the high prevalence of low testosterone levels in male patients with diabetes in a tertiary setting, and argues in favour of universal or targeted screening of this population group.

26. **Male hypogonadism in Addison’s disease: an under-recognised problem**

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**Background:** Male hypogonadism may complicate Addison’s disease, but the prevalence of testosterone deficiency in adult males with primary hypoadrenalism is unknown.

**Method:** Male patients older than 18 years of age, who were enrolled in the South African Addison’s disease national registry and who were clinically well, were screened for biochemical evidence of testosterone deficiency (early morning basal testosterone < 9.9 nmol/l). We also compared cardiovascular risk factors between eugonadal and untreated hypogonadal patients.

**Results:** Of the 42 males studied, 14 (33%) were hypogonadal (five previously diagnosed and nine newly diagnosed). The presence of testosterone deficiency did not relate to age, the duration of disease or the required hydrocortisone dose. The underlying causes of Addison’s disease for the hypogonadal group were autoimmune in 7 (50%), tuberculosis in 3 (21%), X-linked adrenal hypoplasia in 2 (14%). Two (14%) were idiopathic. None of the 14 hypogonadal subjects had antigonadal autoantibodies. Untreated hypogonadal subjects had a higher BMI compared to eugonadal subjects [29.4 kg/m² interquartile range (IQR): 24.8-32.5 kg/m² vs. 24.3 kg/m², IQR: 22.6-26.7, p-value = 0.029], and a higher high-sensitive C-reactive protein (hsCRP)(5 mg/l IQR: 2.5-14 vs. 1.5 mg/l IQR: 0.6-2.8, p-value = 0.001), but there were no significant differences between the two groups with regard to TC, LDL cholesterol, HDL cholesterol, TGs or fasting glucose. Luteinising hormone (LH) and FSH did not differ between the groups. However, dehydroepiandrosterone sulphate was lower in the hypogonadal group [0.31 μmol/l, IQR: 0.27-0.37 vs. 0.75 μmol/l, IQR: 0.51-1.50, p-value = 0.005]. Primary and probable secondary hypogonadism were diagnosed in 2 (22%) and 7 (17%) of the untreated hypogonadal group respectively.

**Conclusion:** Biochemical testosterone deficiency, predominantly secondary hypogonadism, was highly prevalent in this Addison’s disease group, and did not relate to age or the duration of Addison’s disease. Untreated hypogonadal subjects had an increased BMI and hsCRP, but no differences were found in their lipid profiles or glucose levels. It may be worthwhile to evaluate all male patients with Addison’s disease periodically for testosterone deficiency, as testosterone replacement may improve subjective well-being and clinical parameters in the long term.
27. Correlation of basal and timed responses to depot adrenocorticotropic hormone stimulation testing

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Objectives: The use of synthetic ACTH stimulation to identify patients at risk of secondary hypocortisolism is well documented. A dynamic evaluation of the cortisol axis, using a depot preparation of ACTH, requires testing for more than eight hours. In a previous study, we showed a good correlation between 2-hour and 8-hour cortisol responses following ACTH stimulation. The aims of the present study were to investigate the correlation between the 1- and 8-hour responses, and to identify a baseline cortisol level above which stimulation testing may not be required.

Method: Patients with suspected secondary hypoaldrenism were stimulated using an intramuscular injection of 1 000 μg of depot synthetic ACTH. Cortisol responses were evaluated at baseline, 1, 2, 6 and 8 hours. The correlation between 1-, 2- and 8-hour responses was investigated. Independent ROC analyses were performed on baseline and 8-hour responses in excess of 1 000, 900 and 800 nmol/l.

Results: Thirty-two patients were included. A good correlation between the 1- and 8-hour (r = 0.86, r² = 0.74) and the 2- and 8-hour (r = 0.91, r² = 0.83) responses was found. Baseline cortisol values in excess of 500 nmol/l rose to over 1 000 nmol/l at 8 hours [positive predictive value (PPV) = 100%]. If a peak value of over 900 nmol/l was used, then baseline values of above 280 nmol/l did not require ACTH testing (PPV = 100%).

Conclusion: In this group, both 2- and 1-hour responses to depot ACTH stimulation showed very good correlation with the 8-hour response. The study identified a baseline cortisol level of above 280 nmol/l that may predict sufficient adrenal reserve that does not require stimulation testing. This level requires further validation.

28. Retrospective analysis of acromegals at Tygerberg Hospital: preliminary data on early outcomes after pituitary surgery

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Although pituitary tumours that cause acromegaly are benign, the increased morbidity and mortality associated with persistently elevated GH and insulin-like growth factor levels is significant. We present the short-term outcomes (tumour size reduction and change in GH levels) following pituitary surgery, for patients with acromegaly assessed in our unit between 2007 and 2012. Tumour volumes were calculated from magnetic resonance imaging (MRI). A random GH level < 1.0 ug/l represents biochemical control. Baseline and follow-up (3-6 months after surgery) results were compared. Twelve patients (seven women and five men) aged 25-66 years were included. Macroprolactomas were reported on MRI in all patients, except one. Baseline pituitary volumes ranged from < 1.39.5 cm³ (median = 8.7 cm³ and mean = 15.35 cm³). Postoperatively, there was more than a 65% reduction in tumour volume in 8 out of 10 patients (range = 0.13.4 cm³, median = 1.39 cm³, mean = 3.14 cm³). Pre-treatment GH levels were > 20 µg/l in seven of the 12 patients: range 2.65-48 µg/l (median = 30.8 µg/l and mean = 27.3 µg/l). Postoperative biochemical control was documented in 25% of patients: GH range 0.2–40 µg/l (median = 8.5 µg/l and mean = 13.8 µg/l). The initial tumour size, as well as the degree of tumour invasion and GH elevation, were negatively correlated with biochemical control following surgical intervention.

29. The management of differentiated thyroid carcinoma

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The incidence of thyroid cancer has increased almost threefold in the last 30 years, while mortality has been slowly decreasing. Much of the increase is attributable to the incidental finding of papillary microcarcinomas (less than 1 cm in diameter) during neck ultrasound for unrelated reasons. The extent of treatment of these incidentalomas is controversial, as it is for those found during surgery for benign nodular thyroid disease or Graves’ disease. Multiple foci or the presence of B-RAF gene mutations may be an indication that more aggressive therapy is required. However, there is agreement that the treatment for cancers that are greater than 2 cm in diameter is total thyroidectomy with removal of any affected nodes, followed by iodine-131 remnant ablation and serial ultrasound examinations and serum thyroglobulin measurements to indicate remaining or recurrent disease. Simulation with human recombinant TSH (thyrogen) is preferred to LT4 withdrawal for four weeks prior to ablative iodine-131, as it avoids the symptoms of hypothyroidism, but is relatively expensive. The thyrogyrin stimulation test may become redundant as assays for thyroglobulin become more sensitive, and it will be possible to predict a cure or recurrence on the basis of a single basal serum thyroglobulin measurement. The overall 10-year survival rates for middle-aged adults with differentiated thyroid carcinoma are approximately 90-95%. Complete responses can be expected in almost half of all young patients, even with distant metastases, but no significant fluoro-deoxy-D-glucose positron emission tomography.
metabolic syndrome had higher PTH than those without it [p-value < 0.0001], while 25(OH)D levels were not significantly different [p-value = 0.30]. In multivariate analysis, 25(OH)D was not associated with any component of the metabolic syndrome. However, PTH was shown to be positively associated with SBP [p-value = 0.018] and DBP [p-value = 0.005] and waist circumference [p-value < 0.0001] and negatively associated with HDMA [p-value = 0.008] levels. Logistic regression analysis showed that Asian Indian ethnicity [odds ratio (OR) 2.24; 95% CI: 1.57, 3.18, p-value < 0.0001] and raised PTH (OR 2.48, 95% CI: 1.01, 6.08, p-value = 0.04) produced an increased risk of the metabolic syndrome, but 25(OH)D did not (OR 1.25; 95% CI: 0.67, 2.24, p-value = 0.48).

Conclusion: After adjusting for age, gender and ethnicity, there was no significant association between 25(OH)D concentration and the metabolic syndrome. After adjusting for age, gender, ethnicity and 25(OH)D, a significant association remained between PTH concentration and the metabolic syndrome.

31. A survey of vitamin D Status in a northern suburbs’ practice in Johannesburg
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Objective: Adequate vitamin D status is expected in individuals living in high sun-exposed areas, such as Johannesburg. However, worldwide reports indicate that despite seemingly adequate sun exposure, the rate of 25(OH)D deficiency is higher than expected. The aim of this study was to document the 25(OH)D status of a patient population in Johannesburg, a high sun-exposure area, and compare these levels across gender, race, age and co-morbidities such as hypertension, diabetes mellitus and dyslipidaemia.

Method: This retrospective study population consisted of 1,000 patients (adults and children) from a specialist practice in the northern suburbs, Johannesburg. Data were collected from the patients’ files. The mean age was 40 years, SD: 11.81. 71.4% of participants were female and 28.6% male. 2.4% were black, 21.8% Indian and 75.8% white. 25(OH)D was measured using the DiaSorin LIAISON® assay and deficiency levels were defined as: normal > 30 ng/ml, moderate 10.1-30 ng/ml and severe < 10 ng/ml.

Results: Mean serum 25(OH)D was 24.45 ng/ml. Using a cut-off of 30 ng/ml, 82.8% of participants were 25(OH)D deficient. Reported results include comparison across gender, race, age and co-morbidities.

Conclusion: These data suggest that despite living in a city that is adequately exposes to sunlight, 25(OH)D deficiency is pervasive in Johannesburg. Reasons as to the causes should be probed and guidelines for vitamin D supplementation advised.

32. Haemoglobin A1c for the diagnosis of diabetes mellitus in South Africa
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Objective: The 2012 Society for Endocrinology, Metabolism and Diabetes of South Africa (SEMDSA) guidelines for the diagnosis of diabetes mellitus include an HbA1c value of > 6.5% as an alternative diagnostic tool for the diagnosis of diabetes mellitus. The aim of this study was to evaluate the appropriateness of this cut-off value in South Africa, as well as to evaluate the effect of human immunodeficiency virus (HIV) infection, renal dysfunction and anaemia on the relationship between glucose and HbA1c.

Method: The Lancet Laboratory database was used to identify all patients who had a glucose tolerance test between 1 January 2011 and 31 March 2012, and who had an HbA1c measurement available using the same year. For the same period, all patients who had a random glucose, HbA1c, HIV, creatinine or haemoglobin result were also identified. HbA1c measurements were obtained using the BioRad Variant II high-pressure liquid chromatography method.

Results: At the proposed HbA1c cut-off value of 6.5%, sensitivity for the diagnosis of diabetes mellitus was 84% (95% CI: 81.9-86) and specificity was 86.4% (95% CI: 84.8-87.9). Using ROC curve analysis, HbA1c for the diagnosis of diabetes mellitus had an area under the curve of 0.93 (95% CI: 0.92-0.94) [n = 3,304]. Using multiple regression analysis, HIV infection, renal dysfunction and anaemia all had a statistically significant (p-value < 0.0001) effect on the relation between random glucose and HbA1c. Random glucose [mmol/l] = -3.27 + 1.54 x HbA1c (%) + 0.53 x HIV status, where HIV status = 1 if positive, and 0 if negative [n = 10,963]. Random glucose [mmol/l] = -6.17 + 1.98 x HbA1c (%) + 3 x renal dysfunction, where renal dysfunction = 1 if creatinine >120 µmol/l and 0 if creatinine < 120 µmol/l [n = 23,562]. Random glucose [mmol/l] = -6.22 + 2.04 x HbA1c (%) + 2.54 x anaemia, where anaemia = 1 if Hb < 8 and 0 if Hb > 8 [n = 23,040].

Conclusion: Maximum sensitivity and specificity using HbA1c for the diagnosis of diabetes mellitus in this population was obtained at a cut-off value of 6.5%. HbA1c appears to underestimate glucose in patients with HIV infection, renal failure and anaemia.

33. Lipid cut-off values indicating low and high cardiometabolic risk in human immunodeficiency virus-infected Africans
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Objective: South Africa is the country with the highest number of adults living with HIV infection in the world. Besides the traditional risk factors for CVD in the general population, there are specific factors in people living with HIV which could increase the risk of the development of CVD, namely chronic inflammation and metabolic changes (dyslipidaemia). This study proposes the identification of lipid cut-off values as being the most important risk factor for the development of CVD in a cohort of 140 HIV-infected black Africans from the North-West province.

Method: Anthropometric measures, SBP, DBP, heart rate and the carotid artery dorsalis pedis pulse wave velocity (cPWPV) were determined. Blood was analysed with appropriate methods to determine TC, HDL, LDL, TGs and glucose. ROC analysis was used to determine the optimum cut-off values (based on the Youden index) for the low- and high-risk HIV-infected participants to develop CVD for each of the selected variables.

Results: The TG:HDL ratio ≥ 1.49, TC:HDL ratio ≥ 5.4 and a HDL level ≤ 0.76 mmol/l, indicate a risk of the development of CVD in a cohort of black Africans living with HIV in the North-West province.

Conclusion: The results have important health implications for Africans living with HIV as the above lipid levels may be a useful indicator of the risk of developing CVD development in clinical settings.
Abstracts

34. Diabetes mellitus and human immunodeficiency virus in Botswana

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Objective: Data on the interaction of HIV and diabetes mellitus in Africa are sparse. The objective was to assess characteristics associated with the presence of diabetes in HIV-infected persons in Botswana and to determine the impact of diabetes mellitus on immune reconstitution after initiation of antiretroviral treatment (ART).

Method: We conducted a retrospective case study at four sites. Each HIV-infected patient with diabetes mellitus (n = 54) was matched to two HIV-infected controls (n = 108) according to age ± 2 years and sex.

Results: The mean weight of patients with diabetes mellitus was 70.6 kg. It was 59.3 kg (p-value < 0.05) for non-diabetes mellitus controls. Compared with matched controls, patients with diabetes mellitus were more likely to be on an efavirenz-containing regimen (87% cases vs. 60.4% controls, p-value < 0.05). Only three cases and one control were on a protease inhibitor-containing regimen (5.6% vs. 0.9%, p-value = 0.074). Patients with diabetes mellitus had higher baseline CD4 counts (CD4 156.1 vs. 118.5, p-value < 0.05). The mean increase in CD4 count in the first year after antiretroviral therapy initiation was 213 cells for patients with diabetes mellitus and 178 cells for non-diabetes mellitus patients (p-value < 0.05).

Conclusion: These findings suggest a complex interaction between factors, including weight, antiretroviral drug exposure and diabetes in HIV-infected patients in southern Africa. Patients with diabetes were more likely to have higher CD4 counts at baseline and have a more robust initial response to antiretroviral therapy. While confounding explanations cannot be excluded, the relationship between diabetes mellitus and CD4 response warrants further evaluation.

35. Prevalence of the metabolic syndrome in the urban black population of Cape Town

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Objective: Minimal data are available on the metabolic syndrome prevalence in South Africa, particularly according to the Joint Interim Statement criteria. The objective was to determine the metabolic syndrome prevalence in 25- to 74-year-old urban Africans in Cape Town.

Method: In 2008/2009, a representative cross-sectional sample, stratified for age and gender, was randomly selected. CVD risk factors were determined by administered questionnaires, clinical measurements and biochemical analyses, including fasting and 120-minute blood samples. Logistic regression analysis assessed the independent effects of socio-demographic variables on the metabolic syndrome.

Results: There were 1,099 participants: 392 men and 707 women (a response rate of 86%). Crude and age-standardised (Segi) prevalence of the metabolic syndrome was 30.7% (95% CI: 27.4-34.1) and 31.7% (95% CI: 28.4-35.3), respectively, with higher rates among women (43.5% and 44.9%) than men (16.5% and 17.3%) (p-value < 0.001). Key contributors to the higher metabolic syndrome in women, compared to men, were central obesity (86% vs. 20.1%) and low HDL cholesterol (75% vs. 33.4%) while in men, raised BP (51.4%) was the most frequent. In the multiple logistic model, the most likely factors to be implicated in having the metabolic syndrome were women rather than men (OR: 5.13, 95% CI: 3.37-8.84, p-value < 0.001), increasing age (OR: 1.07, 95% CI: 1.05-1.09, p-value < 0.001) and being wealthier rather than poor (middle tertile: OR: 1.68, 95% CI: 1.12-2.51, p-value = 0.012, richest tertile: OR: 1.97, 95% CI: 1.22-3.19, p-value = 0.006).

Conclusion: The high metabolic syndrome prevalence underscores the frequent clustering of CVD risk factors, the need to determine other risk factors if a single risk factor is present, and for comprehensive and integrated approaches to tackle CVD.

36. Metformin from legacy to unrivalled benefits

IW Campbell

Metformin first entered clinical practice in 1957 and is now believed to be the most widely prescribed antidiabetic drug in the world. It targets hyperglycaemia by increasing insulin sensitivity with a resultant reduction in hepatic glucose production and an increase in insulin-mediated glucose disposal. The optimal dose to reduce fasting glycaemia and HbA1c is 2 g daily. The HbA1c reduction with metformin is similar in nonobese and obese type 2 diabetic subjects. Metformin in now established as the cornerstone of antidiabetic therapies and can be combined with all other oral hypoglycaemic agents, as well as injectable therapies, such as insulin and GLP-1 agonists. The main contraindication to metformin is renal dysfunction. The drug should not be prescribed when the estimated glomerular filtration rate (eGFR) is < 30. The risk of lactic acidosis with metformin is zero if prescribed as recommended. Heart failure is no longer a contraindication to metformin use. Many studies have now shown that metformin gives improved clinical outcomes in patients with type 2 diabetes with stable chronic heart failure, provided the renal function is normal. Metformin has a therapeutic diversity, with recognised cardiovascular protective properties and a possible role in cancer prevention and treatment. Metformin has anti-atherogenic, antithrombotic and anti-inflammatory effects. Lessons from the United Kingdom Prospective Diabetes Study (UKPDS) show a legacy effect when metformin therapy is prescribed following diagnosis of type 2 diabetes. The reduction of all-cause mortality and myocardial infarction seen in the UKPDS trial intervention (1977-1997) was sustained in the post-trial monitoring (1997-2007). Type 2 diabetes is associated with an increased risk of cancer and cancer fatality, and an increased risk of all-cause mortality. Epidemiological studies have shown metformin reduces the risk of some cancers developing in subjects with type 2 diabetes mellitus. There is increasing interest in metformin with regard to cancer prevention and/or treatment. There are now over 50 trials on non-diabetic subjects worldwide to evaluate the benefits of metformin in cancer management in controlled clinical trials.

37. Smith-Lemli-Opitz syndrome confirmed biochemically and/or genetically in four families in South Africa

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Objective: The identification and genetic causes of Smith-Lemli-Opitz syndrome in South Africa. Smith-Lemli-Opitz syndrome, a
rare autosomal recessive disorder due to 7-dehydrocholesterol reductase deficiency, causes craniofacial dysmorphism, as well as microcephaly and other malformations of which syndactyly of the toes is prominent. Developmental delay and feeding difficulties are encountered. Numerous patients (and mutations) have been identified in developed countries.

**Method:** On clinical suspicion of Smith-Lemli-Opitz syndrome, blood was obtained from the patients and parents in three families. One infant had died, but the parents were tested for mutations. Sterols were extracted and examined for ultraviolet absorption (234 and 282 nm) to prove the presence of 7-dehydrocholesterol. DNA extracted from circulating leukocytes was subjected to exon-by-exon analysis by high-resolution melting. Sequencing of abnormal patterns was undertaken to determine if reported or novel mutations were present.

**Results:** The parents were unrelated and of European ancestry. The clinical diagnosis was confirmed biochemically in the three live patients, ranging in age from three months to 23 years. None of the patients had hypocholesterolaemia. None of the parents had detectable 7-dehydrocholesterol. Altogether, six mutations, all previously described as common mutations, were found in the following combinations: IVS8-1G>C/7P93M, W115X/V281M, W115X/1289I and G410S/G410S.

**Conclusion:** Smith-Lemli-Opitz syndrome is present in South Africa and can be diagnosed at a biochemical and genetic level. The diagnosis is important, not only for the patient, but also to identify carriers in the family to offer antenatal counselling and diagnosis of a disorder that may have severe sequelae. The prevalence and range of genetic causes of Smith-Lemli-Opitz syndrome remain to be determined in Africa.

38. **Gradient gel electrophoresis demonstration of high-density lipoprotein species in hyperalphalipoproteinaemia**

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**Objective:** A method was developed to describe species within HDLs by non-denaturing gradient gel electrophoresis. HDL cholesterol concentration has a reciprocal association with CVD, but exceptions occur. Severe hyperalphalipoproteinaemia (low HDL) has been reported as atheroprotective, and hyperalphalipoproteinaemia was not protective with torcetrapib, a cholesterol ester transfer protein inhibitor. HDL species may vary according to the metabolic cause and might have implications for risk in various derangements.

**Method:** Whole plasma was pre-stained with Sudan black. A non-denaturing polyacrylamide gradient of 4-8% was separated lipoproteins optimally for analysis, using the migration of albumin to the edge of the gel as a reference, as well as LDL. From normotriglyceridaemic samples with a range of HDL concentrations, areas under the curve as well as LDL, AUC% were derived for recognisable regions labelled HDL1, HDL2, HDL3 and HDL4. Randomly selected samples with HDL cholesterol from 0.9-1.6 mmol/l displayed a distribution of AUC% as follows: HDL1 6-28, HDL2 26-54, HDL3 23-45, HDL4 6-23. There were no correlations of HDL1 and HDL2 on the gel with HDL cholesterol (Spearman), but plasma TG correlated inversely with HDL2 (r = 0.821, p-value = 0.034).

**Results:** The parents were unrelated and of European ancestry. The clinical diagnosis was confirmed biochemically in the three live patients, ranging in age from three months to 23 years. None of the patients had hypocholesterolaemia. None of the parents had detectable 7-dehydrocholesterol. Altogether, six mutations, all previously described as common mutations, were found in the following combinations: IVS8-1G>C/7P93M, W115X/V281M, W115X/1289I and G410S/G410S.

**Conclusion:** Smith-Lemli-Opitz syndrome is present in South Africa and can be diagnosed at a biochemical and genetic level. The diagnosis is important, not only for the patient, but also to identify carriers in the family to offer antenatal counselling and diagnosis of a disorder that may have severe sequelae. The prevalence and range of genetic causes of Smith-Lemli-Opitz syndrome remain to be determined in Africa.

39. **Ethnic differences in the association between lipid metabolism genes and lipid levels in black and white South African women**

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**Objective:** To investigate the association between serum lipid levels and genes implicated in lipid metabolism in black and white South African women.

**Method:** Body composition (dual energy X-ray absorptiometry) and fasting serum lipids were measured from a sample of 204 white and 257 black South African women. Genotypes of the cholesteryl ester transfer protein (CETP) (CETP, rs708272, B1/B2), lipoprotein lipase (LPL) (LPL, rs1328, S/X), hepatic lipase (LIPC) (LIPC, rs1800588, C/T) and proprotein convertase subtilisin/kexin type 9 (PCSK9) (PCSK9, r28362286, C/X) genes were determined.

**Results:** Compared to white women, black women had lower levels of serum TC (TC, p-value < 0.001), LDL cholesterol (LDL cholesterol, p-value < 0.001), HDL cholesterol (HDL cholesterol, p-value < 0.001) and TGs (TGs p-value < 0.001). The frequency of the CETP variant did not vary between ethnic groups (p-value = 0.949). However, there were significant differences in the genotype and allele frequencies between black and white women for the LPL (p-value < 0.001), LIPC (p-value < 0.001) and PCSK9 (p-value < 0.001) genes. There were genotype effects on serum lipid levels in black women only. Specifically, women with the CETP B2 allele had a lower LDL-cholesterol level than those with the B1B1 genotype (p-value = 0.013). Women with the LPL SX genotype had lower TG concentrations than those with the SS genotype (p-value = 0.039). Women with the PCSK9 CX genotype had lower LDL-cholesterol (p-value = 0.046) and TG/ HDL (p-value = 0.038) levels than those with the CC genotype.

**Conclusion:** Polymorphisms within the CETP, LPL and PCSK9 genes were associated with lower LDL cholesterol, TG and HDL levels in black women. This supports the theory that lipid profiles are affected by variations in lipid metabolism genes in black South African women.

40. **Carotid intima media thickness (CIMT) in patients with familial hypercholesterolaemia**

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**Objective:** CIMT is a noninvasive marker of cardiovascular risk and its role in cardiovascular risk stratification is currently being evaluated. Familial hypercholesterolaemia (FH) is a genetic disorder of lipoprotein metabolism characterised by tendon xanthomata, elevated LDL cholesterol and premature CVD. The objective was to explore determinants of CIMT in patients with FH at a tertiary level lipid clinic.
Abstracts

Method: By database linkage, FH patients at the Groote Schuur Hospital lipid clinic with intima media thickness (IMT) data were identified. FH was diagnosed using the Simon Broome criteria. Ultrasound images of the common carotid, carotid bulb and internal carotid far walls (bilaterally) were obtained. IMT was measured offline using Matlab®. The mean, maximum and minimum IMT for each vascular segment was determined, as well as the calculation of the mean of means and mean of maximums for all the combined carotid segments.

Results: There were 320 (135 men and 185 women) patients with FH and IMT data. The median age at the time of CIMT measurement was 44.5 years (a range of 4.4-83.5 years), with a median delay between first presentation at the clinic and IMT evaluation of 1.9 years (IQR: 0.05-7.30 years). Mean (SD) LDL cholesterol at presentation was 6.6 (± 1.8) mmol/l. The prevalence of hypertension, diabetes and a smoking history was 14.4%, 3.4% and 47.2% respectively. The mean of means CIMT was 0.71 [0.17] mm and exceeded 0.85 mm and 1 mm in 18.4% and 5.6% of patients respectively. Age at time of CIMT evaluation (r² = 0.32), SBP (r² = 0.14), DBP (r² = 0.11) and TG (r² = 0.05) correlated significantly with CIMT. IMT was higher in smokers (0.76 vs. 0.67 mm, p-value < 0.0001) and patients with diabetes (0.85 mm vs. 0.69 mm, p-value = 0.0002). In a multifactorial analysis age at time of CIMT measurement, smoking and diabetes were independent predictors of CIMT.

Limitations: We were unable to estimate and correct for the influence of lipid-lowering therapy on CIMT.

Conclusion: Care of patients with FH should not only focus on LDL cholesterol control. All cardiovascular risk factors need to be addressed.

41. Elevated proprotein convertase subtilisin/kexin type 9 (PCSK9) levels in untreated patients with heterozygous or homozygous familial hypercholesterolemia and the response to high-dose statin therapy

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Objective: Proprotein convertase subtilisin kexin type 9 (PCSK9) is an enzyme that impairs low-density lipoprotein (LDL) cholesterol clearance from the plasma by promoting LDL receptor degradation. There is an inverse relationship between PCSK9 expression and LDL-receptor levels in animal models. Patients with FH have reduced or absent LDL receptors. This implies they should have elevated PCSK9 levels.

Method: A total of 51 homozygous FH (HoFH) patients, 20 heterozygous FH (HeFH) patients, and 20 normocholesterolemic controls were studied. Fasting lipograms and PCSK9 levels were measured in all subjects. The levels were repeated after high-dose statin therapy (80 mg atorvastatin or 40 mg rosuvastatin) in a subset of 20 HoFH patients and in the 20 HeFH patients.

Results: PCSK9 and LDL-C levels were significantly higher in untreated HoFH and untreated HeFH patients compared with control subjects (p-value < 0.01). Linear regression analysis showed a significant positive correlation between PCSK9 and LDL-C (r = 0.6769, p-value < 0.0001). High-dose statin therapy was associated with increased mean PCSK9 levels in both groups of patients. However, the correlation between PCSK9 and LDL-C was eliminated (r = 0.2972, p-value = 0.0625).

Conclusion: PCSK9 levels were elevated in untreated FH patients, particularly in those with HoFH. Statin therapy increases PCSK9 levels further. PCSK9 inhibitors might be a beneficial therapy for FH patients, even in those with HoFH.

POSTER PRESENTATIONS

42. Protective effects of Swietenia macrophylla King (seed and endocarp) aqueous-methanolic extract on pancreatic islet histology in streptozotocin-induced diabetic rats

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The oral antidiabetic drug, glibenclamide, stimulates the insulin producing β cells constantly through a harsh mechanism which eventually may permanently reverse its endocrinofunction. The study investigates the protective effects of Swietenia macrophylla King seed and endocarp aqueous-methanol extract on pancreatic islets histology in a type 2 diabetes mellitus rat model. Phytochemical analyses were performed prior to the in vivo study to screen the aqueous-methanolic extract of the combined plant parts. The experimental groups were rendered diabetic by a chemical combination of streptozotocin (65 mg/kg body weight, intravenously) and nicotineamide adenine dinucleotide (230 mg/kg body weight) daily for three weeks. Body weight (g) and fasting blood glucose levels (mg/dl) were determined at treatment intervals of 0, 7, 14 and 21 days. Subsequently, Langerhans’ islets were examined by haematoxylin and eosin staining. Photomicrographs of pancreatic islet revealed that administration of extracts showed improved cellular density, suggesting that the extracts were capable of inducing β-cell recovery and/or regeneration following the destructive effects of streptozotocin. The findings indicate that Swietenia macrophylla King seed and endocarp aqueous-methanolic extract exhibits a protective effect on islet histology and was also involved in the correction of altered biological parameters. Hence, it may serve as a candidate for developing a safe, compliant and promising nutraceutical for the management of diabetes.

43. Use of an online maturity-onset diabetes of the young (MODY) calculator in South African patients with diabetes

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Objective: Maturity-onset diabetes of the young (MODY) is a monogenic form of diabetes, often misdiagnosed as type 1 diabetes. Identification of specific defects in MODY-causing genes of patients diagnosed as type 1 diabetics may make it possible to alter patient treatment, e.g. replacing insulin with sulfonylureas. Therefore, it is of interest to distinguish MODY patients from type 1 diabetics. An online MODY probability calculator was developed for use in European populations. The aim of this study was to determine the usefulness of this calculator in identifying MODY patients among South African diabetics.
Abstracts

Method: The online MODY calculator was used to select patients with at least one in two chance of MODY for screening. Patient DNA was extracted and the HNF1α promoter, coding regions, surrounding intronic regions and 3'-UTR were amplified and sequenced. Mutations in this gene are the most common cause of MODY.

Results: Four suspected MODY3 patients were screened, but no documented MODY-causing mutations were found. Two patients had gene variations that were not found in the online databases of HNF1α variation. The nature of the mutations renders them unlikely to be pathogenic, but it may be useful to screen non-diabetic controls and diabetic and non-diabetic family members to determine if they co-segregate with diabetes.

Conclusion: No documented MODY3 mutations were found in four patients with a high calculated probability of MODY. Two patients show previously unreported sequence variations that warrant further investigation. HNF1α was the only gene to be screened, but the glucokinase and HNF4α genes must also be analysed.

44. Novel therapeutic approaches to treat ischaemic heart disease in patients with diabetes
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The dramatic increase in obesity and type 2 diabetes is a major threat to human health. Since cardiovascular complications are common in patients with diabetes, this further increases the overall disease burden. Recent data from our laboratory show that cardioprotection following ischemia-reperfusion (under hyperglycaemic conditions) is associated with attenuated myocardial ubiquitin-proteasomal system (UPS) activity. In light of this, we hypothesised that a UPS inhibitor (lactacystin) protects the rat heart against ischaemia-reperfusion under hyperglycaemic perfusion conditions. We employed an ex vivo Langendorff heart perfusion model where isolated rat hearts were initially perfused (retrogradely) for 60 minutes with Krebs-Henseleit buffer under normoglycaemic (11 mmol/l glucose) and hyperglycaemic (33 mmol/l glucose) conditions, respectively. This was followed by 20 minutes of global ischaemia and 60 minutes of reperfusion. To determine if lactacystin acts as a cardioprotective agent, a 5 μmol/l dose was administered during the first 20 minutes of recovery after ischaemia vs. controls. Our data demonstrate that lactacystin markedly improved functional recovery during reperfusion in hearts perfused with glucose (p-value < 0.01 vs. untreated high glucose). In parallel, infarction sizes of lactacystin-treated hearts decreased from 60.1 ± 6.3% vs. 39.8 ± 12.6% (p-value < 0.01 vs. untreated high glucose). The current study shows that the UPS may be a unique therapeutic target to treat ischaemic heart disease in patients with diabetes.

45. Altered hexosamine biosynthetic pathway gene expression: a novel diagnostic tool for the earlier detection of type 2 diabetes mellitus?
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Hyperglycaemia increases flux through the hexosamine biosynthetic pathway (HBP), thereby elevating O-GlcNAcylation of target proteins. The HBP usually acts as a fuel sensor. However, when chronically activated, it may result in maladaptation and pathophysiologic outcomes, e.g., insulin resistance. O-GlcNAcylation is a reversible, post-translational modification that is controlled by only two enzymes. Here O-GlcNac transferase (OGT) and O-GlcNAcase (OGA) are responsible for the attachment and removal of O-GlcNac moieties, respectively, to target proteins. Since we previously found increased O-GlcNAcylation of target proteins with diabetes, we hypothesised that OGT and OGA gene expression would be differentially expressed with the onset of prediabetes and diabetes. Healthy, prediabetic and diabetic (FBP and Hba1c, criteria) individuals (30-70 years old) were recruited from the Stellenbosch region (n = 60). RNA was extracted from whole blood, converted to cDNA and relative OGT and OGA gene expression determined (for all three groups) by real-time quantitative PCR. Our data reveal significant differences for OGT and OGA gene expression in diabetic versus normal individuals. The current findings suggest that OGT and OGA gene determination show early promise as a potential diagnostic tool to help improve the detection and management of individuals with type 2 diabetes.

46. Coping, low-grade inflammation, and hypercoagulation: a possible risk for structural vascular disease?: the Sympathetic Activity and Ambulatory Blood Pressure in Africans (SABPA) study
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Objective: A physiologically dissociative active coping (AC) response was previously associated with cardiovascular risk in Africans. Whether or not it may promote a greater state of hypercoagulability than in AC Caucasians, contributing to the development of structural vascular disease (SVD), is unclear. Our objectives were to investigate whether AC African men (n = 61, age 42.8 ± 8.4 years) showed a state of increased hypercoagulation compared to AC Caucasian men (n = 83, age 44.9 ± 11.1 years), and whether hypercoagulation markers were associated with SVD.

Method: Fibrinogen, D-dimer, C-reactive protein, ambulatory BP, left common CIMT thickness of the far wall and left common carotid cross-sectional wall area were measured, and participants completed the Coping Strategy Indicator Questionnaire.

Results: D-dimer, but not fibrinogen, was above the suggested cut-off point in both ethnic male groups, indicating a state of hypercoagulability. AC African men had higher D-dimer levels than Caucasians (450 ng/ml vs. 330 ng/ml, p-value ≤ 0.05). Additionally, AC African men had higher C-reactive protein levels than AC Caucasian men (5.5 mg/l vs. 1.65 mg/l, p-value ≤ 0.05). On average, Africans were above the suggested cut-off point of 3 mg/l for increased CVD risk. In AC African men, C-reactive protein was independently associated with fibrinogen and cross-sectional wall area, whereas 24-hour SBP predicted SVD.

Conclusion: Our findings suggest that AC African men suffer from a state of hypercoagulability and low-grade inflammation, which when driven by hyperkinetic BP, may contribute to the atherosclerotic process.

47. The impact of visceral adipose tissue mass on the differentiation potential of adipose-derived stromal cells harvested from subcutaneous and visceral adipose depots
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Abstracts

**Objective:** Multipotential naive stromal cells can be harvested from many different anatomical locations, including bone marrow and adipose tissue. Previously, we reported that adipose-derived stromal cells isolated from the subcutaneous adipose tissue of male Wistar rats had greater osteogenic potential than their counterparts isolated from perirenal visceral adipose tissue, while perirenal visceral adipose tissue was more adipogenic than subcutaneous adipose tissue. However, more recently, we noticed a considerable decrease in the perirenal visceral adipose tissue mass of our experimental animals, and consequently, we investigated whether this affected the osteoblastic and adipocytic differentiation potential of perirenal visceral adipose tissue.

**Method:** Subcutaneous and perirenal visceral adipose tissue samples were harvested from adult male Wistar rats fed on standard laboratory food. Based on differences in perirenal visceral adipose tissue mass weight, the rats were divided into low-adipose mass and medium-adipose mass groups. Adipose-derived stromal cells were isolated and subcultured, and osteoblast and adipocyte differentiation were induced by means of phenotype-specific culture media [osteoblast media (OM) and adipocyte media (AM)]. Matrix mineralisation, as a marker of osteoblast differentiation, was detected with Alizarin Red S staining. While adipocyte differentiation was determined by staining intracellular lipid droplets with Oil Red O.

**Results:** Low-adipose mass rats had an average perirenal visceral adipose tissue mass of 0.102% ± 0.023% (SD) of total body weight \((n = 4)\), compared to medium-adipose mass rats, with an average perirenal visceral adipose tissue mass of 0.63% ± 0.054% (SD) of total body weight \((n = 4, p-value < 0.0001)\). Alizarin Red-S-positive nodules were present in OM-treated cultures of subcutaneous adipose tissue and perirenal visceral adipose tissue from low-adipose mass rats, in contrast to perirenal visceral adipose tissue from medium-adipose mass rats which did not exhibit an osteogenic response to OM. In addition, whereas perirenal visceral adipose tissue from medium-adipose mass rats was more adipogenic than subcutaneous adipose tissue, the adipogenic potential of perirenal visceral adipose tissue from low-adipose mass rats was significantly reduced.

**Conclusion:** No dietary interventions were performed on either medium-adipose mass or low-adipose mass rats, these results suggest that perirenal visceral adipose tissue mass, possibly as a surrogate marker of baseline metabolic status, may influence the differentiation potential of perirenal visceral adipose tissue. This may suggest fundamental perirenal visceral adipose tissue mass-dependent differences in intracellular signalling in perirenal visceral adipose tissue, and may even provide information on the pathophysiology of visceral obesity.

48. **Molecular docking research analysis of novel natural and synthetic protein tyrosine phosphatase 1B inhibitors as a potential therapeutic target for diabetes mellitus**

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Augmented pervasiveness of type 2 diabetes mellitus and obesity has amplified the medical necessity for new agents to treat these disease states. Both type 2 diabetes and obesity are connected to resistance to the hormones, insulin and leptin. Protein tyrosine phosphatase 1B (PTP1B) has been shown to function as a negative regulator of insulin signaling, as well as leptin signal transduction. At present, copious compounds are synthesised as PTP1B inhibitors. The development of compound libraries with more selective PTP1B inhibitors has been increased by the realisation that many natural products have PTP1B inhibitory activity and therefore are attention-grabbing, biologically leading compounds. This research exertion shows the molecular docking analysis of novel synthetically prepared compounds and new-fangled isolated natural PTP1B inhibitors as a novel target for type 2 diabetes.

49. **Nocturnal and daytime hypoglycaemic events: South African outcomes**

J Snyman, L Pemba

**Objective:** To understand the impact of nocturnal and daytime non-severe hypoglycaemic events.

**Method:** This was a large global survey on patients on insulin, which examined daytime and night-time hypoglycaemic events. Data on the impact on healthcare expenditure (resource utilisation), economic impact (loss of work or productivity), and quality of life (emotional and functional) were collected.

**Results:** Only the South African results are reported for local context. Eight individuals were recruited, ≥ 70% female, with only 30% or less employed. The major causes of events were attributable to stress (≥ 36%), irregular or insufficient food intake (40% daytime and 50% night-time) or poor glucose control (18%). The use of alcohol was 12%. The impact on the healthcare system was mainly driven by additional doctor visits, i.e. 14% and 12%, respectively, for night-time and daytime hypoglycaemic events. In both groups, 11% reduced the insulin dose and used more test strips directly after the event and in the following week. In both groups who arrived late or left work early, were the major employer impacts. Patient quality of life was mostly affected by the impact on daily routine.

**Conclusion:** Non-severe hypoglycaemic events significantly impacted on patients’ well-being with a knock-on societal impact with regard to healthcare costs and work productivity loss. The hypoglycaemia surveys were supported by a grant from Novo Nordisk.

50. **The perceptions and understanding of mothers with gestational diabetes mellitus of the causes, consequences and treatment of their condition: an urban study**

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**Objective:** There has been considerable debate on the determinants of patient treatment adherence. However, little is known about barriers to care for patients with gestational diabetes mellitus and the role that communication plays in mediating these barriers. This study investigated the beliefs of mothers with gestational diabetes mellitus about the causes, consequences and treatment of the condition.

**Method:** Qualitative methods were used. Sixteen mothers with gestational diabetes mellitus participated in the study. Purposive sampling was adopted. Three focus groups were conducted at the diabetes clinic at the Chris Hani Baragwanath Academic Hospital in Johannesburg. Data were analysed using thematic analysis.
Abstracts

Results: Communication emerged as an important mediating factor within themes and varying perceptions were revealed by participants. The findings suggest that research has neglected many chronic conditions in South Africa. It also appears that gestational diabetes mellitus is an unfamiliar condition, associated with various stigma and found to affect entire social groups. The findings revealed inadequate communication in the medical setting. A link between mothers’ perceptions and treatment adherence was noted.

Conclusion: Gestational diabetes mellitus is a complex condition. Communication appears to play an important role in facilitating patients’ understanding and acceptance of the condition, and seems to be a powerful opposing force against barriers to care. Implications of the study include future research into the effect of communication on patient care. Further insight into living with a chronic condition in South Africa should also be gained. Other important implications include the implementation of strategies to improve communication at gestational diabetes mellitus clinics, as well as more emphasis on patient communication in gestational diabetes mellitus policy documents.

51. Case report: Pagetic telangiectatic osteosarcoma
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Malignant transformation is a rare and devastating complication of Paget’s disease of bone, arising in less than 1% of cases. Most commonly, osteosarcoma, chondrosarcoma and giant cell tumours are described in this clinical context. Telangiectatic osteosarcoma, an unusual histological variant of osteosarcoma, is described in approximately 3-10% of cases. We report on such a case. A 60-year-old female patient presented with a six-month history of severe left hip and pelvic pain. Conventional pelvic X-rays revealed features of Paget’s disease of bone, in which the left iliac and pelvic bone were implicated. A mild elevation of serum alkaline phosphate of 227 (normal 35-120 IU/l) was not in keeping with malignant transformation. Urinary deoxyxypyrudinoline and serum osteocalcin levels were not elevated. Skeletal scintigraphy was positive only in the pelvic area described on the X-ray. MRI of this area confirmed destruction of the left superior ramus of the pubic bone and showed a large pelvic mass extending from the left iliac bone, with areas of multiple fluid levels in keeping with telangiectatic osteosarcoma. A biopsy of this latter area was performed. Microscopic sections showed a tumour consisting of osteoid-producing atypical cells with pleomorphic nuclei and increased mitotic figures. These cells lined large telangiectatic spaces filled with red blood cells, and confirmed the diagnosis of telangiectatic osteosarcoma. This case is unusual in many ways. The first presentation of Paget’s disease of bone was osteosarcoma, there was minimal biochemical evidence of increased bone turnover, and histology confirmed an unusual variant of osteosarcoma.

52. Acarcinoma: a local experience
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Adrenocortical carcinoma is a disease that features rare tumours that carry a poor prognosis. Its infrequent occurrence limits extensive clinical experience relating to diagnosis and management. These tumours can either be functional, when their hormonal secretions result in clinical consequences, or nonfunctional. We present a case series of three patients with histologically confirmed adrenocortical carcinomas who presented to our unit over the last 1.5 years. Their clinical presentation and hormonal findings are described, along with the challenges faced in managing these tumours. We review the preoperative and histological characteristics of poor predictive markers for the two patients who succumbed to the disease. We also discuss the therapeutic challenges surrounding the optimal approach of patients who present with advanced disease, as well as the management options available to those patients who survive surgical resection of their tumours. Adrenocortical carcinoma is a heterogeneous disease that carries little expectation of long-term survival if complete surgical removal is not achieved. The limited role of medical management, including mitotane- and cisplatinum-based chemotherapy, indicates that new drugs and treatment modalities are urgently needed for patients diagnosed with this cancer.

53. Thyroid nodules in children
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Thyroid nodules are uncommon in prepubertal children, with a prevalence of approximately 1.5% in childhood. Thyroid nodules that present in childhood have a 26% risk of being malignant. Risks factors for developing thyroid nodules include previous or existing thyroid disease, a family history of thyroid disease, pubertal girls and exposure to irradiation. Because of the increased risk of malignancy, any nodule discovered in childhood should be viewed with suspicion. The diagnostic approach should also be more aggressive in children, than in adults. This should include taking an extensive history and conducting a thorough clinical examination and special investigations, which usually consist of a combination of laboratory, radiological, tissue sampling and molecular techniques, to assist with a diagnosis. Detection of a malignant nodule warrants immediate treatment. Treatment options for benign nodules include observation or surgery, especially if the nodule causes compression symptoms or the diagnosis of malignant nodule is in doubt. Treatment of nodules with T4 may have some benefits, but its efficacy remains low. Novel therapeutic interventions include laser ablation treatment and ethanol injections. However, there are limited data on the efficacy of these treatments in children. We present a case series of three children presenting with thyroid nodules. Case 1 describes follicular carcinoma in a child who was diagnosed with congenital hypothyroidism secondary to Na+/I- symporter defect. Case 2 pertains to papillary carcinoma in a previously euthyroid patient and case 3 relates to a cystic nodule in an euthyroid patient. Our case series aims to demonstrate the management of thyroid nodules in children.

54. A double-headed insulinoma
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Pancreatic neuroendocrine tumours are extremely rare, and although insulinomas are the most common, less than 10% of insulinomas are malignant. We describe a case of malignant insulinoma and highlight the value of endoscopic ultrasound in making the diagnosis. A 61-year-old male patient presented with recurrent hypoglycaemic episodes. Whipple’s criteria were fulfilled.
The physical examination was unremarkable and no co-morbidities were documented. A 72-hour, in-hospital fast was terminated early because of hypoglycaemia symptoms. At the time, blood glucose was 1.4 mmol/l, insulin 46.7 mU/l, C-peptide 2.7 μg/l and cortisol 334 nmol/l, confirming hyperinsulinaemia at the time of hypoglycaemia. Chromagranin levels were elevated at 96.6 ng/ml. Other blood investigations were normal. A Gallium-68 dotatate scan did not highlight any pancreatic or other lesions. Abdominal MRI revealed a vague mass lesion close to the head of the pancreas. Endoscopic ultrasound showed two mass lesions: one clearly defined and close to the head of the pancreas, the other less well defined and difficult to localise. An endoscopic, ultrasound-guided, fine-needle aspiration of the former lesion confirmed its neuroendocrine origin, staining positive for synaptophysin and chromogranin. The second lesion was inaccessible. Intraoperatively, the second lesion was revealed as a large peripancreatic lymph node. A distal pancreatectomy, lymphadenectomy and splenectomy were performed. Intraoperative ultrasound showed no liver lesions. Eleven lymph nodes were dissected, of which seven showed tumour infiltration. This case report describes a WHO grade II insulinoma (pathological stage IIIB). Endoscopic, ultrasound-guided, fine-needle aspiration confirmed the nature of the primary lesion and highlighted the presence of a second lesion, which in this case, turned out to be a metastatic lymph node. The patient remained euglycaemic one month postoperatively.

55. Patients’ experiences of diabetic care services in KwaZulu-Natal: a pilot study

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Objective: This study is presented as a pilot that will form the basis for a PhD degree that explores the role that communication plays in the doctor-patient relationship in the management of a chronic lifestyle disease, such as diabetes mellitus. The management of a chronic lifestyle disease involves a complex mix of education, lifestyle adjustments, risk factor reduction, medication and lifelong adherence to these changes. It is the relationship between healthcare provider and patient that often becomes a challenge within the multicultural and multilingual society of South Africa.

Method: A convenience sample of six attendees at a diabetic centre in Zululand was included in a focus group discussion. A broad interview schedule allowed for open discussion around their experiences of the diabetic healthcare services, healthcare professionals and the management of their chronic disease. Thematic analysis of field notes, as well as the audio-recording of the discussion, are presented.

Results: Patients confirmed the need to address issues of communication between healthcare providers and patients. They highlighted the role that system and logistical issues play in clinical care and the feedback that negative environments have on the people who work within that system. Patients confirmed that the attitude and behaviour of staff towards them is just as important as staff’s knowledge of the disease.

Conclusion: The art of communication and relationships with patients is as important as the science of medicine. Focus needs to be given to improving such issues if an effective and comprehensive service is to be offered to patients.

56. Mucinous cystadenoma of the ovary, producing virilisation in a postmenopausal female

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Cystadenomas of the ovary account for 10-15% of all ovarian tumours. Usually, they are steroidogenically inert. We present a case of a mucinous cystadenoma of the ovary, producing hyperandrogenaemia and virilising features in a patient. A 60-year-old woman presented to Helen Joseph Hospital with frontal androgenic alopecia and hirsutism that had developed over the period of a year. The hirsutism was limited to the upper lip and chin. There was no evidence of excessive hair growth in any other androgen-sensitive region. Cliteromegaly was absent. An androgen profile showed the following: testosterone 5.6 nmol/l, free androgen index 21.5, androstenedione 4.9 nmol/l and DHEAS 4.0 umol/l. Estradiol, FSH and LH levels reflected a postmenopausal status. TSH and prolactin levels were within the normal range. Twenty-four -hour, urine-free cortisol was normal. A 17-hydroxyprogesterone level was within the normal range. Abdominal ultrasound revealed a right adnexal fluid-filled collection, confirmed to be an ovarian cystic mass on CT scan. Bilateral oophorectomy and omentectomy were performed and the histology confirmed the presence of bilateral benign mucinous cystadenomas. One month after surgery, testosterone levels had decreased to 0.7 nmol/l and the Free Androgen Index (FAI) had decreased to 2.5: levels appropriate for a woman with resolution of hirsutism. This was an unusual case of virilisation in a postmenopausal woman, caused by mucinous cystadenoma of the ovary.