49th Congress of the Society for Endocrinology, Metabolism and Diabetes of South Africa

FRIDAY, 11 APRIL 2014

1. Pathology and molecular biology update on neuroendocrine tumours: what clinicians should know in 2014

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The incidence and prevalence of neuroendocrine tumours (NETs) or neuroendocrine neoplasm (NEN) has been increasing recently, especially in the gastrointestinal tract and pancreas. Recently, these tumours were classified into G1, G2 and G3/neuroendocrine (NEC) based upon mitotic counts or Ki-67 labelling index [World Health Organization (WHO), 2010]. This is because the clinical outcome of patients with NEN is largely determined by this newly developed histological and of Malignant Tumours (TNM). However, controversies exist as to the surrogate markers of novel target specific therapies and further subclassification of G3/NEC because of different responses by these patients to platinum-based chemotherapy. In particular, the former relates to the markers of somatostatin analogues and/or inhibitors, while the latter relates to optimal cut-off points of Ki-67 labelling index or the inclusion of histological features of the tumour cells, such as small cell carcinoma in NEC or G3 cases. In addition, it is also important for clinicians to recognise that there are two different TNM classifications, WHO versus ENET, which could yield different stages in the same patients with pancreatic NET. Molecular studies of NETs/NEN have revealed several putative prognostic markers or putative therapeutic targets including Id, ATM, SRC, , heat shock protein 90 and. Endocrinologists should be aware that currently, the clinical algorhythm of NEN patients, especially treatment decisions, is not necessarily based on hormonal features, but rather pathological and molecular features of the disorder.

2. Differential optimal obesity indices identify metabolic syndrome in black men and women in Cape Town: the CRIBSA Study

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Objective: To determine the optimal obesity indices, specifically waist circumference (WC), that identify ≥ 2 other metabolic syndrome (MS) components defined by the 2009 harmonised criteria in the 25- to 74-year-old black population of Cape Town.

Method: In 2008/2009, a representative cross-sectional sample, stratified for age and sex, was randomly selected. Data were collected by administered questionnaires, clinical measurements and biochemical analyses, including fasting and 120-minute blood samples. Optimal obesity cut-off points were estimated by the Youden index. Logistic regression analyses, adjusted for age, determined whether or not obesity cut-off points that identified ≥ 2 MS components occurred at true inflection points.

Results: There were 1 099 participants; of whom 392 were men and 707 women. The optimal cut-off points and 95% confidence intervals (CIs) were men, WC 83.9 cm (81.6-86.2), waist-to-hip ratio (WHR) 0.89 (0.87-0.90), waist-to-height ratio (WHtR) 0.50 (0.48-0.52), and body mass index (BMI) 24.1 kg/m^2 (22.0-26.1); and women, WC 94 cm (91.9-96), WHR 0.85 (0.83-0.87), WHtR 0.59 (0.57-0.60), and BMI 32.1 kg/m^2 (29.7-34.6). The presence of ≥ 2 MS components was significantly associated with raised WC in men: WC 84-93.9 cm [odds ratio (OR) 3.19, 95% CI: 1.73-5.85 and WC ≥ 94 cm, OR: 8.50, 95% CI: 4.44-16.25] compared to WC < 84 cm; and in women, WC 80-93.9 cm, OR: 2.93, 95% CI: 1.32-6.54 and WC ≥ 94 cm, OR: 5.33, 95% CI: 2.40-11.85, compared to WC < 80 cm. The presence of ≥2 MS components in the logistic model with BMI for women was not associated with overweight (p-value 0.063), while obesity was significantly related (OR: 3.60, 95% CI: 1.82-7.10).

Conclusion: WC and other obesity cut-off points currently recommended in the black population should be re-evaluated and adjusted accordingly.

3. Insulin secretion in relation to insulin sensitivity differs in black South African men and women with increasing age

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We have previously shown that premenopausal black South African women are more insulin resistant than their white counterparts and hypersecrete insulin to maintain normoglycaemia. This study aimed to examine the effect of age and sex on insulin secretion relative to insulin sensitivity in black South African men and women. The subjects were men (n = 237) and women (n = 346), aged 25-74 years, without known diabetes, randomly selected from a peri-urban setting in Cape Town. They underwent an oral glucose tolerance test (OGTT), from which insulin sensitivity [insulin sensitivity index (ISI0, 120)] and secretion [insulinogenic index (IGI)] were estimated, and the disposition index (DI) calculated, i.e. DI = ISI x IGI. Despite marked differences in BMI between the men and women [median (interquartile range): 23.5 (20.1-25.8) vs. 32.3 (26.3-36.9) kg/m^2, p-value < 0.001], the prevalence of impaired glucose tolerance (IGT) (15.2 vs. 13.3%) and type 2 diabetes (3 vs. 4.6%) did not differ (p-value 0.508), and increased similarly with age in both sexes (p-value < 0.001). However, ISI0, 120 was higher [7.4 (4.3-9.1) vs. 5.2 (3.6-6.1) mg.l2/mU.minute, p-value 0.009), but both IGI 25.4 (6.8-30.8) vs. 58.3 (12.8-62.7) mU/mmol, p-value < 0.001) and DI [100.6 (37.9-232) vs. 140 (51.1-303.3) mg.l2/

mmol.minute, p-value 0.01)] were lower in men than in women, after adjusting for age and BMI. ISI decreased in men with increasing age, but not in women (p-value 0.006), whereas the rate of decrease in IGI with increasing age was greater in women than in men (p-value 0.025). Consequently, the decrease in DI with increasing age did not differ by sex (p-value 0.090), but remained significantly higher in women than men across all age categories (p-value 0.015). In conclusion, insulin secretion in relation to insulin sensitivity decreases with increasing age, but remains higher in women than in men across all age categories, independent of BMI.

4. Adipose tissue extracellular matrix gene expression in black and white South African women has a different association with insulin sensitivity in obesity

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Objective: We have previously shown that black South African women have higher subcutaneous adipose tissue (SAT) inflammatory gene expression and reduced adipogenic capacity in the gluteal SAT depot, which correlates with reduced insulin sensitivity (SI) in black, but not white, women. We hypothesise that this phenotype in black women may be associated with increased expression of extracellular matrix (ECM) components in SAT, compared to that in white women. Therefore, the aim of the study was to compare the gluteal SAT expression of ECM components between normal-weight and obese black and white women, and to examine the ethnic-specific associations with SI.

Method: Body composition was determined using dual-energy X-ray absorptiometry (DXA) and computed tomography (CI). SI [frequently sampled intravenous glucose tolerance test (GTT)] and gluteal SAT gene expression levels of ECM-related genes [collagen 5a1 (COL5a1), collagen 6a1 (COL6a1), fibroblast growth factor 1 (FGF1), hypoxia-inducible factor 1 (HIF1), lysyl oxidase 1 (LOX1) and adipogenic gene, i.e. peroxisome proliferator-activated receptor γ (PPARγ), as well as vascular endothelial growth factor α (VEGFα)] were measured in normal-weight (BMI 18-25 kg/m^2) and obese (BMI > 30 kg/m^2) black (n = 26) and white (n = 22) South African women.

Results: The gluteal SAT expression of HIF1, LOX1 and FGF1 were higher in obese than in normal-weight women (p-value < 0.01). VEGFα and PPARγ were downregulated in obese black, but not white, women (p-value 0.016 and p-value 0.015, respectively). COL5a1 and COL6a1 expression was higher in obese black women (p-value < 0.000, p-value 0.029) than in obese white women. When adjusting for fat mass, HIF1 and COL6a1 expression correlated negatively with SI in black (r = -0.55, p-value 0.005; r = -0.47, p-value 0.019), but not in white women.

Conclusion: Black South African women have higher ECM gene expression than white women, and the relationship between ECM gene expression and insulin resistance is stronger in black than in white women. Increased ECM deposition may be another contributing factor to increased insulin resistance, as observed in black women.

5. Bariatric surgery: effects on glucose homeostasis

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SATURDAY, 12 APRIL 2014

6. Do we need new criteria for gestational diabetes?

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Various approaches to diagnosing gestational diabetes are in use throughout the world, but none are based on their prediction of adverse pregnancy outcomes. The Hyperglycemia and Adverse **Pregnancy Outcome** (HAPO) collected outcome data on over 23 000 pregnancies in nine countries after a blinded 75-g, two-hour OGTT at 24-28 weeks gestation [HAPO Study Cooperative Research Group, et al. N Engl J Med. 2008; 358(19):1991-2002]. All four primary outcomes (large for gestational age, primary Caesarean section, neonatal hypoglycemia and high cord C-peptide), and most 2-degree outcomes, e.g. pre-eclampsia, preterm birth, shoulder dystocia and birth injury, were significantly and directly related to each of the three plasma glucose measurements. With no inflection point in the curves relating to maternal glucose and pregnancy outcomes, assignment of thresholds for gestational diabetes was relatively arbitrary. The International Association of Diabetes and Pregnancy Study Group recommendations [Diab Care. 2010;33(3):676-682] include the use of a 75- g, two-hour OGTT with one or more elevations diagnosing gestational diabetes. Thresholds are fasting plasma glucose ≥ 92 mg/dl (5.1 mmol/l), at one hour ≥ 180 mg/dl (10 mmol/l) and two hours ≥153 mg/dl (10.5 mmol/l). These recommendations are being considered for adoption throughout the world because they are pregnancy outcome-based, the 75-g glucose load will bring consistency to GTTs, universal adaption will lead to consistency of diagnostic criteria worldwide, studies of treatment at similarly mild levels of glycaemia have demonstrated improvement in outcomes, and use of a single abnormal value will obviate the confusion arising when one elevated value is encountered. They have been adopted by the WHO.

The primary argument against using the new recommendations is the fact that the prevalence of gestational diabetes will rise to 16-18%. Increased cost in dollars and healthcare provider time will result. The health concerns of the increasing epidemic of obesity, prediabetes and diabetes throughout the world should be balanced against these cost concerns. For example, in the USA in 2010, 31% of women of childbearing age had prediabetes (26.4%) or diabetes (4.5%).

7. High prevalence of cardiometabolic abnormalities in urban dwelling South Africans with diabetes: the CRISBA study

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Objective: This study aimed to determine the prevalence and associations of other cardiometabolic risk factors with diabetes 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. Cardiometabolic 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 associations of cardiometabolic risk factors with diabetes.

Results: Of the 1 099 study participants, 160 (45 men and 115 women) were identified with diabetes. Participants with diabetes had a significantly higher prevalence of blood pressure (BP) ≥ 130/80 mmHg or hypertension treatment (82.6% vs. 53.5%), total cholesterol > 5 mmol/l (37.3% vs. 22.3%), triglycerides > 1.5 mmol/l (32% vs. 14%) and low-density lipoprotein cholesterol (LDL cholesterol) > 3 mmol/l (63.3% vs. 39.8%) than those without it. Obesity indices were higher in those with diabetes than in those without it: BMI ≥ 25 kg/m^2: men 54.9% vs. 25.9%, women 98.5% vs. 80.3%; WC: men ≥ 94 cm: 51.9% vs. 16.4%, women ≥ 80 cm: 99.4% vs. 83.8%. These rates were similar in known and unknown diabetes. In the multiple logistic model, after adjusting for age and gender, diabetes was significantly associated with raised BP (OR 2.19, 95% CI: 1.18-4.06, p-value 0.013), raised LDL cholesterol (OR: 1.58, 95% CI: 1.04-2.40, p-value 0.030) and raised WC (OR: 3.61, 95% CI: 2.01-6.48, p-value > 0.001).

Conclusion: The high prevalence of cardiometabolic abnormalities with diabetes reinforces the importance of searching for and treating these risk factors in urban Africans with diabetes to reduce complications.

8. Screening for diabetes and hypertension in Zandspruit, Johannesburg

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Objective: Sixteen screening days were carried out in the Zandspruit and Cosmo City area of Johannesburg as part of a larger study that focused on the improvement of community awareness of diabetes and hypertension.

Method: Final-year nursing students, supervised by a registered nurse from the Empilweni Nursing College, with the support of community volunteers, screened patients who provided consent to have their BP, BMI, WC and random glucose measured. Patients received a patient information leaflet in which there was space for their results to be captured. After the last test, patients sat with a nurse to discuss their results and possible next steps. Results were captured anonymously, except for those deemed to be in need of immediate referral. Patients' data were classified according to the 2012 Society for Endocrinology, Metabolism and Diabetes of South Africa (SEMDSA) guidelines.

Results: We screened 5 525 people. 55.3% were female and the mean age was 35 years. Only 46% of those screened had normal random glucose (defined as < 5.6 mmol/l) and only 37.9% had a systolic blood pressure (SBP) below 120 mmHg. The mean SBP and diastolic blood pressure (DBP) for the screened population was 128 mmHg and 82 mmHg, respectively. There was a significant difference in the BMI between men and women. Also, 80% of men had a WC below 94 cm, whereas only 21.5% of females had a WC below 80 cm.

Conclusion: In a relatively young population of Zandspruit and Cosmo City in Johannesburg, a large proportion of persons with high SBP and random glucose values was found. The data guided an intervention with the establishment of a privately funded clinic to assist with both diabetes and hypertension care in the Zandspruit and Cosmo City settlements.

9. The prevalence and incidence of diabetes mellitus and other disorders of glycaemia in South African black patients on antiretroviral therapy

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This study determined the prevalence, incidence and predictors of dysglycaemia in adult subjects of second-generation Zulu descent on antiretroviral therapy (ART).

Human immunodeficiency virus (HIV)-infected ART-naive patients eligible for ART (group 1, n = 150); and age, gender, ethnically matched HIV-infected patients who were not eligible for ART (group 2, n = 88); as well as HIV-negative subjects (group 3, n = 88) were included. WHO criteria for diabetes mellitus, IGT and impaired fasting glucose (IFG), using the OGTT and haemoglobin $A1_c$ ($HbA1_c$) were used to compare prevalence in the groups at baseline. Group 1 was followed for 24 months on ART.

At baseline, the prevalence of diabetes mellitus was 0% in groups 1 and 2, and 4.94% in group 3, p-value 0.005; IGT prevalence was 2.96%, 2.4% and 3.7%, and IFG 0.7%, 1.2% and 0%, in groups 1, 2 and 3, respectively. Of 150 persons in group 1, 13 developed diabetes mellitus during 219.2 person-years follow-up (PYFU), [incidence: 5.9 cases per 100 PYFU (95% CI: 3.2-10.1)]; 11 developed IGT during 217.9 PYFU [incidence: 5 cases per 100 PYFU (95% CI: 2.5-9)]; and eight developed IFG during 216.3 PYFU [incidence: 3.7 cases per 100 PYFU (95% CI: 1.6- 7.3)]. Significant predictive risk factors in multivariate analysis for future dysglycaemia included SBP for diabetes melliuts [OR 1.05 (95% CI: 1.01-1.09)], p-value 0.03); SBP [(OR 1.04 (95% CI: 1.0-1.07), p-value 0.01)] and CD4 cell count [OR 0.98 (95% CI: 0.97-0.99), p-value 0.02)] for IGT and visceral fat by CT scan for IFG [OR 1.02, 95% CI: 1.004-1.03), p-value 0.01].

There is a high incidence of dysglycaemia in these subjects on ART and this underscores the importance of monitoring.

10. Testosterone deficiency, replacement and safety in cardiovascular disease

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Low testosterone is associated with an increased risk of all-cause and cardiovascular mortality in the majority of prospective community-based and cardiovascular disease (CVD) population studies. Endogenous testosterone levels in the mid- to upper-normal range are associated with the lowest cardiovascular events and mortality. Testosterone deficiency is associated with an adverse effect on the cardiovascular risk profile, which includes central adiposity, dyslipaemia, hypertension, glucose intolerance, endothelial dysfunction and raised inflammatory cytokines. The question arises as to whether or not low testosterone is merely a biomarker for chronic inflammation or contributes to the progression of atherosclerosis. Animal studies on low testosterone states promote early changes of atherogenesis which are ameliorated by testosterone. Carotid intimal-media thickness is greater with low testosterone and worsens over time. Hypogonadism and/or erectile dysfunction may be the first symptoms of CVD.

The second question is whether or not testosterone replacement therapy would have a beneficial effect on men with CVD, apart from those that relate specifically hypogonadism. When testosterone has been replaced and carefully titrated to the mid range, no

increased risk in cardiovascular events occurred, and there were benefits with regard to cardiovascular risk factors, cardiac ischaemia and functional exercise capacity in heart failure. No initial diagnosis of hypogonadism or poor comparator groups then cardiovascular events may be expected in studies where either subjects may be over- or undertreated. Careful diagnosis, titrated replacement and monitoring are important.

11. Tissue non-specific alkaline phosphatase functions to generate inorganic phosphate which mediates lipid accumulation in 3T3-L1 preadipocytes

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Background: Within osteoblasts, tissue-nonspecific alkaline phosphatase (TNSALP) hydrolyses inorganic pyrophosphate (PPi), an inhibitor of bone mineralisation, into inorganic phosphate (Pi), an activator of differentiation and mineralisation. Intracellular lipid accumulation in the preadipocyte cell line, 3T3-L1, is characteristic of cell maturation (adipogenesis) and is blocked by inhibition of TNSALP. We hypothesise that TNSALP mediates intracellular lipid accumulation in preadipocytes by increasing the intracellular levels of Pi.

Method and results: While undergoing adipogenesis, treatment of 3T3-L1 cells with an inhibitor (probonecid) of the progressive ankylosis protein (ANK) transported PPi out of cells, leading to significant increases in intracellular PPi concentration (p-value < 0.05), (148%, 11.25), TNSALP activity (283%, 57.8), intracellular Pi level (148%, 34.44) and increased intracellular lipid accumulation (150.44%, 24) when compared to untreated cells (100%). Inhibition of TNSALP activity, with levamisole, resulted in a cessation of intracellular lipid accumulation, an effect that was reversed by the addition of Pi.

Conclusion: Therefore, the function of TNSALP in intracellular lipid accumulation is to generate intracellular Pi, which may act as a regulator of gene expression in preadipocytes. Pi is known to increase expression of the transcription factor, Nrf2, within osteoblasts, a molecule that is also essential for adipogenesis within preadipocytes.

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12. Seroprevalence of antithyroid peroxidase and antiparietal cell antibody positivity in patients with type 1 diabetes in KwaZulu-Natal

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Objective: To assess the prevalence of antithyroid peroxidase antibodies and antiparietal cell antibodies in patients with type 1 diabetes attending the outpatient tertiary diabetes clinic at Inkosi Albert Luthuli Hospital in Durban, KwaZulu-Natal.

Method: This was a cross-sectional observational study on subjects with type 1 diabetes attending the adult diabetes clinic at Inkosi Albert Luthuli Hospital in Durban. Information collected from patients included history, a clinical examination and laboratory tests. Blood tests included those for the anti-glumatic acid decarboxylase (GAD) antibody, antithyroid peroxidase (anti-TPO) antibody, antiparietal antibody, coeliac antibodies, B_{12}, folate, ferritin, thyroid-stimulating hormone (TSH), free thyroxine, creatinine, serum lipids and $HbA1_c$.
Results: A total of 202 (90 male to 112 female) patients were recruited. The ethnic composition was African (56.4%, n = 114), Indian (31.7%, n = 64), white (4.5%, n = 9 and coloured (7.4%, n = 15). The mean age of the study population and mean duration of diabetes was 26.4 + 11.4 and 10.7 + 9.1 years, respectively. The mean BMI was 21.6 + 6.3 kg/m^2. Twenty-three patients (11.4%) were known to have primary hypothyroidism on chronic thyroxine therapy, either due to Hashimoto's disease (n = 21) or Graves' disease post-radioiodine therapy (n = 2). The GAD antibody was found in 63.37% (n = 128) of the total study group. Anti-TPO and antiparietal antibody prevalence was 18.91% (n = 39) and 8.91% (n = 17), respectively.

Conclusion: Patients with type 1 diabetes frequently have co-existent autoimmune thyroid disease and evidence of gastric autoimmunity. Screening for these conditions should be undertaken in patients with type 1 diabetes, although the optimal timing of initial screening and subsequent testing requires further investigation.

13. The low frequency of screening for metabolic syndrome in patients with severe mental illness in Durban

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Objective: The objective of this study was to document the frequency of testing for all the components of MS in patients with severe mental illness in Durban.

Method: This was a cross-sectional study, undertaken from January to June 2012, on outpatients with severe mental illness who were treated with antipsychotic medication for at least six months. The study measured the proportion of participants who were tested for MS and their general medical care in the previous year.

Results: The study included 331 (167 male to 164 female) participants, with a mean age of 35.2? 11.98 years. The majority (78.8 %) were black South Africans. Only 2 subjects (0.6 %) were screened for all five components of MS. Regarding the individual components, 99%, 0.6%, 3.9% and 1.8% were screened for raised BP, abdominal obesity, hyperglycaemia, hypertriglyceridaemia and decreased HDL cholesterol, respectively. Forty-two per cent relied on the psychiatric clinic for their general medical health care.

Conclusion: It is unacceptable that less than one per cent of participants were screened for modifiable risk factors. Therefore, these results highlight the need to translate guidelines into action.

14. Adrenal incidentalomas: spectrum of disease at a tertiary hospital in South Africa

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Objective: The aim of this retrospective clinical audit was to assess the spectrum of disease in patients who were referred to the Endocrine Division with an adrenal incidentaloma.

Method: Patients referred over a four-year period with an adrenal incidentaloma were assessed. Only patients who met the strict definition of a true adrenal incidentaloma were included in this study.

Results: Twenty-one patients met the inclusion criteria. Demographic data were as follows: mean age 53 ? 12 years, 57.1% female; 52.4% of patients were of mixed ancestry, 38.1% white; and the mean BMI was 31.5 ? 9.3 kg/m^2. The mean size of the adrenal incidentalomas on radiological imaging was 3.4 ? 2.2 cm. 35.3% of lesions were greater than 4 cm, the size regarded as an indication for surgery. Functionality was confirmed in four patients: two phaeochromocytomas, one subclinical Cushing's syndrome and one positive screening test for hyperaldosteronism. Features that necessiated active intervention were present in nine of the 21 patients. Eight patients underwent surgery, and histology revealed two phaeochromocytomas, a leiomyoma, a multicystic renal cell carcinoma, one metastatic lesion and three adrenal cortical adenomas.

Conclusion: Nonadenomatous pathology was confirmed in 24% of this cohort of patients. Despite small patient numbers and lack of uniform biochemical evaluation, the spectrum of disease appears to be in keeping with that described in the literature.

15. Gluteal adipose expression of oestrogen receptor alpha associated with ethnic differences in body fat distribution in South Africa women

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We have previously reported on ethnic differences in the relationship between the distribution of body fat and IS. The reasons for this are not known, but could be explained, in part, by differences in sex hormones, which play an important role in determining body fat mass and its distribution. Therefore, the aim of this study was to compare the expression of oestrogen receptors, ERα and ERβ, and aromatase [cytochrome P450 (CYP) 19A)] in gluteal SAT, and examine their associations with body fat distribution and insulin sensitivity in black and white women. Body composition (DXA), insulin sensitivity (frequently sampled intravenous GTT) and ERα, ERβ and aromatase mRNA levels were measured in gluteal SAT of 48 normal-weight and obese black and white premenopausal South African women. Gluteal SAT aromatase mRNA levels did not differ by ethnicity, but were positively associated with total body fat in black and white women ($r = 0.37$, p-value < 0.01 and $r = 0.41$, p-value < 0.01, respectively). ERα mRNA levels were higher in black than in white women (1.08-0.02 vs. 1.02-0.01 AU, p-value < 0.05), and in black women only, were negatively associated with centralisation of body fat ($r = -0.27$, p-value 0.02) and insulin resistance (homeostasis model assessment of insulin resistance, $r = -0.4$, p-value <0.01), independent of total and central body fat. In conclusion, lower centralisation of body fat in black compared to white South African women may be associated with their higher gluteal SAT expression of ERα, which may also protect against insulin resistance.

16. The effects of thiazolidinediones on the osteogenic differentiation potential of primary adipose-derived mesenchymal stem cells

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Obesity is associated with serious co-morbidities, including insulin resistance which can lead to overt type 2 diabetes mellitus. Thiazolidinediones are potent insulin sensitising agents prescribed to patients suffering from type 2 diabetes mellitus, and work predominantly through the activation of the PPARγ, a master regulator of adipogenesis. However, treatment is associated with serious side-effects, including secondary osteoporosis, which limit therapeutic benefit. This may be owing to the skewing of stem cell differentiation away from an osteogenic, and towards an adipogenic phenotype.

This study aimed to directly compare the influence of three thiazolidinediones with either a high or low affinity for PPARγ on the osteogenic commitment of primary mesenchymal stromal cells (MSCs). MSCs were cultured from subcutaneous and peri-renal visceral adipose depots isolated from male Wistar rats. Cells were characterised using flow cytometry and the effects of thiazolidinediones on osteogenesis (mineralisation). Any aberrant lipid accumulation was quantified.

Cells incubated in an osteogenic stimulating medium, supplemented with thiazolidinediones, did not present with a decrease in mineralisation, but instead concurrent mineralisation and lipid droplet formation was observed. Rosiglitazone and pioglitazone (high PPARγ affinity) induced more lipid accumulation than netoglitazone, a dual PPARγ/α agonist.

In contrast to current thinking, in this model, which makes use of primary stem cells with an uncorrupted cell cycle, thiazolidinediones did not promote adipogenesis at the expense of osteogenesis. Instead, both processes continued in parallel. In order to develop an efficacious treatment for type 2 diabetes mellitus, the mechanisms by which thiazolidinediones negatively affect bone need to be studied further.

17. Determinants of obesity and metabolic programming. Why is it so difficult to lose weight?

J Dixon

SUNDAY, 13 APRIL 2014

18. Pathology and molecular biology update of endocrine hypertension: what clinicians should know in 2014

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The great majority of endocrine hypertension is caused by the adrenal diseases, particularly pheochromocytoma (intraadrenal paraganglioma) and primary aldosteronism. Marked advances in molecular pathology have been reported in these disorders. Recent studies on pheochromocytoma demonstrated there are more cases of hereditary or genetic, malignant and extra-adrenal cases than previously considered. In particular, the abnormalities of SDHX genes have been demonstrated to be far more prevalent than those of RET and VHL. These abnormalities could be screened by succinate dehydrogenase subunit B (SDHB) immunohistochemistry. However, it is still impossible to discern malignancy of resected pheochromocytoma using any molecular pathology diagnostic means at this juncture. Primary aldosteronism is currently not considered to be a rare disease. It represents 5-10% of patients with hypertension in general. With the advent of intravenous adrenal sampling, more cases of CT negative adenomas have been detected. Recently developed CYP11B1/2 and 3βHSD 1/2 immunostaining has made it possible to determine the precise sites of intraadrenal biosynthesis and more daughter, satellite tumours and nodules have been demonstrated to be involved in aldostrone biosynthesis in these adenomas. Somatic mutations of KCNJ5 or ATP1A1 or ATP2B3 result in increased aldostrone biosynthesis frequently discovered in many primary aldosteronism adenomas,

possibly through calcium-channel regulations and increased CYP11B2. It has become important for clinical endocrinologists to have these advances above to manage the endocrine hypertension patients.

19. Comparison of human leukocyte antigen genotype and 21-hydroxylase autoantibody positivity in Addison's disease in South Africa and the USA

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Background: Few data examine (HLA) associations in Addison's disease in South Africa. It is likely that are similarities with patients from the USA. We hypothesised that differences may reflect heterogeneity in ethnicity and environment, and that similarities might indicate a similar aetiology.

Method: South African patients were enrolled as part of a nationwide study of Addison's disease, and matched for healthy control subjects' gender and ethnicity (n = 73). Patients had clinical signs of Addison's disease, positive 21-hydroxylase autoantibodies (21OH-AA), (n = 83) in the USA. pHLA alleles were determined using DNA-based typing for DQA1, DQB1, and DRB1 class II antigens, as well as HLA-B class I antigens. Serum autoantibodies were tested at the Barbara Davis Center for both cohorts.

Results: In all SA Addison's disease HLA-DR3, DR4, the combination DR3/DR4 predominated versus controls (p-value ≤ 0.01). This was more pronounced in 21OH-AA+ SA-AD. The greatest similarities in were in patients with 21OH-AA. The known high-risk USA genotype of DR3+/DR4+ (p-value 0.05) and HLA-B8 (p-value 0.02) occurred less frequently in the South African group. DQB1*0202 was associated with protection from Addison's disease in 21OH-AA positive patients only, despite allelic similarities with high-risk DQB1*0201. HLA-B8 did not have an independent effect, apart from the DR3 haplotype. HLA-B7 was also higher in the South African 21 OH-AA+ versus 21OH-AA negative and control populations.

Conclusion: SA-Addison's disease and US-Addison's disease 21OH-AA+ patients have similar HLA risk, indicating similar genetic aetiology. HLA class II haplotypes distinguish Addison's disease risk versus controls. Distinct differences in HLA risk between autoantibody-positive patients, negative patients, and controls, implicate the need to test both 21OH-AA and HLA genotypes in clinical risk assessment. Differences in class II haplotypes are also potential contributors to the development and/or persistence of 210H-AA.

20. Greater hepatic steatosis and lower hepatic insulin sensitivity in white compared to black South African women

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Hepatic steatosis is an important factor that links obesity to insulin sensitivity. However, to our knowledge, this relationship has not been examined in South African women in whom insulin sensitivity differs by ethnicity. Therefore, we examined ethnic differences in hepatic steatosis in relation to hepatic and peripheral insulin sensitivity in obese white and black South African women. Body composition (DXA), hepatic steatosis (proton magnetic resonance spectroscopy) and insulin sensitivity (two-step isotope labelled, hyperinsulinaemic euglycaemic clamp with 10 mU/m^2/minute and 40 mU/m^2/minute insulin infusions) were measured in 16 obese white and 16 obese black premenopausal South African women. White and black women were matched for age (37.4 vs. 36.5 years, p-value 0.670), BMI (35.2-3.6 vs. 37.8-4.9 kg/m^2, p-value 0.097) and WC (97.3?7.3 vs. 101.6?10, p-value 0.170). White women had more liver fat than black women (7.8?9.4 vs. 2.1?1.8%, p-value 0.0.37). Neither whole body insulin sensitivity (M/I: 6.7?3.8 vs. 6.8?3.2 mg/minute/kg lean body mass/mU/l, p-value 0.872), nor rate of disposal of glucose during the high-dose clamp [247 (183-326) vs. 240 (195-312) mg/minute, p-value 0.880] differed between white and black women. However, the rate of disposal of glucose during the low-dose clamp was lower in white compared to black women [141 (124-188) vs. 188 (107-229) mg/minute, p-value 0.029)]. Furthermore, white women had greater hepatic glucose production (HGP [mean (**interquartile range**): 103 (60-115) vs. 45 (0-82) mg/minute, p-value 0.006], and lower suppression of HGP [18 (8-52) vs. 62 (34-100)%, p-value 0.008)] than black women. In conclusion, when compared to age- and BMI-matched black women, white women had lower hepatic insulin sensitivity, which corresponded to their higher liver fat content. These findings suggest that the pathogenesis of insulin resistance may differ by ethnicity.

21. Diabetes in pregnancy

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One hundred years ago, half of diabetic gravidas died during pregnancy, as did half of the offspring of surviving mothers. Subsequent advances have lowered these risks remarkably to a level that is not much higher than that of the general population. Near-normalisation of maternal glucose levels was the most important advance, but techniques for foetal evaluation and neonatal care were also critical.

While preprandial glucose monitoring is often recommended in nonpregnant individuals, one-hour or two-hour post-meal testing best predicts foetal outcome. The newer insulin analogues have improved our ability to manage glycemic control. Rapid-acting analogues have not been shown to cross the placenta, and are commonly used in pregnancy. Longer-acting analogues have been less fully evaluated for pregnancy, but are probably safe. Oral agents such as glyburide and metformin both cross the placenta, although neither has been shown to be detrimental to the fotus. Longer-term follow-up studies are needed, and these drugs are unlikely to be effective in gravidas with pre-existing diabetes because pregnancy provokes marked increases in insulin resistance. Pregnancy may hasten worsening of diabetic retinopathy, and transiently worsen nephropathy.

The biggest remaining challenge is to increase the participation of women with diabetes in pre-pregnancy counselling and management, with the goal of lowering glycaemia to prevent congenital malformations, which occurs duinring the first 10 weeks of gestation.

22. Ethnic-specific associations between insulin sensitivity and skeletal muscle gene expression in black and white South African women

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We hypothesise that differences in the skeletal muscle expression of genes involved in insulin signaling and glucose transport may explain our previous finding that black South African women are more insulin resistant than white South African women. Therefore, we examined ethnic differences in skeletal muscle gene expression and the association with insulin sensitivity in black and white South African women. Body composition (DXA), insulin sensitivity (euglycaemic hyperinsulinaemic clamp) and the expression of insulin receptor substrate 1 (IRS-1), syntaxin 4 (STX4) and vesicle-associated membrane protein (VAMP) in skeletal muscle were measured in 16 obese black and 16 obese white premenopausal South African women matched for age (36.5 vs. 37.4 years, p-value 0.670) and BMI (37.8-4.9 vs. 35.2-3.6 kg/m^2, p-value 0.097). In contrast to our previous findings, there were no differences in insulin sensitivity (M/I: 6.7?3.8 vs. 6.8?3.2 mg/minute/kg lbm/mU/l, p-value 0.872) between the two ethnic groups. Furthermore, there were no differences in skeletal muscle gene expression (IRS-1: 1.2?0.05 vs. 1.2?0.07, p-value 0.757; STX4:1.1?0.04 vs. 1.1?0.07, p-value 0.669; VAMP: 1.1?0.04 vs. 1.1?0.07, p-value 0.710) between black and white women, respectively. However, in black but not white women, there was a positive association between M/I and the expression of IRS-1 (r = 0.59, p-value 0.045) and the type 4 glucose transporter isoform transport genes; STX4 (r = 0.86, p-value 0.001) and VAMP (r = 0.76, p-value 0.004). In conclusion, the association between insulin sensitivity and genes involved in skeletal muscle insulin signaling and glucose transport differs by ethnicity in South African women. These results suggest that the pathogenesis of insulin resistance and the risk of type 2 diabetes may differ in these two ethnic groups.

23. Are current clinical trials addressing important issues in diabetes care?

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Objective: Projections that diabetes prevalence will grow globally highlight the need for appropriate clinical trials which assess interventions to prevent and treat diabetes and its complications. To determine whether or not current clinical trials in diabetes adequately address these needs, we conducted a descriptive analysis of diabetes-related trials registered with ClinicalTrials.gov from 2007-2010.

Method: From a dataset including 96 346 studies registered in ClinicalTrials.gov downloaded on 27 September 2010, a subset of 2 484 interventional trials was created by selecting trials with disease condition terms relevant to diabetes.

Results: Most diabetes-related trials were designed to enrol ≤ 500 participants (91%). 3.7% of trials targeted persons aged ≤ 18 years, 0.6% targeted persons ≥ 65 years, and the majority excluded those >75 years. Therapy was the primary purpose in 74.8% of trials, while 10% were preventive. Interventions included drugs (63.1%) and behavioural (11.7%). Primary outcomes that included mortality or clinically significant cardiovascular complications were listed in 1.4% of trials. The distribution of trials according to global region and the USA state did not correlate with the prevalence of diabetes.

Conclusion: Most diabetes-related trials include a relatively small number of participants, exclude those at the extremes of age, involve mainly drug therapy, rather than preventive or non-drug interventions, and do not focus on significant cardiovascular outcomes. Recently registered diabetes trials may not sufficiently address important diabetes care issues or involve affected populations.

24. Can point-of-care testing for plasma ketones replace the manual enzymatic method in hyperglycaemic patients with suspected diabetic ketoacidosis?

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Background: Urine dipsticks for ketones are a widely used screening test when diabetic ketoacidosis (DKA) is suspected in patients with hyperglycaemia. If urinary ketones are positive, patients are referred for further management, often inappropriately, as it is a poor surrogate for plasma ketones. Plasma β-Hydroxybutyrate (β-OHB) levels > 3mmol/l are diagnostic of DKA, while levels below 1 mmol/l are insignificant.

Objectives: To evaluate a hand-held electrochemical [point-of-care testing (POCT)] ketone monitor and compare it with the gold standard manual enzymatic method (MEM) for the detection of plasma ketones.

Method: In a prospective and comparative study, we evaluated the measurement of β-OHB by means of POCT and MEM in 61 consecutive samples from patients at Tygerberg and Karl Bremer Hospitals with suspected DKA. Capillary (for POCT) and plasma samples (for MEM) were obtained simultaneously and compared for accuracy. Precision was assessed with control samples.

Results: The POCT method was precise [coefficient of variation (CV) < 4.5%] and there was a good correlation between the two methods with r = 0.95. Regression analysis showed a proportional bias with POCT reading higher than MEM. However, when assessed at the relevant medical decision limits (β-OHB > 3 mmol/l and < 1 mmol/l), the total allowable error (bias plus imprecision) was not exceeded. Therefore, patients will still be classified correctly. The POCT had a sensitivity of 100% and specificity of 89% for DKA (β-OHB >3 mmol/l), while sensitivity was 100% and specificity 87.5%.at levels below 1 mmol/l.

Conclusion: The POCT device provided an accurate and precise result, and can be used as an alternative to MEM in the diagnosis of DKA.

25. Testosterone, insulin resistance and type 2 diabetes

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There is increased prevalence of hypogonadism in men with type 2 diabetes. International guidelines now recommend that testosterone should be measured in men with diabetes with symptoms suggestive of testosterone deficiency. Hypogonadism is a syndrome complex which comprises both the symptoms and biochemical evidence of testosterone deficiency. Testosterone deficiency is associated with reduced insulin sensitivity, hyperglycaemia, visceral adiposity, dyslipidaemia, endothelial dysfunction, inflammation and hypertension. All of these are key components of MS and type 2 diabetes. Low testosterone reduces glucose utilisation and increases fat deposition.

Epidemiological studies have found that low testosterone is a strong independent risk factor for MS and diabetes. Androgen suppression therapy for prostate carcinoma increases incident diabetes and worsens glycaemic control. Recent population- and disease-specific (including diabetes) studies have found that low testosterone at baseline is associated with an increase in all-cause and cardiovascular mortality.

Testosterone replacement therapy (TRT) in hypogonadal diabetic men in short-term trials reduces insulin resistance and percentage of body fat, and has beneficial effects on glycaemic control, WC, leptin, cholesterol, inflammatory markers, and sexual health. Androgen receptor sensitivity may affect the response to TRT. More recently, we have reported evidence that showed that TRT in hypogonadal men with type 2 diabetes improves survival.

Recent data support the role of testosterone in diabetic men, provided a diagnosis of hypogonadism is made and TRT carefully monitored.

POSTER PRESENTATIONS

Clinical posters

CP1. Dysglycaemia and lifestyle factors in Calabar South, East Nigeria

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Objective: To determine the relationship between dysglycaemia and lifestyle factors in residents of Calabar South, East Nigeria.

Method: A cross-sectional survey, comprising 1 134 subjects (645 males and 489 females), and representative of the entire population of Calabar metropolis aged 15-79 was studied. A multistage sampling method was applied to select the subjects for the study, which involved the selection of four wards by randomisation from the 22 wards of Calabar, and 50 households from each of the four wards, who were selected using the table of random numbers, from which eligible individuals aged 15-79 years from the 200 households selected were recruited. Using a modification of the WHO STEPS instrument, the information obtained included anthropometric indices, smoking, physical activity and alcohol intake. Anthropometric indices were expressed as a mean (SD). The comparison of means between groups was performed using independent Student's t-test. The strength of association between the quantitative variables was determined using Pearson's product-moment correlation coefficient. The level of significance was taken to be p-value < 0.05.

Results: The overall prevalence of dysglycaemia was 23.6% (24.2% males and 22.9% females), and undiagnosed diabetes mellitus was present in 6.5% (7.9% in males and 4.7% in females). Lifestyle factors significantly associated with dysglycaemia in this study were alcohol intake, smoking and physical inactivity. Others risk factors were a family history of diabetes mellitus and hypertension.

Conclusion: There is significant association between dysglycaemia and lifestyle factors.

CP2. Physical activity and hypertension in South African adults

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Objectives: Estimates suggest that approximately 6-million South Africans have hypertension, with half classified as stage 1 (mild). Mindful of the cost of lifelong drug therapy, the South African Hypertension Society guidelines suggest delaying drug therapy through lifestyle modification (increased physical activity and weight management) in all but those with the highest risk. This pilot study examined the relationship of BP with physical activity and bodyweight in black South African adults employed in physical occupations.

Method: Service industry employees (n = 52, 27% male, mean age of 42 years, SD 9.4) were recruited from their workplaces. Clinic BP was measured with an automated Omron® device and a 24-hour Mobil-O-Graph® ambulatory blood pressure monitor (ABPM) fitted. A waterproof triaxial accelerometer (GENEActiv®) was placed on the non-dominant wrist for seven-day physical activity measurement.

Results: A total of 53% (25 of 47) of the participants had ABPM in the hypertensive ranges. With either office BP or ABPM measures, > 70% of those with hypertension were stage 1. Overweight and obesity (BMI > 25kg/m^2) prevalence was 74%. We found that BP correlated with WHtR (p-value < 0.05). Physical activity (mean sum of vector magnitude, i.e. a summary measure of physical acitivity/day), age and WHtR accounted for 25% of the variance in daytime ABPM (adjusted R2).

Conclusion: We found that most hypertension cases are stage 1, and that both physical activity and WHtR are independently associated with BP. In future lifestyle intervention studies, accurate estimations of physical activity and obesity will be important to adequately assess the effectiveness of lifestyle modification in South Africa.

CP3. Correlate testosterone levels and the international Ageing Males' Symptoms questionnaire in African type 2 diabetic male patients

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University of Witwatersrand

Objectives: To describe testosterone status in African type 2 diabetic male patients at Chris Hani Baragwanath Academic Hospital and to validate the use of an internationally accepted questionnaire [Ageing Males' Symptoms (AMS questionnaire] to identify testosterone deficiency.

Method: Male patients with type 2 diabetes attending the diabetes clinic at Chris Hani Baragwanath Academic Hospital over a six-month period were asked to complete an AMS questionnaire. The questionnaire was made available in both English and *iZulu* format. Each patient underwent an early morning total testosterone blood test. This is a substudy of a PHD titled, *To describe the androgen status (testosterone and dehydroepiandrostenedione sulphate levels) in chronic diseases (diabetes, cardiac disease, autoimmune disease and renal failure) and to measure various clinical, psychological, biochemical, genetic and biometric markers before and after treatment with androgens.*

Results: The AMS questionnaire was not adequate in identifying the African male patient with type 2 diabetes and testosterone deficiency. Testosterone deficiency was found in half of our patients.

Conclusion: This study's result concur with previously published international data that approximately 50% of type 2 diabetic patients have testosterone deficiency. The study identifies the need for a screening tool other than the AMS questionnaire.

CP4. Opportunistic screening as a tool for identification of early diabetes mellitus in the sub-Saharan Africa population: are we targeting the right people?

KM Leshabari, M Matemu, R Bushiri, R Kalikawe
Walter Hospital, Dar Es Salaam, Tanzania

Objective: To estimate the prevalence of undiagnosed diabetics in residents of a typical cosmopolitan area in sub-Saharan Africa by using opportunistic screening technique.

Method: A high-risk cohort of residents who included relatives and friends of patients living with diabetes mellitus, at-risk staff at the municipal hospital, staff of the municipal director's office, as well as relatives of other patients seeking care for CVD at the municipal hospitals during National Diabetes Week were invited at random to participate in the study. FBG, as well as postprandial glycaemic measurements (using capillary blood measurements) were taken together with other cardiometabolic risk variables or opportunistic screening, and analysed using SAS® statistical software version 9.2. An alpha level of 5% was considered to be significant for disproving the null hypothesis. Screened positive respondents underwent further tests for confirmatory purposes.

Results: The study recruited a total of 189 participants. Three per cent of the screened participants were found to have blood glucose values in the diabetes range. One in three (32.86%) respondents reported that they had a positive family history of diabetes. There was a strong and positive correlation between a family history of diabetes and a family history of hypertension (γ = 0.6, p-value < 0.0001). BMI positively correlated with hypertension screening outcomes (γ = 0.266, p-value 0.0017), but not diabetes screening outcomes (γ = -0.01, p-value 0.9066).

Conclusion: The positive yield for diabetes screening was relatively low in this study population using conversional diagnostic tests. Glycaemic measurements in this study population were revealed to have a mixture distribution.

CP5. Age at initiation of diabetes-targeted screening in sub-Saharan Africa: how applicable are American Diabetes Association recommendations to African settings?

B Mphumuhila, K Leshabari, R Bushiri
Temeke Municipal Hospital, Dar Es Salaam, Tanzania

Objective: To estimate appropriate age at initiation of diabetes opportunistic screening in adults living in a typical cosmopolitan area of sub-Saharan Africa.

Method: A cross-sectional analytical targeted screening was conducted in a high-risk group in the Ilala Municipality in Dar es Salaam. Glycaemic measurements included fasting or two-hour postprandial glycaemia. Data were collected using a locally prevalidated questionnaire provided by the Tanzania Diabetes Association. Analysis was performed using SAS® version 9.2, and mainly involved Student's t-test and Pearson's product-moment correlation coefficient for continuous variables, as well as the chi-square test for categorical variables. Type 1 error rate was fixed at 5% level. Verbal informed consent was sought from participants before screening.

Results: One hundred and eighty-nine volunteers were randomly invited to participate in a targeted screening exercise. There was a slight female preponderance (50.5% vs. 49.5%). Trend test of association between age categories and screening outcomes for diabetes revealed a highly significant association ($\chi2$ = 8.5269, df = 1. p-value 0.0041). There were more people with pre-diabetes in the age group 30-45 years than in the age groups < 30 years or > 45 years ($\chi2$ = 35.63, df = 4, p-value < 0.01). Weak but significant association was present between age and BP (γ = 0.12, p-value < 0.0001), and BMI (γ = 0.23, p-value 0.004). No evidence of correlation between age and gender (p-value 0.45) was apparent, but when age was categorised according to American Diabetes Association recommendations, the association was strong and significant ($\chi2$ = 12.02, df = 2, p-value < 0.001).

Conclusion: Young age had weak correlation with pre-diabetes. Older individuals tested positive for diabetes than younger individuals.

CP6. Cardiometabolic risk factors in a high-risk adult population in Dar Es Salaam in Tanzania: what went wrong?

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Temeke Municipal Hospital, Dar Es Salaam, Tanzania

Objective: To compare the cardiometabolic risks of frank diabetics and a high-risk population group in a typical setting in sub-Saharan Africa.

Method: Cross-sectional, analytical targeted screening was conducted in a pre-defined high-risk group in Temeke Municipality in Dar es Salaam, Tanzania. Considered glycaemic measurements were either FBG or two-hour postprandial glucose measurements. Data were collected using a locally pre-validated questionnaire provided by the Tanzania Diabetes Association. Analysis was performed using SAS® version 9.2 and mainly involved Student's t-test and Pearson's correlation for continuous variables, as well as the chi-square test statistics for categorical variables. Type 1 error rate was fixed at 5% level. Verbal informed consent was sought from participants before screening.

Results: Compared to frank diabetics group (n = 35), those with negative screening results in respect of diabetes were likely to be younger than 30 years (p-value 0.02) and of male gender (p-value 0.05). Evidence of the difference between the two groups with respect to BMI (p-value 0.37), SBP (p-value 0.07) or DBP (p-value 0.08), as well as alcohol history (p-value 0.046), was barely significant or non-significant. Pearson's correlation between age and SBP, as well as DBP, was significant in the diabetic group (Y = 0.404, p-value < 0.01), but not for the high-risk group who were screened negative (0.30907, p-value 0.0801).

Conclusion: There appears to be a difference between high-risk groups who were negative in respect of screening for frank diabetics in this study population.

CP7. A retrospective study of myocardial perfusion imaging at Inkosi Albert Luthuli Central Hospital, Durban, over a 12-month period

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Objective: The relationship between myocardial perfusion imaging (MPI) abnormalities, diabetes mellitus and glucose control in South

African populations is unknown. It was hypothesised that in subjects undergoing MPI for suspected coronary artery disease (CAD), those with diabetes would have more extensive perfusion defects, and that diabetes control would influence MPI abnormalities. The objective was to examine the relationship between the severity of CAD diagnosed with MPI in subjects with and without diabetes, and to determine the relationship between diabetes control and the extent of CAD.

Method: The study was a retrospective chart review of 340 subjects in whom MPI scans were performed over a 12-month period.

Results: Subjects with diabetes had a higher prevalence of abnormal MPI, with more extensive ischaemia, compared to subjects without diabetes [85.6 vs. 68%, relative risk (RR) 1.26, p-value < 0.01]. Glycated $HbA_{1c} \geq 7\%$ was associated with a higher risk of abnormal MPI, with more extensive ischaemia, compared to that in those with diabetes and $HbA_{1c} < 7\%$ (RR 1.13, p-value 0.04), and that in subjects without diabetes (RR 1.33, p-value < 0.01).

Conclusion: Subjects with diabetes have more extensive myocardial ischaemia compared to subjects without diabetes. Furthermore, poorer diabetes control is associated with more abnormalities on MPI scanning.

CP8. The impact of gender differences on the risk of diabetes mellitus in high-risk group in a typical sub-Saharan African environment

K Leshabari, R Bushiri, B Mphumuhila, R Kalikawe
Walter Hospital, Dar Es Salaam, Tanzania

Objective: To assess the impact of gender differences on the risk of diabetes mellitus in an adult community in sub-Saharan Africa.

Method: Cross-sectional, analytical targeted screening was carried out in a high-risk group in the Ilala Municipality in Dar es Salaam, Tanzania. Glycaemic measurements included fasting and/or two-hour postprandial glycaemia. Several independent risk factors were compared with respect to gender. Analysis was carried out using SAS® version 9.2, and mainly involved Student's t-test for continuous variables, as well as chi-square test statistics for categorical variables. An alpha level of 5% was used to disprove the null hypothesis. Verbal informed consent was obtained from participants before screening.

Results: The study recruited a random high-risk sample of 189 participants. Females constituted 50.5% of the sample. During screening, 20.2% and 23.2% of participants screened positive for diabetes mellitus and hypertension, respectively. A positive diabetes family history was reported in 13.7% of the sample. Females recorded higher glycaemic levels than men (p-value 0.0399). No evidence was found of a statistical significant differences between gender and age (p-value 0.45), BMI (p-value 0.33), and SBP (p-value 0.37). Diabetes status showed a significant association with age ($\chi 2 = 12.2735$, df = 4, p-value 0.015). The correlation between diabetes family history and diabetes screening outcome were barely significant ($\gamma = 0.45$, p-value 0.058).

Conclusion: There was fairly high yield of positive screening outcome for both diabetes and hypertension in the sample. Females had higher careened glycaemic levels than males. Positive diabetes outcome was found in older than younger participants. Most participants revealed no previous history of diabetes screening.

CP9. Diabetes mellitus research: Tanga City, Tanzania

E Kitiku, S Moizali

Background: Tanga City has eight districts. Diabetes management and care are carried out in only two centres, Bombo and Teule District Hospitals. An important aspect of management and care is providing health education on nutrition, lifestyle modification and exercises; and conducting basic investigations into the self-management of diabetic patients in order to prevent diabetes complications. According to statistics at Bombo Hospital, there were 1 580 patients between January 2004 and March 2012. There were more females than males. The monthly record of attendance included patients on injection insulin, type 1 patients, children younger than 18 years, patients on oral hypoglycemic drugs, patients on special diets and who exercise, and those with diabetic complications.

Method: Activities performed in the diabetes clinic include providing health education on diabetes and its general predisposing factors, as well as on diet, lifestyle changes, and the importance of exercise, self-management, investigations and screening for diabetes complications, treatment, BMI calculations, the taking of vital signs, completing follow-up forms and general management and care, which are all performed at the Bombo Region Referral Hospital.

Results: Bombo Hospital had 1 580 patients between 2004 and 2012. Other findings were that male diabetes patients were more underweight than females and that females diabetes patients were more obese than males, and very obese patients were female. More than 75% of the diabetes patients were hypertensive. Education on a healthy diet and dietary modification and the importance of exercise is needed. More than 50% of diabetes patients has uncontrolled blood glucose. More than 85% type 1 and type 2 diabetes mellitus patients on injection insulin were underweight. Poverty and cultural beliefs contribute to this.

Conclusion: According to data obtained through self-administered oral questions, interviews and observations, 95% of diabetes patients didn't know the importance of modified management and care with respect to diet, and self-management with regard to injections, storage, injection technique and sites, or even what to do in the event of hypoglycemia. Only 5% of health personnel had an idea of how to advise diabetes patients to modify their diet or lifestyle. Most of them did not have an idea of what to suggest. Obstacles hindering diabetes services include poor health personnel participation in diabetes services, a shortage of staff, the fact that the community does not have information on diabetes, predisposing factors, signs, symptoms and the prevention thereof. Diabetes services are not available in dispensaries and district hospitals. Staff are not motivated or incentivised. It is recommended that workers and communities should be trained with respect to diabetes services so that all can test for diabetes mellitus and be familiar with it.

CP10. Lipoma of the clitoris presenting as a disorder of sex development: a case report

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Introduction: The term, disorders of sex development (DSD), is used to describe conditions in which development of chromosomal, gonadal, or anatomical sex is atypical. A working diagnosis of DSD should be followed using timely investigations to enable management decisions to be taken without undue delay.

Case report: A three-day-old infant presented to the neonatal ward at Dr George Mukhari Hospital and was assessed as having an enlarged clitoris. The mother was 28 years of age, and had not used any medications during pregnancy and had no evidence of virilisation. An examination of the infant revealed no abnormalities other than an enlarged clitoris of 1.8 cm, with no palpable gonads, and a normal anal orifice. The birthweight was 3.3 kg, and the length and head circumference were normal for gestational age. The infant was not dehydrated, with normal BP. A pelvic ultrasound confirmed the presence of a uterus. A working diagnosis of DSD was made owing to congenital adrenal hyperplasia. 17-α-hydroxyprogesterone levels at age five days were 16 nmol/l, with testosterone levels of 0.1 nmol/l. Repeat 17-α-hydroxyprogesterone levels at one month of age were 2.5 nmol/l. Chromosomes results were 46 XX. The infant was referred to the urologist, who performed a clitoral reduction. A biopsy of the clitoral body revealed a lipoma. The external genitalia appearance was satisfactory one month postoperatively.

Conclusion: Lipomas of the vulva are rare and typically occur in adults. The clitoromegaly that was observed raised suspicions of DSD, which turned out to be incorrect.

CP11. Pseudohypoparathyroidism type IA: the Chris Hani Baragwanath Hospital series

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Chris Hani Baragwamnath Academic Hospital; and University of the Witwatersrand

Objective: Pseudohypoparathyroidism (PHP) is a rare disorder (1:100 000), first described in 1942 by Albright et al. It is characterised by hypocalcaemia and hyperphosphataemia due to resistance to the parathyroid hormone (PTH). Various types of PHP have been described. It may be due to an abnormality involving the α-subunit of the stimulatory G-protein, i.e. type I, or a defect involving adenylate cyclase, i.e. type II. Type IA is the most common, and is associated with a typical phenotype, known as Albright's hereditary osteodystrophy (AHO). The objective was to report the first cohort of PHP-IA patients in the South African population.

Method: Eight black patients, five females and three males, aged six months to 28 years at the time of initial presentation, attending the Endocrine Clinic at Chris Hani Baragwanath Academic Hospital, were studied.

Their presenting symptoms, family history, phenotypic characteristics, biochemical and hormonal profiles and radiological findings were documented.

Results: Patients were initially hypocalcaemic, with elevated PTH levels. Regarding other markers of hormone resistance, TSH levels were raised in five of the patients in the presence of normal thyroid hormone levels (62.5%), and luteinising hormone (LH) levels were elevated in three patients (37.5%). All of the patients had one or more features of AHO, but only three (37.5%) had brachymetacarpalia. Intracranial calcifications were documented in six patients (75%) by CT scanning.

Conclusion: This is the first documented cohort of patients with PHP in South Africa.

CP12. A rare case of Cushing's syndrome

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A 42-year-old male patient was referred by a specialist physician with features of Cushing's syndrome, as well as recently diagnosed hypertension and type 2 diabetes mellitus. Clinical features included moon facies, a dorsicervical hump, telangiectasia, proximal myopathy, centripetal obesity and purple striae. Special investigations revealed an elevated 24-hour urinary-free cortisol with elevated midnight salivary cortisol, and failure to suppress using the low-dose dexamethasone suppression test. ACTH values were also elevated. Magnetic resonance imaging showed a normal pituitary gland with only a right-sided antrochoanal polyp of 1.5 x 1 cm, that extended into the middle ethmoidal cells. Contrasted CTs of the chest and abdomen to evaluate for an ectopic ACTH focus were performed and found to be normal. A technetium-99m ^{scan} was then performed which demonstrated a mass in the right paranasal area with somatostatin receptors. Surgical removal and a histopathological examination confirmed it to be an ACTH-secreting adenoma.

CP13. Are African children with diabetes adequately supported by their families?

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Objectives: Coping with diabetes control is difficult for newly diagnosed and experienced patients; the former because of the complex technical requirements that they suddenly have to face, and the latter because of constant repetition in respect of tests, insulin administration and dietary vigilance. Some of our patients have stored insulin inappropriately or measured it incorrectly. Children need to be able to give their own insulin or conduct home blood glucose monitoring without help before they can be expected to cope with such complex tasks. The objective was to establish whether or not patients are adequately supported by their family in terms of giving injections and conducting monitoring.

Method: Patients attending the paediatric and young adult diabetic clinics were interviewed. Permission was granted by the ethics committee and informed consent obtained.

Results: Forty subjects were interviewed. Ages varied from 7-31 years. Twenty-five were younger than 18 years of age. The duration of diabetes varied from three months to 10 years in paediatric patients. Of 25 patients, 17 measured the insulin themselves, while five mothers did so. Twenty children then administered the injection. The dosages were checked in seven cases. The mothers of four children younger than 10 years measured their insulin, but the children injected it themselves. Eight of the nine children aged 1-15 years measured and injected their insulin themselves. However, the dosages were checked by an adult in only two cases.

Conclusion: It is appropriate that older children take responsibility for measuring and injecting their insulin. However, younger children do not seem to be sufficiently supported by their families.

CP14. A case of primary pigmented nodular adrenocortical disease

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Primary pigmented nodular adrenocortical disease (PPNAD) is a rare cause of Cushing's syndrome. The various forms of nodular adrenocortical disease account for 10% of cases of ACTH-independent Cushing's syndrome, and PPNAD comprises a small fraction thereof.

A 14-year-old male was referred to the endocrine clinic at Chris Hani Baragwanath Hospital by the paediatric department with clinical features of Cushing's syndrome. His older brother had a history of having been managed surgically for Cushing's syndrome. Biochemistry confirmed the diagnosis of Cushing's syndrome, as evidenced by an elevated midnight cortisol of 566 nmol/l (138-220 nmol/l), an elevated urine-free cortisol of 1 052 nmol/24 hours (57.7-806.8 nmol/24 hours), as well as failure of suppression on the 1 mg overnight dexamethasone suppression test.

Furthermore, a paradoxical increase in his urinary cortisol excretion followed the low-dose dexamethasone suppression test, rising from 680 nmol/24 hours to 1649 nmol/24 hours, characteristic of PPNAD. Adrenal aetiology was supported by an undetectable ACTH level.

CT imaging of the adrenal glands showed no evidence of either an adenoma or bilateral adrenal hyperplasia. However, adrenal vein sampling revealed bilateral marked elevations of cortisol bilaterally, as compared to peripheral cortisol levels (right adrenal vein 4 265 nmol/l, left adrenal vein 1 1185 nmol/l, and peripheral 455 nmol/l).

The patient underwent bilateral laparoscopic adrenalectomy. Histology confirmed a diagnosis of primary pigmented nodular adrenal hyperplasia. The patient displayed no clinical features of Carney complex. Genetic testing was not undertaken.

PPNAD is a rare cause of ACTH-independent Cushing's syndrome, but remains an important consideration, especially since radiological features may be misleading.

CP15. Disseminated large cell neuroendocrine carcinoma associated with ectopic adrenocorticotropic hormone secretion

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EAS secretion is associated with a heterogenous spectrum of NETs, as well as non-NET tumours. Both EAS and NET are relatively uncommon. LCNEC is considered to be a poorly differentiated NET and is very rarely associated with EAS. Only case reports of EAS associated with LCNEC have been documented. We present a case of disseminated LCNEC associated with EAS. The LCNEC was diagnosed on bone marrow trephine biopsy, and the likely but unproven primary was a NET arising from the superior mediastinum, which also caused superior vena cava syndrome at presentation.

CP16. Diabetes care via telemedicine in South Africa

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Objective: Type 2 diabetes mellitus is a national epidemic. Excellent treatment algorithms and medications exist, yet the ability to achieve SEMDSA-specified glycaemic targets remains poor for a number of reasons, including heavy reliance on self-care, inappropriate systems, patient and doctor barriers to insulin initiation, and intensification and the requirement for data-driven therapy modification.

Method: Four hundred and eighty insulinised type 2 diabetes mellitus patients volunteered to participate. After an initial structured face-to-face education session with a Doctor of Nursing Education (DNE), ongoing data-driven instruction on dose titration to reach SEMDSA-defined glycaemic targets and coaching on meal planning, exercise and insulin use were carried out via DNEs in a call centre operating on the Guidepost® software platform. Patients submitted structured self-monitoring of glucose readings to the platform via SMS. The frequency of structured testing and clinical interactions varied per patient.

Results: The overall uptake and acceptability of the programme was high, with over 26 000 glucose readings submitted. Patient and doctor feedback was positive, with 88% retention over 18 weeks. Target range pre-meal blood glucose values between 4 and 7 mmol/l increased 62% from baseline to week 18, and the time spent in the hyperglycaemic (blood glucose > 11 mmol/l) and hypoglycaemic (≤ 3.9 mmol/l) ranges declined by 46% and 25%, respectively.

Conclusion: A patient-centered diabetes care and education telemedicine programme in insulin-treated subjects with type 2 diabetes mellitus, that utilises a combination of structured testing, SMS-based data input, periodic data-driven telephonic coaching and validated learning has a good uptake, is acceptable to patients and healthcare providers, and results in improved glycaemia.

CP17. To determine the precalence of lipodystriphy and metabolic changes in human immunodeficiency virus-infected patients on highly active antiretroviral therapy at Ilala HIV clinics between 2009 and 2010

D Narciss
Dar Es Salaam

Objective: MS refers to a clustering of cardiovascular risk factors that include diabetes, obesity, ageing, physical inactivity, dyslipidaemia, hypertension and lipodystrophy. Lipodystrophy is more common in people living with acquired immune deficiency syndrome (AIDS) using highly active antiretroviral therapy (HAART), and there is little data on MS in people living with AIDS using HAART in our environment. This study was carried out to determine the prevalence of lipodystrophy and metabolic changes in HIV-infected patients on HAART at Ilala HIV clinics between 2009 and 2010.

Method: A retrospective study was performed and analysed using SPSS® programme version 15, whereby 652 people older than 18 years living with HIV/AIDS, who had been tested for lipids profile and using HAART for not less than nine months, were recruited from five care and treatment centres out of 13 centres in Ilala District in Dar es Salaam, Tanzania. This study was performed for one year from January 2011 to December 2011.

Results: Of 652 people living with HIV/AIDS, 332 (50.9%) were females and 320 (49.1) males. Approximately 60% of the participants were obese, and three quarters (75) of the obese participants were aged 35-54 years (p-value < 0.01). Of the 156 participants with elevated BP, only 37 (23.7%) were on antihypertensive drugs, and there were serum triglycerides in two thirds of participants with elevated BP aged 35-54 years (p-value < 0.01).The magnitude of MS in the protease inhibitor (PI)-based regimen was significantly higher than that in the

non-nucleoside reverse-transcriptase inhibitors (NNRTI)-based regimens, in those participants who had been using HAART for more than 18 months (p-value < 0.01).

Conclusion: This study observed that there was high prevalence of MS by 42% in people living with AIDS using HAART, with a strong association of person, age group, dyslipidaemia and duration in both NNRTI- and PI-based regimens.

CP18. Diabetes self-management education programmes in high- and low-mortality developing countries

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Objective: Diabetes mellitus is often considered to be a disease of the affluent, but is increasingly becoming a burden for the developing countries as well. Self-management education is a key factor in the care of diabetic patients. However, its implementation in developing countries is not well documented. The objective was to identify and synthesise published literature on diabetes self-management education interventions in high- and low-mortality developing countries to determine current practices, identify gaps and assess effectiveness.

Method: PubMed, Medline, PsycInfo, PsycArticles and Google Scholar were searched for peer-reviewed articles on type 2 diabetes or pre-diabetes published in English between 2009 and 2013. The World Bank and WHO burden of disease criteria were applied to distinguish between developing countries with high and low mortality. Information on intervention characteristics, cultural sensitivity and access by people with low literacy was extracted using a validated check-list.

Results: Twenty-three studies described in 25 articles and three reviews were identified. Studies from high-mortality countries were mostly observational, those from low mortality, mostly experimental. The interventions were generally effective on behavioural change and glycaemic control by patients on short-term follow-up (≤ 6 months). Information about the theoretical basis of diabetes self-management education interventions was often missing. Fifty-seven per cent of studies reported on the cultural tailoring of interventions. Only 17% reported on the training of providers, and only 39% of programmes were accessible to people with low literacy.

Conclusion: Diabetes self-management education programmes in developing countries are effective in the short-term, but must be tailored to cultural aspects of the target population.

BASIC SCIENCE POSTERS

BS1. Effects of commercially available sugar substitutes in an experimentally induced rat model of type 2 diabetes

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Diabetic patients increasingly substitute sucrose with non-nutritive sweeteners (NNS). Most studies have been conducted using NNS in their pure form, although this is not what people consume in general. Hence, the present study investigated the effects of commercially available NNS in a type 2 diabetes rat model. Six-week-old male Sprague-Dawely rats were randomly divided into seven groups: normal control, diabetic control, diabetic aspartame diabetic sucralose, diabetic cyclamate, diabetic saccharin and diabetic stevia. Type 2 diabetes was induced experimentally in all groups, except the normal control group. Animals with blood glucose levels > 300 mg/dl were considered to be diabetic. During the 13-week experimental period, the two control groups were given normal drinking water, while the other groups received aspartame-, sucralose-, sodium cyclamate-, saccharin- and stevia-based NNS solutions *ad libitum*, respectively, at a concentration equivalent to the sweetness of a 10% sucrose solution. Significantly increased food intake was only observed in the diabetic cyclamate group, while increased fluid intake was observed in both diabetic cyclamate and diabetic stevia groups. Alkaline phosphatase (ALP) was significantly increased in both diabetic sucralose and diabetic saccharin groups, while lactose dehydrogenase (LDH) was elevated in the diabetic sucralose and diabetic stevia groups. All the treated groups had higher but nonsignificantly elevated non-FBG levels than the diabetic control group. The results of this study indicate that some of the commercially available NNS may cause increased body weight, polydipsia, polyphagia, serum ALP and LDH in type 2 diabetes, and may worsen the diabetic condition in the long term.

BS2. Effects of commercially available non-nutritive sweeteners on diabetes-related parameters in non-diabetic rats

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Type 2 diabetes is a global health problem, and continues to affect more and more people. In South Africa, the epidemiological transition has led to lifestyle changes, such as unhealthy diet and reduced physical activity, which has led to an increase in the prevalence of type 2 diabetes. Overweight, obese and diabetic individuals substitute sucrose with NNS to reduce their total calorie intake, and also to avoid the quick spike of blood glucose levels and other associated complications.

The present study aimed to examine the effects of commercially available NNS on diabetes-related parameters in non-diabetic rats. Six- to seven-week-old male Sprague-Dawley rats were randomly divided into seven groups: control, sucrose, aspartame, sucralose, stevia, cyclamate and saccharin. The control group received normal drinking water, while the sucrose, aspartame, sucralose, stevia, cyclamate and saccharin groups received sucrose, aspartame, sucralose, stevia, sodium cyclamate and saccharin-based NNS, respectively. Each NNS was used at a concentration equivalent to the sweetness of 10% sucrose. At the end of the five-week experimental period, most of the diabetes-related parameters had worsened in the aspartame- and cyclamate-consuming groups, while opposite results were obtained for the stevia-fed group, compared to the control and sucrose-fed groups. No significant effects were observed in the sucralose- and saccharin-fed groups. The data of this study suggest that aspartame- and cyclamate-containing sweeteners may not be suitable for diabetic patients when stevia can be a better NNS with anti-diabetic potential.

BS3. Functional rescue of inactivating mutations of the human G protein-coupled receptors and luteinising hormone receptors with cell-permeant small molecules: a new pharmacological target

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Mutations in G protein-coupled receptors (GPCRs) have been identified for almost all endocrine hormone-signalling deficiencies. Although some inactivating mutations impair ligand binding or coupling to signalling pathways, the majority cause protein misfolding, consequent failure of translocation to the cell membrane and intracellular degradation. Some cell-permeant ligands (pharmacological chaperones) have been shown to "rescue" the cell surface expression of misfolded mutant GPCRs by stabilising their correct folding within the endoplasmic reticulum. We examined the ability of GnRH small-molecule antagonists and allosteric small-molecule LH agonists to rescue poor expression and restore signalling of mutant human GnRH and LH receptors. The majority of mutant receptors were retained in the cytoplasm while wild-type receptors were localised at the cell membrane. Incubation of cells expressing the mutant receptors with cell-permeant small molecules increased receptor expression and cell surface localisation. Moreover, stimulation of signalling with natural hormones was restored. We also showed that the LH allosteric agonist was able to restore signalling to mutant receptors that were incapable of binding LH. This is the first demonstration of a small-molecule GPCR allosteric agonist that functionally rescues both intracellularly retained and ligand-binding-deficient mutant LH receptors. This is particularly pertinent for the treatment of infertile patients bearing LH mutations for whom there is no current therapy.

BS4. Exploring the molecular basis and phenotypic spectrum of reproductive disorders in South Africa

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Objective: Congenital hypogoandotropic hypogonadism (CHH) is a reproductive endocrine disorder caused by absent gonadotropin-releasing hormone (GnRH) secretion or action. This rare genetic disorder (1:10 000) is characterised by absent or incomplete puberty, with resulting infertility. This disorder has a strong genetic component with 20 disease genes discovered to date, yet no known genetic cause is attributed to two thirds of CHH patients. This project aimed to elucidate the genetic basis of reproductive disorders in South African CHH patients, and explore the biology of identified human mutations using cutting-edge approaches. This will be accomplished via a partnership between groups with complementary expertise in GnRH biology, clinical medicine and human genetics.

Method: The method involved detailed clinical phenotyping studies, next-generation sequencing platforms (exome sequencing), bioinformatics, and in vitro characterisation of identified mutations.

Results: The initial bioinfomatic pipeline has been developed to specifically filter exome data and identify high-quality novel candidate genes that relate to reproduction. Presently, confirmation studies are underway to characterise three novel genes. Efforts to identify additional clinical South African partners, i.e. endocrinologists, pediatricians and geneticists, for collaboration, is ongoing.

Conclusion: We believe that this collaboration will identify novel genes that underlie CHH, and will reveal new areas in the biology of reproduction via the work of the South African team. Also, this network will provide a resource for providers who care for CHH patients to address clinical questions and problems relating to this rare disorder. Ultimately, we aim to use this scientific insight to identify novel biomarkers and to target therapies for infertility that will benefit patients and families.

BS5 The insulin-mimetic agent, vanadate, impedes lipid accumulation in adipose-derived stem cells

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Objective: Vanadate has been described as an insulin-mimetic agent because vanadate treatment improves glucose homeostasis in diabetic patients. Although vanadate does not bind to the insulin receptor, it activates insulin signalling by inhibiting protein tyrosine phosphatase 1B (PTP1B), a negative regulator of the insulin receptor pathway. Activation of the insulin signalling pathway leads to the synthesis and accumulation of lipids in order to store energy and the differentiation of preadipocytes into mature adipocytes. Previously conflicting results have been reported on the role of PTP1B during differentiation of immortalised 3T3-L1 preadipocytes into mature adipocytes. In one study, PTP1B knockdown improved adipogenesis, while in another, the PTP1B inhibitor, vanadate, prevented adipogenesis. These conflicting reports led us to investigate the effects of vanadate on adult, primary, adipose-derived stem cells (ADSCs), as immortalised cell lines such as 3T3-L1 have disrupted cell cycles which may influence differentiation.

Method: ADSCs were isolated from subcutaneous and perirenal visceral rat tissue, cultured, differentiated into adipocytes in the presence or absence of vanadate, and followed by quantification of the lipid content by Oil Red O® staining.

Results: Vanadate significantly reduced lipid accumulation during adipogenic differentiation in subcutaneous and perirenal visceral ADSCs by 45% (SD 0.7%, p-value < 0.05) and 46% (SD 3%, p-value < 0.05) respectively, in three independent experiments.

Conclusion: Our results demonstrated that the PTP1B inhibitor, vanadate, reduced lipid accumulation, in contrast to that in the PTP1B knockdown studies. This suggests that although vanadate may inhibit PTP1B, the effects of vanadate on lipid accumulation may be mediated via the modulation of other pathways.