

SEMDSA Congress 2021 - Oral presentations

SESSION 1 – Friday, 26 March 2021

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Associations of glycated albumin and fructosamine with dysglycaemia in urban black South Africans

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Background: Shortcomings with oral glucose tolerance tests (OGTTs) have led to research on glycated albumin (GA) and fructosamine as alternate tests for diabetes screening. This study examined the associations of GA and fructosamine in urban black South Africans.

Methods: Based on OGTTs, glycaemic status included 1) normal glucose, 2) dysglycaemia (impaired fasting glycaemia, impaired glucose tolerance, newly diagnosed diabetes), and 3) known diabetes.

Results: Among 392 men and 700 women, aged > 21 years, mean GA and fructosamine levels increased significantly by age and higher glycaemic status. Mean GA, but not fructosamine, levels were significantly higher in women vs men and BMI (kg/m²) ≥ 30 (obese) vs < 30 (non-obese). For dysglycaemia, correlations of GA and fructosamine with fasting and 2-hour glucose levels were higher in obese (0.342–0.449) vs non-obese (0.094–0.163). Optimal GA threshold to identify dysglycaemia was 15.35% and comparable, but with lower sensitivity (0.54, 95% CI: 0.46–0.62) and specificity (0.55, 0.47–0.62), to the 15–16% reported in Asian populations. For fructosamine, the optimal cut-point was 221.50 μmol/l and approximated the ≥ 230 μmol/l described in the literature. Dysglycaemia and known diabetes were significantly associated with GA and fructosamine in models adjusted for age, gender, and obesity. Obesity was significant only in the model with fructosamine (β coefficient: -10.406, -19.102 to -1.710).

Conclusion: Although the associations of GA and fructosamine in this study, generally accorded with the literature, these were not optimal. Further research is required to clearly elucidate the utility of GA and fructosamine, and the likely effects of adiposity on their diagnostic performance in South Africans.

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Waist circumference cut-points for the prediction of incident dysglycaemia and type 2 diabetes in middle-aged African men and women

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Background: The study aimed to determine the waist circumference (WC) cut-points for the prediction of incident dysglycaemia and type 2 diabetes (T2D) in black South African (SA) men and women, and compare these to advocated Europid cut-points (IDF).

Methods: Black SA men ($n = 502$) and women ($n = 527$) from the AWI-Gen study who had normal or impaired fasting glucose (WHO criteria) and WC measures (2011–2015) were followed up between 2017–2018. At follow-up, glucose tolerance was assessed using an oral glucose tolerance test (WHO criteria). The Youden index was used to determine the optimal cut-point of WC to predict incident dysglycaemia and T2D.

Results: At follow-up, the incidence of dysglycaemia and T2D was 17.0 (95% confidence interval: 13.4–28.1)% and 4.4 (2.5–5.9)% in men, and 24.0 (19.9–41.1)% and 10.7 (7.8–16.8)% in women, respectively. In men, the optimal WC cut-point for dysglycaemia and T2D was the same at 96.8 cm (sensitivity 56 and 70%, specificity 74 and 70%, respectively). In women, the WC cut-point for dysglycaemia was 91.8 cm (sensitivity 86%, specificity 37%) and for T2D was 95.8 cm (sensitivity 85%, specificity 45%). The IDF Europid cut-point of 94 cm in men performed similarly, while the IDF Europid cut-point of 80 cm in women had higher sensitivity (97 and 100%), but lower specificity (12 and 11%) to predict dysglycaemia and T2D, respectively.

Conclusion: We show for the first time using prospective cohort data from Africa that WC using African-specific cut-points performs better than the IDF Europid cut-points to predict incident dysglycaemia and T2D.

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Could a glucocorticoid receptor polymorphism be protective against hypothalamic-pituitary-adrenal axis suppression in asthmatic children on corticosteroids?

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Background: Asthmatic children on corticosteroids with single nucleotide polymorphisms (SNPs) rs242941 & rs1876828 of the corticotrophin-releasing hormone receptor 1 (CRHR1) and rs41423247 of the glucocorticoid receptor (NR3C1) gene were found to have lower and higher basal cortisol (C) levels respectively. A study was performed to determine whether these SNPs are associated with hypothalamic-pituitary-adrenal axis suppression (HPAS) in asthmatic school children on corticosteroids.

Methods: DNA was extracted from saliva of 96 asthmatic children. HPAS was diagnosed if C was < 83 nmol/l or the post-metyrapone ACTH (PACTH) < 106 pg/ml and 11 deoxycortisol (11DOC) < 208 nmol/l and 11DOC+C < 400 nmol/l. 36 children were classified as suppressed. According to their PACTH, 29 were sub-classified into a middle and 31 into a high ACTH response group.

Results: Only rs41423247 was inversely associated with HPAS (OR = 0.27 [0.06–0.90]). Its CC genotype was associated with BMI z-score (effect size = 1.04, $p = 0.049$). GC genotype was inversely associated with HPAS (log odds = -1.28, $p = 0.021$). \sqrt{PACTH} was associated with the CC (effect size = 10.85, $p = 0.005$) and the GC genotype (effect size = 4.06, $p = 0.023$). This effect is inherited in an autosomal dominant fashion (effect size = 4.79, $p = 0.005$). In the high PACTH response group, both genotypes affected the ACTH response (effect sizes 1.41 and 15.46; p -values 0.023 and < 2x10⁻²⁶ for the GC and CC genotype respectively).

Conclusions: Rs41423247 was found to be protective against HPAS. The CC genotype is associated with a higher PACTH response.

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Metabolic Syndrome and impact of HIV infection in urban Black South Africans: the Durban Diabetes Study (DDS)

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Background: The Durban Diabetes Study (DDS), a population-based cross-sectional study of participants aged ≥ 18 years, allowed for determination of the prevalence of metabolic syndrome (MetS), and the impact of HIV infection and antiretroviral treatment (ART).

Methods: All subjects had demographic, anthropometric and laboratory tests. HIV infection was determined by ELISA; current ART was self-reported. Participants were categorized as having no HIV (HIV -), untreated HIV (HIV+ ART -) and ART-treated HIV (HIV+ ART+). Prevalence of MetS, using the Joint Interim Statement (JIS) criteria, was calculated for the total group, and when stratified by HIV and ART status.

Results: In the total group ($n = 1178$; 843 women), 43.7% ($n = 515$) were HIV+. The overall prevalence of MetS was 29.9% ($n = 353$), higher in women (38%) than in men (9.8%, $p = 0.000$). Peak prevalence was in ≥ 65 year group in women (71.9%) and men (26.3%). The most frequent individual MetS component was elevated waist circumference (WC) in women and abnormal blood pressure (BP) in men. MetS was more frequent in the HIV- (33.3%) than HIV+ group (26.5%), and in HIV+ ART- (62.5%) vs HIV+ ART+ (28.6%) group. In the HIV+ group, there was a female preponderance for MetS (29.7% vs 11.4%), peak prevalence was in 55–64 year group, and elevated WC was the most frequent individual component.

Conclusion: In this urban black South African population, the prevalence of MetS was high overall, and higher in the HIV-group. ART was not associated with a higher MetS prevalence in HIV+ participants.

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Sex differences in type 2 diabetes risk and the association with total and regional adiposity

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Background: There is little data on sex differences in the pathophysiology of type 2 diabetes in African populations. Therefore, the study aimed to compare insulin sensitivity, clearance and beta-cell function between middle-aged black South African men and women and to explore sex-specific associations with total and regional adiposity.

Methods: This cross-sectional study included 804 black South African men ($n = 388$) and women ($n = 416$). Dual-energy x-ray absorptiometry was used to measure total and regional adiposity. Insulin sensitivity (Matsuda index), secretion (C-peptide index) and clearance (C-peptide/insulin ratio) were estimated from an oral glucose tolerance test.

Results: Linked to their higher body fatness (44 ± 4.8 vs 26.3 ± 6.2 %, $p < 0.001$), women were less insulin sensitive than men (median (25th–75th percentile): 5.0 (3.1–8.4) vs 7.1 (3.6–13.2) mg/mUmin, $p < 0.001$), but compensated with a higher insulin secretion (2.73 (1.56–4.57) vs 2.25 (1.27–3.79) ng/mmol, $p = 0.002$) and lower insulin clearance (0.20 (0.15–0.27) vs 0.28 (0.20–0.39) ng/mLU, $p < 0.001$). However, after adjusting fat mass index, men were less insulin sensitive than women ($p < 0.001$), with the strength of the association with total and central adiposity being greater in men than women ($p < 0.001$ for interactions). Further, the association between total adiposity and type 2 diabetes risk was also greater in men than women (relative risk ratio (95% confidence interval): 2.05 (1.42–2.96), $p < 0.001$ vs 1.38 (1.03–1.85), $p = 0.031$).

Conclusion: These findings suggest that with increasing adiposity, particularly increased centralisation of body fat, black African men will be at greater risk for type 2 diabetes than their female counterparts.

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Greater barriers exist in the diagnosis and management of Addison's in sub-Saharan Africa compared with the Middle East

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Background: The burden and management of Addison's disease (AD) in Africa have not been well documented. We hypothesised that barriers in the diagnosis and management exist.

Methods: We conducted an online survey of a large pool of medical practitioners with AD management experience from Africa and the Middle East, using a commercial database.

Results: Of the 1334 responses received, 589 were complete, 332 respondents confirmed that they manage patients with hypoadrenalism. Of the 5787 patients reported with hypoadrenalism (2746 females, 3041 males), 2302 had primary hypoadrenalism (AD). The likely causes of AD in sub-Saharan Africa (SSA) versus Middle East North Africa (MENA) included autoimmune disease (20% versus 60.3%; $p < 0.001$), tuberculosis (34% versus 4.1%; $p < 0.001$), AIDS (29.8% versus 1%; $p < 0.001$). Most patients, 83.7% presented with typical AD symptoms, however (16%) presented in an Addisonian crisis in both regions. Non-availability of diagnostic tests across both regions included tetracosactide in at least 45.7% by serum cortisol as a surrogate marker for ACTH stimulation, adrenal antibodies (64.1%), and adrenal CT scans (49.1%). Hydrocortisone monotherapy due to poor availability of fludrocortisone in SSA was 588 (39.9%), versus MENA 780 (94.2%); $p < 0.001$. Only 241 patients in SSA (16.4%) versus 493 (59.6%) MENA patients; $p < 0.001$ used medical emergency identification.

Conclusion: We identified significant challenges in the diagnosis and management of AD in SSA, compared with the MENA region, which may likely herald high mortality. Autoimmunity as a cause for AD predominates in the MENA, whereas tuberculosis and AIDS predominate in SSA.

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The clinical characteristics, presentation, and treatment outcomes of prolactinomas at Groote Schuur hospital

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Background: Prolactin-secreting tumours are the commonest type of pituitary tumour, however, there remains sparse data from Africa, and South Africa, on the clinical presentation, hormonal deficiencies and treatment outcomes.

Methods: A retrospective study of all patients with a diagnosis of prolactinoma attending the Endocrine and Pituitary Clinics at Groote Schuur Hospital over a 12-month period. Patients folders were reviewed to retrieve the following: demographic data, clinical presentation, prolactinoma phenotype, hormonal deficiencies, treatment modalities and clinical outcomes.

Results: 52 patients were included in this study. A macroprolactinoma was present in 67.3% ($n = 35$) and 32.7% ($n = 17$) of patients had a microprolactinoma. In the macroprolactinoma group: common presenting symptoms were headache 88.6% ($n = 33$), altered vision 40% ($n = 14$) and, in females, amenorrhea 63.6% ($n = 14$). In the microprolactinoma group the common presenting symptoms included amenorrhea 75% ($n = 12$), galactorrhea 70.6% ($n = 12$), headache 64.7% ($n = 11$). On presentation, patients with a macroadenoma had hypogonadism 73.1% ($n = 19$), hypothyroidism 53.8% ($n = 14$) and hypoadrenalism 30% ($n = 8$). Over 50% of patients with a giant adenoma had panhypopituitarism with hypogonadism in 100%, hypothyroidism in 77.8% ($n = 7$) and hypoadrenalism in 66.7% ($n = 6$). Hormonal deficiencies in the microadenoma group on presentation included hypogonadism 64.7% ($n = 11$), hypothyroidism 35.3% ($n = 6$) and one patient had hypoadrenalism. After a median follow-up of 46.5 months, the median prolactin level decreased from 322.5 ug/l (94.0–4282.0) at presentation to 17.5 ug/l (8.6–82.5) at follow-up. In parallel there was a reduction of 12.2 ± 9.7 mm in tumour size after a mean of 59.8 ± 53.3 months.

Conclusion: Most patients with a prolactinoma are symptomatic and have at least one hormone deficiency on presentation. With medical management, most patients experienced a reduction in prolactin levels, a reduction in tumour size and resolution of hypogonadism.

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HbA1c for the diagnosis of diabetes in black South Africans: impact of anaemia, HIV infection, and antiretroviral treatment (ART)

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Objective: South Africa has amongst the highest burden of HIV infection and anaemia globally. These conditions may cause glycated haemoglobin (HbA1c) to falsely over- or underestimate glycaemia, but have not been investigated in African populations. We assessed the association of anaemia, HIV infection, and antiretroviral therapy (ART) with HbA1c and implications for the detection and diagnosis of diabetes in a South African population.

Research Design and Methods: In 1067 participants without history of diabetes diagnosis in the Durban Diabetes Study, a population-based cross-sectional survey in the eThekweni municipality South Africa, we conducted HbA1c, oral glucose tolerance test (OGTT), HIV diagnostic tests, and full blood count measurements. Crude and adjusted linear regression models were fitted to obtain the absolute mean difference in HbA1c between subgroups of participants.

Results: After adjustment for plasma glucose measures and potential confounders, normocytic and microcytic anaemia were associated with higher HbA1c ($\beta = 0.10\%$, $p < 0.01$ and $\beta = 0.19\%$, $p < 0.001$), whilst macrocytic anaemia and ART-treated HIV were associated with lower HbA1c ($\beta = -0.30\%$, $p < 0.001$ and $\beta = -0.11\%$, $p < 0.01$). However, there were no statistically significant differences in the prevalence of diabetes based on HbA1c or OGTT in those with anaemia (2.9 vs 3.3%), untreated HIV (1.6 vs 1.6%) or ART-treated HIV (2.8 vs 1.3%).

Conclusion: In this South African population, the associations between anaemia, HIV, ART, and HbA1c were modest and unlikely to affect the utility of HbA1c for the detection of diabetes.

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The relationship of body fat, insulin resistance and adiponectin with processing speed and incidental recall in midlife African women

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Background: Obesity is associated with reductions in cognitive function and memory. It has been suggested that these associations are mediated by insulin resistance (InsR), adipokines, inflammation or vascular damage. The aim of the current study was therefore to investigate the relationship of adiposity measures, adipokines and InsR with cognition and short-term memory in a cohort of middle-aged African females.

Methods: Serum adiponectin and leptin levels, InsR (HOMA), socio-demographic variables, and body fat measures were assessed in 608 black, urban, midlife women participating in the Study of Women Entering and in Endocrine Transition (SWEET). Cognitive function (processing speed) and incidental recall were measured using the symbol-digit modalities test (SDMT) and used as dependent variables in separate multivariable regression models. The relationship of incidental recall with InsR was analysed by comparing incidental recall across HOMA tertiles.

Results: Regression models demonstrated that the main determinants of cognitive function were age ($\beta = -0.19$, $p < 0.0001$), education level ($\beta = 0.42$, $p < 0.0001$), employment status ($\beta = 0.12$, $p = 0.0006$), visceral fat ($\beta = -0.08$, $p = 0.049$) and adiponectin ($\beta = -0.10$, $p = 0.006$), whilst for incidental recall the determinants were education ($\beta = 0.20$, $p < 0.0001$), visceral fat ($\beta = -0.10$, $p = 0.018$) and InsR ($\beta = 0.09$, $p = 0.043$). The incidental recall levels for HOMA tertiles 1, 2 and 3 were as follows: 4.35 ± 3.42 , 5.25 ± 3.85 and 4.98 ± 3.54 , respectively ($p = 0.036$ by ANOVA).

Conclusion: These data suggest that visceral fat has a weak, negative effect on both cognition and incidental recall independently of adipokines or InsR, whilst adiponectin specifically attenuates cognitive function. Furthermore, incidental recall increases with rising levels of InsR, but plateaus at high HOMA levels.

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Antioxidant and antidiabetic effects of Xylitol and Erythritol: a comparative study

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Background: There has been a growing interest in the use of sugar substitutes in the management of diabetes and its related complications. Studies have focused on sugar alcohols as they display various biological functions and hold enormous health benefits. Xylitol and erythritol are widely used sugar substitutes, however, it is not clear which one is better between them. Thus, we aimed to investigate comparatively the antioxidant and antidiabetic potential of xylitol and erythritol in vitro and ex vivo.

Methods: Carbohydrate digestive enzymes inhibitory action and free radical scavenging activity (DPPH, NO- and FRAP) of increasing concentrations of xylitol and erythritol

(90–720 mM) were executed in vitro. Additionally, their increasing concentrations (360–2880 mM) on the effects of glucose uptake, LPO and GSH concentrations, and on the activity of CAT, SOD, GR and GPx enzymes were investigated in psoas muscle from rats *ex vivo*.

Results: Xylitol exhibited a greater concentration-dependent inhibition of α -amylase, and α -glucosidase, with a significant ($p < 0.05$) DPPH and NO- scavenging activity and FRAP compared to erythritol. Xylitol dose-dependently increased muscle glucose uptake, GSH levels and, decreased glucose absorption and LPO levels greater than erythritol. Xylitol further increased the activity of the antioxidant enzymes more effectively.

Conclusion: The data of this study suggest that both xylitol and erythritol reduce intestinal glucose absorption, increases muscle glucose uptake, scavenges free radicals, however, xylitol showed better effects in almost all aspects compared to erythritol. Further studies are still required to ascertain these preliminary findings in humans and experimental animals.

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Increased insulin response in pre- and post-menopausal African women living with HIV

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Adiposity, body fat distribution, menopause and HIV status are linked to diabetes risk: we investigated the association of these factors with glycaemia, insulin secretion and insulin sensitivity in black South African women using an oral glucose tolerance test (OGTT) and a frequently sampled intravenous glucose tolerance test (FSIGT). A total of 82 black South African (SA) women, with normal glucose tolerance were divided into 4 groups: pre-menopausal HIV-negative (PRE-; $n = 19$); pre-menopausal HIV-positive (PRE+; $n = 7$); post-menopausal HIV-negative (POST-; $n = 39$) and post-menopausal HIV-positive (POST+; $n = 17$). The study subjects underwent a dual-energy x-ray absorptiometry scan, an OGTT and a FSIGT. From the OGTT and FSIGT, insulin sensitivity (Matsuda Index and SI) and first-phase insulin response (insulinogenic index [IGI] and acute insulin response to glucose [AIRg]) were obtained. Visceral adipose tissue (VAT) was higher in post- than pre-menopausal women ($p = 0.023$) but did not differ by HIV status. Insulin response was greater (IGI: $p = 0.015$, AIRg: $p = 0.005$) in HIV-positive women compared to HIV-negative women, and insulin sensitivity tended to be lower ($p = 0.052$) only when using FSIGT in HIV-positive women. Importantly, this study is the first to suggest that hyperinsulinemia in African women may be exacerbated by HIV. Further investigations are therefore needed to understand whether the greater capacity to secrete insulin precedes the development of T2D among South African women including putative mediators of increased insulin secretion.

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Comparison of cardiometabolic risk factors between pre- and post-menopausal women from diverse sub-Saharan African populations

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Background: Menopause is associated with increased risk of cardiometabolic diseases (CMDs) however, there are few data in African populations despite the high prevalence of these diseases. This study assessed differences in CMD variables between pre- and postmenopausal women from diverse African populations.

Methods: This is a sub-study of the Africa Wits-INDEPTH partnership for Genomics studies (AWI-Gen) across 5 sub-Saharan African (SSA) study sites in Ghana (Navrongo), Burkina Faso (Nanoro), Kenya (Nairobi), and South Africa (Soweto and Dikgale). The analysis comprised 3609 (1740 pre- and 1869 postmenopausal) women. Demographic, anthropometric and cardiometabolic variables were compared between pre- and postmenopausal women, within and across sites using regression analyses.

Results: Across all sites, after adjusting for confounding variables, postmenopausal women had higher waist circumference ($\beta = 0.8$, $p = 0.01$), abdominal subcutaneous fat ($\beta = 0.04$, $p = 0.01$), diastolic blood pressure ($\beta = 0.01$, $p = 0.04$), LDL-cholesterol ($\beta = 0.10$, $p = 0.01$) and triglycerides ($\beta = 0.06$, $p = 0.003$), but lower BMI ($\beta = -0.02$, $p = 0.01$). However, after removal of the two west African sites from the regression models these significant differences were lost.

Regression analyses within individual sites showed that postmenopausal women had significantly higher waist circumference, abdominal subcutaneous fat, carotid intima media thickness and blood pressure with lower BMI only in the west African sites. Triglycerides were higher in postmenopausal women from one of the South African sites (Dikgale).

Conclusion: These data show that postmenopausal status is associated with more pronounced elevations in CMD risk factors in west African sites when compared to those in east Africa and South Africa. These novel findings must be confirmed in longitudinal studies.

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The associations of childhood abuse with cardiovascular disease risk factors in young South African women: A cross-sectional study

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Aim: To determine the associations of childhood abuse (CA) (sexual, physical, emotional and/or parental neglect) with cardiovascular disease risk factors (CVDRF) in women aged 18–40 years in Durban.

Methods: Data collection included self-reported history of CA (< 18 years), lifestyle behaviours, and clinical and biochemical assessments. Logistic regression analyses, adjusted for age, education and employment, described associations of CA with CVDRF.

Results: Among 1613 women (median age, 24 years (IQR, 21–28)), 55.2% had experienced at least one type of CA. The most common was physical abuse (41%), parental neglect (25%), emotional abuse (21%) and sexual abuse (12.5%). A quarter of participants experienced a single type of CA, and 30.2% were exposed to multiple types of abuse. Current smoking and alcohol consumption were associated with all types of CA, increasing number of types and frequency of CA experienced. Hypertension was associated with sexual abuse (AOR: 1.72, 95%CI: 1.16–2.54), emotional abuse (AOR: 1.80, 95% CI: 1.29–2.50) and parental neglect (AOR: 1.40, 95% CI: 1.04–1.89), increasing CA types (AOR: 1.19, 95% CI: 1.06–1.33) and increasing frequency of CA (AOR: 1.05, 95% CI: 1.01–1.09). Triglycerides > 1.7 mmol/l was associated with parental neglect (AOR: 1.69, 95% CI: 1.04–2.76), while HDL-C < 1.3 mmol/l was inversely associated with increasing frequency of physical abuse (AOR: 0.90, 95% CI: 0.82–0.98). No association was found for HbA1c ≥ 5.7%, known hyperglycaemia or diabetes.

Conclusion: CA is common in South Africa and associated with hypertension, dyslipidemia, tobacco smoking and alcohol use in young women. Prevention of CA should be included in strategies to address CVDRF in South African women.

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Association of HIV infection, antiretroviral therapy (ART) and cardiometabolic disease (CMD) risk factors in urban black South Africans: the Durban Diabetes Study (DDS)

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The DDS, a population-based cross-sectional study of participants > 18 years, allowed for the assessment of the

association between HIV infection, ART and CMD risk factors, in urban black South Africans.

Methods: All subjects had demographic, anthropometric and blood tests. HIV infection was determined by ELISA; current ART was self-reported. Participants were categorised as having no HIV (HIV-), untreated HIV (HIV+ART-) and ART-treated HIV (HIV+ART+). Crude and adjusted linear and Poisson regression models were fitted for the absolute mean difference in continuous CMD risk factors and risk ratio (RR) based on categorised CMD risk factors between subgroups.

Results: In 1178 participants (843 women), the prevalence of HIV was 43.7% (n: 515); of these, 326 (63.3%) were classed HIV+ART- and 189 (36.7%) HIV+ART+. Both the HIV+ART- and HIV+ART+ groups had lower BMI, sBP, FPG and 2PG than the HIV- group and lower prevalence of obesity, hypertension, diabetes and metabolic syndrome. Mean serum TC and LDL was lowest in the HIV+ART- while mean TG was highest in the HIV+ART+ group.

In adjusted models, relative to HIV-, HIV+ART- was associated with lower BMI ($p < 0.01$), sBP ($p < 0.01$), TC ($p < 0.001$), LDL ($p < 0.01$) and HDL ($p < 0.001$); HIV+ART+ was associated with lower BMI ($p < 0.001$), sBP ($p < 0.001$) and 2PG ($p < 0.001$), and higher TG ($p < 0.05$). HIV+ART- was less likely to be obese (RR 0.77), but more likely to have low HDL (RR1.49); HIV+ART+ was more likely to have high TG (RR1.53).

Conclusion: In this population, there is evidence for association of HIV infection and ART with CMD risk factors.

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Paediatric abdominal adiposity measurements: conventional anthropometry versus ultrasound

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Background: Maternal and childhood obesity are not only related but may also track from childhood into adolescence and finally adulthood. Abdominal visceral adiposity is more detrimental to cardiometabolic health than generalised adiposity. Aim: using abdominal adipose tissue ultrasound measurements to demonstrate the effect of in utero exposure to teratogens and compare it with conventional anthropometry.

Methods: This prospective cohort study is a follow-up study of children born in the Safe Passage Study where data was collected from 500 mother-child pairs at antenatal, birth and five year visits. Maternal data were collected at antenatal clinics and all other assessments were done at follow-up study visits at Tygerberg Hospital. Dependent variables included: body weight (BW), body length (BL) skinfold thickness (SFT), waist circumference (WC) and ultrasound measurements of the visceral adipose tissue

(VAT) at age five years. Independent variables included: in utero exposure and maternal adiposity measurements at enrolment.

Results: In utero exposure ($r = 0.11$ at $p = 0.01$) was significantly associated with VAT as measured by ultrasound. Anthropometric adiposity measurements of did not correlate with in utero exposure. Reduced odd ratio for low BMI for males born to smoking mothers (OR = 0.66, CI 0.45–0.96). Regression analyses revealed, maternal BMI ($r = -0.20$, $p = 0.04$), MUAC ($r = 0.20$, $p = 0.05$) and BW of the child at age five ($r = 0.63$, $p < 0.01$) were significantly associated with SFT at age five years ($p < 0.01$) adjusting for in utero exposure.

Conclusion: Ultrasound is a more sensitive measuring tool for abdominal VAT whereas anthropometry is valued in peripheral adiposity measurement.

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An audit of children with Type 1 diabetes mellitus presenting to a tertiary institution in Johannesburg, South Africa

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Introduction: The rate of diabetes ketoacidosis (DKA) at initial diagnosis varies between countries (15–67%) and may be associated with lack of awareness of early signs and symptoms.

Methodology: A retrospective review of Type 1 DM patients' medical records admitted to CHBAH from 01 January 2009 to 31 December 2018 was conducted and subdivided into two groups (Group 1: 2009–2013 ($n = 75$); Group 2: 2014–2018 ($n = 78$)). Group 1 included annual follow-up data for 5 years: anthropometry, HbA1C, insulin therapy, and recurrent episodes of DKA admissions.

Results: Total number of newly diagnosed Type 1 DM patients was 153. The median age at presentation was 10.5 years (IQR 7.4–12.3), 56% females and 88% black. Sixty-five percent ($n = 100$) presented in DKA, 56% of those being severe with an increasing prevalence of DKA between group 1 and 2 (56% vs 72%; $p=0.06$). At presentation, the median HbA1C was 12.5 (IQR 11.1–14.3) and C-peptide was 0.2ug/L (IQR 0.1–0.4) (normal range 1.1–1.4). Anti-GAD antibodies were positive in 82% ($n = 82/101$) of results available. HbA1C increased at Year 3 follow up with pubertal status. Despite changing to more intensive insulin therapy, mean HbA1c and DKA readmissions remained unchanged over the 5 years.

Conclusion: Majority of newly diagnosed patients presented in severe DKA, similar to Red Cross War Memorial Children's Hospital (2005–2009), with an increasing prevalence over the ten years which could be attributed to the lack of awareness of Type 1 DM in our population. An education campaign is needed to improve community knowledge about diabetes.

SESSION 9 – Sunday, 28 March 2021

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Rescue of function of mutant human follicle-stimulating hormone receptors by pharmacological chaperones

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Introduction: Follicle-stimulating hormone (FSH) and its cognate receptor (FSHR) are crucial in the endocrine control of reproduction. FSHR is a G protein-coupled receptor. FSHR mutations can cause receptor misfolding and failure to traffic to the cell membrane, which results in reproductive dysfunction. Pharmacological chaperones (PCs) can rescue cell surface expression of misfolded GPCRs and have therapeutic potential. Here, inactivating mutations of the FSHR in patients with reproductive dysfunction were characterised and the ability of cell-permeant small molecule FSH analogs to rescue their cell surface expression was examined.

Methods: 19 FSHR mutations were identified from the literature, introduced into a FLAG tagged mammalian expression vector by site-directed mutagenesis and expressed in HEK293-T cells. Cell surface and total cellular expression was determined by ELISA and the ability of six different small molecule FSH analogs to restore cell surface expression was examined.

Results: 16 of the 19 mutant FSHRs were retained intracellularly. When treated with four of the test compounds (LHR-Chap, 1402, 1404 and 1405) cell surface expression of 13 mutant FSHRs was restored.

Conclusion: the deficiency in cell surface expression of the majority of FSHR mutants could be overcome by treatment with PCs. These findings have implications in the treatment of patients with inactivating mutations of the FSHR.

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Characterisation of human LGR5 and P2RY14 G protein-coupled receptor mutations in hypogonadotropic hypogonadal patients

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Background: Defective G protein-coupled receptor (GPCR) signaling in the hypothalamic-pituitary-gonadal (HPG) axis underlies congenital hypogonadotropic hypogonadism (CHH) which is characterized by pubertal failure and infertility. With collaborators we have undertaken whole-exome sequencing of a cohort of European patients with CHH; revealing novel polymorphisms in GPCRs. Amongst these, putative inactivating

mutations were characterised in leucine-rich repeat containing G protein-coupled receptor 5 (LGR5) and purinergic receptor 14 (P2RY14).

Methods: DNA extracted from blood of CHH patients (> 300) were subjected to whole-exome sequencing (HiSeq 2500) to identify rare sequence variants of GPCRs expressed in the hypothalamus. Phenotypically and reproductively normal individuals were used for comparison. Of the mutant GPCRs identified we characterised the LGR5 and P2RY14 mutant receptors. These mutations were constructed and epitope-tagged GPCRs in pcDNA 3.1 and expressed in HEK293-T cells and characterized for cell surface expression and functional signaling.

Results: Three rare sequence variants of LGR5 (T674M, H218R, and P888L) were present at the cell surface but ligand failed to activate a β -catenin-responsive reporter when compared to the wild-type. The variant of P2RY14 (P301L) had cell surface expression of 84% relative to wild-type, but importantly, displayed no basal or ligand inositol phosphate signaling response and no basal or ligand cyclic AMP response whereas the wild-type receptor displayed high levels of constitutive activity.

Conclusion: Our current studies show that LGR5 and P2RY14 rare sequence variants may have reduced signaling activity and contribute to the CHH phenotype.

SESSION 10 – Sunday, 28 March 2021

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Placement of forefoot bend in women's shoes - risk factor for diabetic foot ulcer

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Background: Footwear used by diabetic patients could have a specific location of sole flexibility unsuited to actual anatomical fulcrum location. Mismatched fulcra decrease function, cause hyperkeratosis and reduce hemodynamics.

This study compared location of the fulcrum of the first metatarsophalangeal joint (MTPJ-1) in a multi-ethnic sample to the forefoot flexion position in footwear lasts to find whether mismatches were likely.

Methods: The study used laser-scanned three-dimensional foot images of 453 female participants to establish the location of MTPJ-1.

The length in millimeters between the participant's heel and MTPJ-1 was expressed as a percentage of the overall length of the measured foot. Corresponding measures were taken for sandals and closed shoes, and values derived were compared to last manufacture parameters.

Results: This study found that mismatch exists as locations of MTPJ-1 ranged from 70% to 79% of total foot length, significantly different from last design parameters placing flexion at 63% or 66.6% ($p < 0.0001$). The range of MTPJ-1 locations in same size feet were distributed in a wide 24.4 mm mediolateral band under the forefoot.

Conclusion: We found evidence that a multi-ethnic population contains individuals whose MTPJ-1 does not match the footwear fulcrum location. Mismatched fulcra result in forces on the joint, reduce hallux function to hallux rigidus. Compensatory abduction of the foot increases force and flexion moments on the minor digits and metatarsals, resultant increased pressure is a DFU risk. Absence of forefoot flexion prevents raising the arch in ambulation, limiting hemodynamics. Recommendations are described.

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The metabolic outcomes following hyperglycaemia first detected in pregnancy in Soweto, South Africa

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Background: There is concern over the long-term implications of gestational diabetes (GDM). Women who have had GDM during pregnancy have 20–40% chance of developing metabolic syndrome within 2–20 years and 17–63% developing T2DM within 5–15 years. We examined the differences in health of women following GDM with that of a control group.

Methods: Women diagnosed and treated for GDM at a major tertiary hospital in Soweto, South Africa between 2014 and 2017, were eligible for a prospective cross-sectional follow-up study 2–5 years post-delivery. Enrolled participants were matched for time since delivery in a 1:1 ratio to GDM negative controls. Post-partum outcomes were measured.

Results: 204 women were enrolled into the study. Women with prior GDM were older (38 years SD \pm 5.7 vs 34 SD \pm 5.7), more likely to be multiparous (85% vs 65% $p = 0.001$), more obese (BMI > 30) (68% vs 46% $p = 0.0015$) and had higher rates of hypertension (20.6% vs 10.9% $p = 0.05$). The rate of any form of dysglycaemia was significantly higher in the group with GDM when compared with controls (77% vs 9% $p = 0.0001$), as was the presence of metabolic syndrome (68% vs 46% $p = 0.0002$). Amongst those exposed to GDM whom progressed to T2DM vs the non-progressors, there was no difference in obesity rates (75% vs 64% $p = 0.23$), although a significance was found for family history of T2DM (71.4% vs 45.5% $p = 0.008$) and breastfeeding (75% vs 97% $p = 0.001$).

Conclusion: Post-partum adverse metabolic outcomes including hypertension, obesity, and progression to T2DM were elevated in those with prior GDM.

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Altered epigenetic signatures in South African women with gestational diabetes mellitus

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Background: Gestational diabetes mellitus (GDM), which refers to glucose intolerance that develops during pregnancy, is associated with adverse pregnancy outcomes. This study investigated whether epigenetic mechanisms, DNA methylation and microRNAs (miRNAs) hold potential as screening tools for GDM in a South African population.

Methods: Pregnant women were recruited at a level 1 clinic in Johannesburg, South Africa and GDM was diagnosed using the International Association of Diabetes and Pregnancy Study Group criteria. DNA and RNA were isolated from blood and subjected to DNA methylation and miRNA analysis, respectively. Global DNA methylation, a crude marker of overall genomic methylation, was quantified using the MDQ1 Imprint® DNA Quantification Kit, genome-wide methylation was measured using the Illumina Infinium HumanMethylationEPIC BeadChip® array, and CpG-specific methylation of the adiponectin gene was measured using pyrosequencing. miRNAs were quantified using miScript® miRNA PCR arrays.

Results: Global DNA methylation did not differ between GDM and non-GDM groups, although higher levels were observed in obese compared to non-obese pregnant women. Genome-wide methylation analysis and pyrosequencing of the adiponectin gene identified 1046 and two differentially methylated CpG sites, respectively, between the GDM and non-GDM groups. The expression of miR-20a-5p and miR-222-3p was decreased in women with GDM compared to those with normoglycemia. HIV infection altered the association between GDM and these epigenetic processes.

Conclusion: This study highlights the potential of epigenetic processes to serve as biomarkers of GDM. Incorporation of DNA methylation and miRNAs signatures into risk assessment

algorithms may aid early detection of GDM and facilitate earlier intervention.

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The Vitamin D receptor polymorphisms BsmI [rs1544410], ApaI [rs7975232], and TaqI [rs731236] are not associated with the development of T1D in the South African black population

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Background: Type 1 diabetes (T1D) is a condition associated with the autoimmune mediated destruction of the pancreatic β -cells. Recently, vitamin D3 has been shown to play an immunomodulatory role in T1D. Vitamin D3 exerts its effect through the vitamin D receptor (VDR), a ligand activated transcription factor. Activation of the VDR, through binding to vitamin D3 mediates the suppression of pro-inflammatory cytokines which inhibit Th1 cell differentiation. Th1 cells are responsible for the death of the β -cells. VDR gene polymorphisms (rs1544410, rs7975232 and rs731236) have been shown to be associated with T1D however, these findings are not consistent. To our knowledge there is no data looking at these associations in the black South African population. This study, therefore, aimed to determine the prevalence and association of these VDR gene polymorphisms with T1D in the South African black population.

Methods: Clinically diagnosed black T1D patients (cases; $n = 186$) and non-diabetic black participants (controls; $n = 153$) were recruited. All participants were genotyped for the three VDR SNPs using PCR-RFLP.

Results: In our cohort the mean age at diagnosis was 20.7 ± 8.4 years with a median duration of 7 [2; 11] years. There was no statistical difference in allelic frequency for the rs1544410 (G allele frequency 0.81 vs 0.79; $p = 0.331$), rs7975232 (A allele frequency 0.65 vs 0.70; $p = 0.210$) or the rs731236 (T allele frequency 0.83 vs 0.78; $p = 0.129$) polymorphisms between cases and controls.

Conclusion: The VDR gene polymorphisms are not associated with T1D in the South African black population.