Remission in type 2 diabetes
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Given our previous observation that black South African (SA) women are less insulin sensitive than their BMI-matched white counterparts, we aimed to characterise ethnic differences in lipid levels in relation to insulin sensitivity (SI) in black and white SA women matched for BMI.

Methods: Fasting serum lipids, body composition (DXA) and SI (frequently sampled intravenous glucose tolerance test with Minimal Model analysis) were measured in 56 lean (BMI < 25 kg/m²) and obese (BMI > 30 kg/m²) black and white SA women.

Results: There were significant ethnic differences in lipid profiles and SI (Table 1).

Conclusions: Despite lower insulin sensitivity, black women had more favourable lipid profiles than white women, corroborating findings from the USA. Serum lipid levels in black women did not correlate with SI as observed in white women. Longitudinal studies are required to determine whether the relatively low lipid levels and the attenuated association with SI in black women are in fact cardioprotective.

Aims: The aims of this study were to investigate the influence of daily physical activity on abdominal fat levels and to analyse the metabolic consequences of visceral fat in a population of healthy South African females.

Methods: CT-scans were used to measure both hepatic lipid deposition (using the liver-to-spleen attenuation ratio) and visceral and subcutaneous (SC) fat volume at the level of L4/5 in 32 (14 Indian and 18 African) non-diabetic, female volunteers. Daily physical activity was assessed using an activity monitor (the Sensewear R PRO2, Bodymedia) which was worn for a minimum of 7 days. Fasting blood samples were taken for total cholesterol, HDL, LDL, triglyceride, insulin and glucose levels. Insulin resistance was quantified using the HOMA method.

Results: The mean (± SD) BMI of study subjects was 27.4 ± 6.4 (range, 16.4–41.6). Multiple regression analysis showed that the principal determinants of visceral fat volume were BMI ($\beta = 0.73$, $p < 0.0005$) and number of steps ($\beta = -0.30$, $p < 0.05$). The ratio of visceral to SC fat correlated with the liver-to-spleen attenuation ratio ($\beta = -0.57$, $p < 0.005$). Visceral fat volume was the major determinant of triglyceride ($\beta = 0.61$, $p < 0.005$), HDL ($\beta = -0.57$, $p < 0.005$), insulin ($\beta = 0.58$, $p < 0.005$) and HOMA ($\beta = 0.63$, $p < 0.005$) levels.

Conclusions: Simple physical activity i.e. walking can attenuate visceral fat volume. Fatty liver is associated with a high ratio of visceral to subcutaneous fat. High levels of visceral fat are related to insulin resistance and increased triglyceride and reduced HDL concentrations.
4 Insulin is often not required for long-term management after diabetic ketoacidosis (DKA) for patients with recently diagnosed type 2 diabetes. Results from an audit of DKA admissions

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Aim: A retrospective audit of all patients with DKA admitted to Victoria Hospital, Wynberg during 2006 and 2007 with more than 12 months follow-up after admission was carried out. This study describes the outcome in the subgroup of patients with type 2 diabetes (T2DM).

Methods: Patients were classified as T2DM if they were: 1.) Antibody negative, 2.) Fasting c-peptide after stabilisation > 0.3nmol/l, 3.) Not insulin dependent within 12 months of diagnosis of diabetes.

Patients were treated in standard manner with intravenous insulin and fluids. In all patients classified as type 2 diabetes, consideration was given to conversion to treatment with oral agents either pre discharge or at follow-up as an outpatient.

Results: There were 109 admissions, (99 patients) for DKA in the study period. 63% of patients were classified as T1DM, 31% (n = 31) T2DM and 6% other or unclassifiable DM. No patient with T2DM was admitted with more than on episode of DKA. Data is provided on 30 patients with T2DM:

Mean age was 40 (range 14–76), acanthosis nigricans was present in 97%, a family history of diabetes was obtained in 60%. All patients were on treatment with metformin, 80% were on a sulfonylurea and 30% on insulin. BMI 29.1 (range 23.2–48.4), pH 7.13 (7.08–7.27), SBC 12.8 (9.1–17), M:F 1:1, HbA1c 9.2% (7.8–16.4%), fasting c-peptide 0.7 (0.33–1.6), duration of DM 6 years (0–15). A precipitant was identified in 14 cases, 13 due to infection and 1 insulin omission.

Six patients (20%) were discharged without insulin therapy. Two months post admission another 12 patients were taken off insulin. At follow-up at least 12 months post discharge 11 (50%) patients were treated with oral agents alone. Twelve months post admission HbA1c of patients on oral agents alone was 7.8% (5.5–8.1%), for patients on insulin and oral agents it was 8.8% (8.2–10.1%).

Patients who were successfully treated without insulin were characterised by having a shorter duration of diabetes (mean 3 years ± 2 vs 8 years ± 8; p < 0.01), by being a younger age (35 ± 8 vs 50 ± 12; p < 0.01) and were not on insulin pre admission (1 vs 8 patients) as compared with patients who required ongoing insulin therapy. Weight, BMI, admission HbA1c and pH and C-peptide results were no different in the two groups.

Conclusions: DKA in patients with T2DM occurs commonly in the absence of a precipitant in our population. 50% of patients could be successfully treated longterm without insulin after acute management of their DKA, suggesting reversible beta cell dysfunction/glucotoxicity may be particularly prevalent in this population. Follow-up is too short to assess for ‘phasic insulin dependence’ however.

5 New approaches to insulin resistance

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Objective: The aim of the study was to evaluate the effects of obesity and ethnicity on the inflammatory gene expression of abdominal deep and superficial subcutaneous (DSAT and SSAT) and gluteal (GLUT) adipose tissue depots.

Methods: Real-time polymerase chain reaction was used for expression analysis of 14 inflammatory genes in 15 normal-weight (BMI 18–25 kg/m²) black, 13 normal-weight white, 15 obese (BMI > 30 kg/m²) black and 13 obese white South African women.

Results: GLUT had significantly lower expression of adiponectin, but higher expression of leptin, macrophage markers (CD68, CD14 and CD163), proinflammatory cytokines (MIF, IL-18, TNF-alpha, CCR2) and the anti-inflammatory cytokine, IL-10, than DSAT and SSAT. The expression of leptin and all inflammatory markers were higher in obese compared to normal-weight women, for all three AT depots (P < 0.01). Black women had significantly higher expression of CD68, TNF alpha, CCL2, CSF-1, in all three depots than their white counterparts, independent of total body fatness and VAT (P < 0.01).

Conclusions: GLUT had higher inflammatory gene expression than the abdominal SAT depots. Obesity was associated with an increased inflammatory gene expression in central and peripheral SAT depots, and the black women in this cohort had higher gene expression levels than the white women. Future studies are required to explore the implications of these findings in relation to metabolic risk.

6 Effects of obesity and ethnicity on depot-specific adipose tissue inflammation

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Objective: The aim of the study was to evaluate the effects of obesity and ethnicity on the inflammatory gene expression of abdominal deep and superficial subcutaneous (DSAT and SSAT) and gluteal (GLUT) adipose tissue depots.

Methods: Real-time polymerase chain reaction was used for expression analysis of 14 inflammatory genes in 15 normal-weight (BMI 18–25 kg/m²) black, 13 normal-weight white, 15 obese (BMI > 30 kg/m²) black and 13 obese white South African women.

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Conclusions: GLUT had higher inflammatory gene expression than the abdominal SAT depots. Obesity was associated with an increased inflammatory gene expression in central and peripheral SAT depots, and the black women in this cohort had higher gene expression levels than the white women. Future studies are required to explore the implications of these findings in relation to metabolic risk.
Metabolic derangements (with obesity, pre-diabetes) may alter signaling cascades, thereby decreasing translocation of the insulin-responsive glucose transporter (GLUT4) from intracellular vesicles to the sarcolemma. As a result, glucose uptake is diminished leading to the onset of muscle/cardiac insulin resistance. Previous studies suggest that greater flux via the hexosamine biosynthetic pathway (HBP) and increased O-GlcNAcylation of target proteins may lead to insulin resistance. In light of this, we hypothesised that increased HBP flux impairs myocardial GLUT4 translocation by greater O-linked glycosylation of the insulin signaling pathway, ultimately leading to myocardial insulin resistance.

Rat cardiac-derived H9c2 myoblasts were cultured until ~ 80-90% confluent and thereafter sub-cultured in Lab-Tek chamber slides for 24 hours. Cells were then serum starved for 3 hours followed by 100 nM insulin administration for 5 minutes. We quantified the relative proportion of GLUT4 at the sarcolemma using immunofluorescence microscopy- and flow cytometry-based models for visualisation and assessment of myocardial GLUT4 translocation. To evaluate the role of HBP in this process our experimental protocol included several HBP activators (high glucose; 50 µM PUGNAc; or glucosamine treatment) and an HBP inhibitor (40 µM DON).

HBP activation impaired myocardial GLUT4 translocation as assessed by immunofluorescence and flow cytometry. Conversely, myocardial GLUT4 translocation was restored when cells were treated with DON. In parallel, HBP activation resulted in an overall increase in O-GlcNAcylation while administration of DON reversed this effect.

Our data show that chronically activated HBP flux impairs myocardial GLUT4 translocation. It is likely that the HBP becomes dysregulated during the pre-diabetic/early diabetic state and that O-GlcNAcylation of members of the insulin signaling pathway occurs during this stage. This will lead to myocardial insulin resistance, and in the long term, will contribute to the onset of the diabetic cardiomyopathy.
Aim: The aim was to study the perinatal mortality rate due to Diabetes Mellitus (DM) in the sites that uses the Perinatal Identification Program (PPP) throughout South Africa.

Methods: South Africa is a developing country. The PPP data from the 1st of January 2000 until the 31st of December 2007 was analysed. PIPP was started in 2000 and at that stage included 27 sites which were regional and level 3 hospitals throughout South Africa. PIPP is constantly expanding in South Africa. In 2007 180 health care centers took part in the PPP audit. All the centres are from the public health sector. The sites are distributed through the metropolitan, urban and rural areas in South Africa. As the program expanded it included also Midwife Obstetric Units (MOU) in South Africa. During the period 2006 and 2007 the program covered 40% of deliveries in South Africa. This is institutional data from voluntary sites taking part in the PPP audit. The perinatal mortality rate was calculated for all deaths that were found to be due to Diabetes Mellitus. Diabetes Mellitus is inclusive of Type 1 DM, Type 2 DM and Gestational Diabetes Mellitus (GDM). The study also evaluated the perinatal mortality from unexplained stillbirths, which are defined as deaths of infants weighing more than 4 kg. The perinatal mortality rate is expressed per 1000 deliveries.

Results: From the 1st of January 2000 until the 31st of December 2007 there were a total of 1 809 347 deliveries recorded in the PIPP sites. In total there were 373 deaths recorded due to DM. From this group of deaths that were related to DM, 96 of the deaths had a birth weight of more than 4 kg. The perinatal mortality rate (PMR) is presented in table 1.

Perinatal mortality due to DM in PIPP sites in South Africa

| Years | 2000* | 2001* | 2002 | 2003 | 2004 | 2005 | 2006 | 2007 |
|-------|-------|-------|------|------|------|------|------|------|
| Total deliveries | 62931 | 88306 | 164144 | 254294 | 265991 | 315344 | 362041 | 297768 |
| PMMR (DM) | 0.485 | 0.336 | 0.196 | 0.290 | 0.202 | 0.259 | 0.272 | 0.277 |
| PMMR (B>4) | 0.039 | 0.129 | 0.084 | 0.124 | 0.109 | 0.121 | 0.195 | 0.182 |
| Sum | 0.524 | 0.465 | 0.280 | 0.414 | 0.311 | 0.380 | 0.467 | 0.458 |

* Only regional and level 3 hospitals (MOU’s) excluded

Since 2002 there is a steady increase in the perinatal mortality rate due to DM in South Africa. We were unable to calculate a perinatal mortality rate specific for women with DM.

Conclusion: Since 2002 there is a steady incline in the perinatal mortality rate due to DM. The decline from 2000 until 2002 is probably due to the inclusion of MOU’s and not a true decline in the perinatal mortality rate. In South Africa we are not meeting the St Vincent declaration.

**Note:** The above text is a transcription and summary of the research paper titled “Perinatal Mortality due to Diabetes Mellitus recorded with the Perinatal Problem Identification Program (PPPI) in South Africa.” The table data provided is a summary of perinatal mortality rates due to diabetes mellitus in South Africa from 2000 to 2007, including details on deliveries and mortality rates.

**Question:** How does the study evaluate the correlation between different diagnostic criteria for gestational diabetes mellitus (GDM) in pregnant women from Africa?

**Table: Comparing the different diagnostic criteria applied to the same patient**

| Diagnostic criteria | WHO | CDA | EASD |
|--------------------|-----|-----|------|
| ADA                | 0.686 | 0.903 | 0.575 |
| WHO                | 0.584 | 0.643 | 0.001 |
| CDA                | 0.413 | 0.076 | 0.575 |

The table compares the correlation (κ) values between different diagnostic criteria for GDM in pregnant women from Africa. The κ values range from 0.001 to 0.903, indicating varying levels of agreement between the criteria.

**Conclusion:** The prevalence of GDM was 10% in the women tested. In the group of women with out risk factors 5% had GDM compared to the 13.9% of women with GDM. This was not statistically significant. The WHO criteria picked up most of the women from Africa with GDM. There is a high correlation between the WHO and ADA criteria in the patients form Africa. Almost half of the patients who will develop GDM do not have any risk factors.
On 14 November 2008 the world celebrated World Diabetes Day. The Department of Internal Medicine of the University of the Free State in collaboration with the Free State Department of Health, also partake in the celebrations by means of an outreach to the community. The purpose of the outreach was to make the community aware of the rapid increase in the diabetic pandemic.

The “Outreach Team” consisted of Prof Willie Mollentze, Dr Thabiso Mofokeng, Sr Petro du Plooy and Sr Portia Mokoena of the Department of Internal Medicine, Me Lucia Meko, a dietician of the Department of Human Nutrition, the MEC of Health in the Free State, Mnr TS Belot, Me L Nomtshongwana, Me G Nhenthe and Me Elke de Wit of the Department of Health and various other medical representatives.

Because the emphasis of World Diabetes day was placed on the child, it was elected to visit High School Springfontein in the Southern Free State in the Xhariep Municipal District. Springfontein which is situated on the N1 on the way to Cape Town. It once served as an important railway junction between Gauteng and the Eastern Cape, but with the decrease in the number of trains and trucks its growth came to a rather abrupt halt. Today it is one of the poorest communities in the district.

Consequently the prevention of diabetes and the benefits of a healthy lifestyle were brought under the attention of the children and teachers in the community. More than 82 pupils were screened on this day. Their ages ranged between 12 and 19 years. No diabetics were identified, but it was shocking to see the malnutrition and underweight present of mostly all the children.

Education plays an enormous role to educate and uplift a community. It doesn’t matter what their circumstances or level of education might be. Knowledge expels fear and with the right information and guidance, type 2 diabetes can be prevented.
15 The prevalence of sexual dysfunction among type 2 diabetic men in Jos, North Central, Nigeria

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Objective: Sexual dysfunction (SD) i.e. disorders of erection, libido and ejaculation, is a common but often neglected complication of diabetes in men. The current pilot study aims to determine the prevalence of erectile dysfunction (ED), disorder of libido and their associations, among type 2 diabetic men in Jos, North Central Nigeria.

Material and method: Consecutive type 2 diabetic male patients attending a diabetic clinic in Jos were interviewed with the aid of a questionnaire on socio-demographic characteristics and on the different domains of sexual functions, using IIEF – 15 (International Index of Erectile function). The IIEF-15 is a multidimensional scale for assessment of ED which also provides a broad measure of sexual function by assessing 5 domains of sexual function (erectile function, orgasmic function, sexual desire, intercourse satisfaction and overall satisfaction).

Folders were also reviewed for information on duration of diabetes, medical and drug history.

Results: Information on sexual function was obtained in 66 patients. The patients’ age (mean ± SD) was 56 ± 8.8 years, and the median diabetes duration was 7 years (range < 1 – 20).

Forty Five (68.2%), 17 (25.8%), 3 (4.5%), and 1 (1.5%) of participants were on oral hypoglycemics (OHA), insulin and OHA, insulin, and lifestyle modification respectively. 67% of the patients were hypertensives, while 77% of those interviewed were on one form of antihypertensives or the other (including ACE inhibitor).

Any form of erectile dysfunction was found in 87.9% of participants with 7 (10.6%), 16 (24.2%), 16 (24.2%) and 19 (28.8%) having mild, mild-to-moderate, moderate and severe ED respectively.

Disorder of libido, orgasmic function, and intercourse satisfaction was found in 80.3%, 62.1%, and 90.9% of participants respectively.

Conclusion: The prevalence of sexual dysfunction is high among male type 2 diabetics in Jos, Nigeria. The goal of management in this group of patients should not only be on blood sugar control but also in promoting a satisfactory sexual life.

16 Factors influencing non-compliance with clinic appointments in diabetic patients at a Gauteng hospital

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Objective: To determine the factors influencing non-compliance with clinic appointments in diabetic patients at a Gauteng Hospital in 2007/2008.

Setting: Diabetes clinics that offer more specialised outpatient care to adult patients with diabetes type 1 and 2. These clinics are at a secondary level hospital.

Design: Between 21 November 2007 and 12 March 2008, a convenience sample of consecutive non-compliant diabetic patients (n=76), was prospectively recruited for the study. A survey of the non-compliant patients was conducted using two data collection methods, namely face-to-face interviews and telephone interviews. This was a descriptive study. Patient demographics, reasons for non-compliance, perceived severity of diabetes, and perceived encouragement from others to attend was investigated. The data was analysed for the characteristics of the non-compliant patients and for the reasons for non-compliance.

Results: Of the 520 patients who were booked during the study period, 35% were not compliant. The mean age of the patients was 51 years (range 18-85). All patients perceived diabetes to be a serious disease. Of the interviewed patients 83% perceived their health to be either good or excellent. Of the interviewed patients 95% claimed that a clinic visit assisted them in managing their diabetes. Only 20% of the patients diarised the appointment dates while the rest simply used the appointment card given by the clinic.

Conclusion: Patient factors are very important in explaining non-compliance with clinic appointments.
Introduction: Inflammation is considered a common unifying mechanism in the development of atherosclerosis. High sensitivity C-reactive protein (hs-CRP), a hallmark of inflammation, has emerged as an independent risk indicator of atherosclerosis.

Aim: This retrospective study aimed to assess the role of hs-CRP as a marker of atherosclerosis in patients with Familial hypercholesterolaemia (FH) who are known to develop extensive premature atherosclerosis.

Method: Blood was collected from 37 homozygous and 20 heterozygous FH patients (both off and on lipid lowering therapy) attending the Johannesburg hospital Lipid clinic. Hs-CRP and fasting lipogram analyses were performed on the Roche Modular analyser. Results were compared to those from a group of normocholesterolaemic controls (n=20). The presence and extent of atherosclerosis was assessed by measurement of carotid intima media thickness (CIMT). Data was analyzed using ANCOVA and multiple regression analysis.

Results: (Data is median [interquartile range]): hs-CRP levels were 0.86 [0.77] mg/L in controls, 1.28 [1.96] in the FH heterozygotes and 1.92 [3.09] in the homozygotes (p<0.005 by ANCOVA) off statin therapy. hs-CRP levels were reduced by statin therapy, particularly in the homozygous FH group (2.07 [3.16] vs. 0.67 [1.64]; p<0.05). Multiple regression analysis demonstrated that BMI (β=0.37, p<0.0005), gender (β=0.36, p<0.005), LDL (β=0.27, p<0.05) and HDL (β=−0.27, p<0.05) explained 37.3% of the variance in CRP levels in controls and FH patients not receiving statins. However, no association was found between hs-CRP and CIMT.

Conclusion: hs-CRP is modestly raised in FH patients although the median is not above the accepted high risk cutoff for atherosclerosis of 3mg/L. hs-CRP concentrations are lowered by statin therapy, possibly as a consequence of the reduction in LDL and increase in HDL as well as due to a possible anti-inflammatory effect. This study suggests that although atherosclerosis in FH patients maybe characterized by a mild pro-inflammatory state, hs-CRP levels cannot be used to determine the severity and extent of atherosclerosis in FH patients.

Lipoatrophic diabetes mellitus with severe hypertriglyceridaemia in a top female athlete: A case report

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Introduction: Severe hypertriglyceridaemia is uncommon, but most prevalent with type 2 diabetes mellitus and high level ethanol abuse.

Case Presentation: An 18 year old Black female athlete with newly diagnosed diabetes mellitus was referred to us for glucose control following her collapse at an athletic event. She had no symptoms of pancreatitis or stigmata of hyperlipidaemia. She had generalised lipotrophy, acanthosis nigricans and acromegaloid facies. Her initial fasting triglyceride was 280mmol/L; fasting plasma glucose 29mmol/L, HbA1C 12.5%; total cholesterol 27.5mmol/L. She was started on insulin, Bezelip 400mg and Zocor 20mg at night. Her fasting glucose remained high despite increasing her bi-daily insulin, which was 50U and 30U in the morning and at night, respectively on discharge. Three months later her HbA1C was 9.3%; TG=1,7mmol/L; AST 61 mmol/L and ALT 59mmol/L. She did not have any muscle complaints despite continuing her intensive training programme.

Conclusion: This case demonstrates the role of combined statin and fibrate therapy in lowering triglycerides and cholesterol. It also suggests that it is possible to continue intensive exercise programme on dual statin and fibrate therapy.
A 23-year old man presented with bilateral retinal haemangio-blastomas. He also had a prior history of two phaeochromocytomas in his right adrenal 9 years ago, which was surgically removed. On further investigations he was found to have a new phaeochromocytoma in his left adrenal, a midbrain haemangioblastoma, and also multiple spinal cord haemangioblastomas. On the basis of this clinical picture he was diagnosed with von Hippel-Lindau disease, confirmed on genetic testing. He was successfully operated on for the phaeochromocytoma, and is being carefully followed up for the other complications of this disease, especially for renal carcinomas. We report the details of this case.

The syndrome of apparent mineralocorticoid excess was confirmed on measurement of urinary glucocorticoid metabolites by GCMS, with normal deoxycorticosterone levels (DOC), an elevated urinary free cortisol to cortisol ratio and an elevated urinary cortisone: cortisol metabolite ratio (THF + 5αTHF : THE of 10).

The patient was managed with salt restriction, spironolactone and Amiloride combination.
Tumour-induced osteomalacia. A curable condition

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Introduction: Osteomalacia in adults usually results from an abnormality of vitamin D nutrition or metabolism, or a state of chronic phosphate deficiency.

Case Study: A 47 year old well-nourished black female patient presented to Chris Hani Baragwanath Hospital with acute infective bronchitis and hypertension. She also complained of left hip pain, bilateral leg weakness and had a waddling gait. Biochemical workup identified a hypophosphataemia of 0.58mmol/L (n 0.8-1.4mmol/L), but normal calcium and renal function. PTH was 62 pmol/L (n 12-72pmol/L), and vitamin D levels were normal. Alkaline phosphatase however was 431IU/L (normal 40-120IU/L). Muscle enzymes were normal. Her TRP (tubular reabsorption of phosphate) was 0.58 (n > 0.8). Glicosuris was absent. Hip X-rays demonstrated pseudofractures. There was no history of malabsorption, antacid use, or family history of either osteomalacia or rickets. A diagnosis of oncogenic osteomalacia was considered. The FGF-23 level was < 2RU/ml (n 18-108RU/ml). She was treated with oral phosphate replacement and 1α hydroxyvitamin D (1ug daily). After three months her phosphate level rose to 0.9 mmol/L and muscle strength improved somewhat. An 111In-octreotide scan, 18 months later, demonstrated a small, abnormal area of uptake behind the right knee. A benign mesenchymal tumour was excised. One Alpha therapy was discontinued. She has maintained normal serum phosphate levels.

Conclusion: Oncogenic osteomalacia is a rare cause of osteomalacia, usually caused by mesenchymal tumours which are often small and clinically undetectable. Many have been shown to secrete a phosphaturic hormone such as FGF-23. It is important to consider this diagnosis in all cases of unexplained hyophosphatemia, the more so, since resection is curative.

Hypophosphataemic rickets in a 23 year-old black man

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A 23 year-old black male presented to the Orthopaedics Department with sequential pathological femur fractures.

Except for the fractures, the patient's history, as well as his family's, was of no significance. No clinical abnormalities could be found on examination.

X-rays demonstrated the fractures only. The DXA-scan revealed Z-values suggestive of severe osteopenia.

The patient's biochemistry revealed an s-phosphorus level of 0.30 mmol/L (Reference range: 0.80-1.40 mmol/L). The rest of his biochemical markers were normal.

Biochemical analysis of his urine demonstrated isolated hyperphosphaturia. His renal phosphate reabsorption was severely decreased (TMP/GFR=0.06; Reference range: 0.8-1.38).

A double tetracycline-labeled cortical bone biopsy was suggestive of rickets/ osteomalacia.

The differential diagnosis for isolated hyperphosphaturia includes: X-linked hypophosphatemic-, autosomal dominant rickets and tumor-induced osteomalacia/ rickets. Neither the clinical- nor the biochemical features could be attributed to a specific condition.

All of these conditions have one pathophysiological factor in common: phosphatonin.

Conclusion: The fact that our patient has features suggestive of phosphatomin at play, but no clear cut diagnosis, emphasises the role of further research into the interesting field of the phosphatomin, as well as the effect of genetic variability on these factors.
**23 Von Hippel-Lindau Syndrome in a black family**

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**Aim:** To describe a black family presenting with the von Hippel-Lindau (VHL) Syndrome

**Methods:** Review of patients’ records. Genetic testing performed by the Department of Human Genetics, University of Pretoria

**Results:** A 26 year-old man was admitted to CHBH on Aug 2008. His presentation was dominated by neurological abnormalities: vertigo, unsteadiness of gait and loss of balance, and chronic headache. He also complained of weight loss and occasional palpitations. Examination revealed a thin patient with a Marfanoid habitus, a marginally elevated blood pressure, horizontal nystagmus and an inability to stand up. MRI scan showed a large haemangioblastoma in the cerebellar vermis associated with obstructive hydrocephalus. Urinary normetanephrine was elevated; abdominal CT scan showed a right adrenal phaeochromocytoma. A diagnosis of VHL Syn. was made. His father had had a posterior fossa tumour removed in 1994 at JHB (details unobtainable). Subsequent investigation in 2008 revealed bilateral renal cell carcinoma. His other children, a daughter of 21 years and a son of 13, are well. The typical germ-line mutation associated with VHL Syn. is present in the father, the index patient (older son), and daughter. The index patient has had his phaeochromocytoma and cerebellar haemangioblastoma successfully removed. He is well, free of headache, and fully ambulant.

**Conclusion:** This case report highlights the complexity of one of the 4 familial syndromes, VHL Syn. associated with phaeochromocytoma and the importance of genetic screening.

**24 Sheehan’s syndrome presenting with diabetes insipidus**

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A 27-year-old patient, Ms. SH, was admitted to the intensive care unit at Chris Hani Baragwanath Hospital with hypotension and sepsis following sub-total hysterectomy for severe post-partum haemorrhage. She had delivered a healthy baby girl by vaginal delivery 13 days earlier. She was treated with inotropes, IV hydrocortisone and antibiotics. Three days after admission, the patient became polyuric, passing 27L of urine in 24-hours. Her urine and serum osmolality were 228 mosm/kg and 308 mosm/kg, respectively, and a diagnosis of diabetes insipidus (DI) was made. The patient was managed with IV saline and DDAVP in response to which the urine output decreased.

Baseline testing suggested panhypopituitarism.

- TSH 1.27 mU/L, T4 7.9 pmol/L, T3 1.3 pmol/L; PRL 7.0 µg/L;
- FSH < 0.3IU/L, LH < 0.1IU/L; GH 0.9 µIU/L; IGF-1 < 20.0µg/L

MRI scan showed pituitary atrophy in keeping with Sheehan’s syndrome.

Oral thyroxine (100 µg/d) was commenced and the hydrocortisone dose was increased to 100mg tds. With resolution of the sepsis, her clinical condition improved and she was discharged on prednisone, thyroxine, and intra-nasal DDAVP.

DI has been thought to be an uncommon complication of Sheehan’s syndrome with an estimated frequency of 5%. However, investigations indicate that posterior pituitary functions are more often affected than was previously thought and are attributed to neurophyseal and anterior hypothalamic ischaemia. Most patients, however, do not manifest clinically. This patient presented with severe DI as well as panhypopituitarism.
A rare cause of acromegaly – A case report

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Introduction: Acromegaly caused by ectopic growth hormone-releasing hormone is a rare entity. Here we describe a case of probable ectopic GHRH secretion by a carcinoid bronchial tumour.

Case Report: A 42 year old woman was referred to us from the Oncology Department. She had been diagnosed with a neuroendocrine tumour in 2005 for which she was treated with chemotherapy and radiation therapy. The patient appeared acromegalic. Her IGF-1 level was 1036ng/ml (ref range 101-267ng/ml). MRI of her brain revealed a 0.3 cm hypointense focus within the pituitary that was suggestive of either a microadenoma or a colloid cyst. CT of her chest showed a 7.36 cm X 6.10 cm mass in the right upper lobe of the lung that extended to the hilum and Octreotide scanning confirmed increased uptake in the same area.

Conclusion: The criteria for the diagnosis of acromegaly due to ectopic GHRH secretion (ie. confirmation of active GH secretion, unequivocal demonstration of GHRH production and secretion from an extrapituitary tumour and cure of acromegaly after tumour removal) could not be fulfilled as, unfortunately, our patient refused any surgical intervention. However, the rare diagnosis is likely from the suggestive clinical scenario.

Although ectopic GHRH production is very rare, endocrinologists should be aware of the possibility if a pituitary tumour is not found.

An unusual case of thyrotoxicosis

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The patient is a 19 year old woman with hyperoxaluria and a combined liver-kidney transplant at 12 years. This was followed by a 3-gland parathyroidectomy for tertiary hyperparathyroidism. She is on methylprednisolone, FK506 and mycophenolate; calcium and iron supplements.

She was diagnosed with thyrotoxicosis at 13 years, 18 months after the transplant. Anti-microsomal and anti-thyroid peroxidase antibodies were negative. She was treated with neomercazole for 2 years and stopped when she became hypothyroid.

Two years later, a suppressed TSH was noted. Thyroid antibodies remained negative; TSH receptor antibodies were also negative. Two thyroid scans provided puzzling images which were not consistent with Grave’s disease or thyroiditis.

Neomercazole was ineffective in controlling the thyrotoxicosis and she was given I131 despite the scan findings. She is still thyrotoxic and has been referred for thyroidectomy.

We have not found any reports of an association between thyrotoxicosis and hyperoxaluria, and have not demonstrated a cause of the disease, although immunosuppression complicates interpretation of the antibody results.

We suggest that the thyroid scan findings are explained by hyperoxaluric damage to the thyroid gland before the liver-kidney transplant, and would welcome alternative theories.
Development of a real-time PCR genotyping method for detection of 5 LDLR gene mutations in South African FH patients

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Familial hypercholesterolaemia is mainly caused by mutations in the LDL receptor gene. Five mutations are very prevalent in South African FH patients - Afr1, Afr2, Afr3, P664L (all single nucleotide polymorphisms - SNPs) and FH Lithuania (a 3 bp deletion). Identifying these mutations has been difficult using conventional methods, especially in patients who are heterozygotes. The gold standard for SNP detection is sequencing which is a very expensive method and impractical for routine use. The aim of this project was to design an affordable and reliable method to genotype FH patients.

We designed two methods to detect these mutations using real-time PCR. The first method was based on a TaqMan probe approach and the second method used high-resolution melt (HRM) analysis. Real-time PCR was performed on the RotorGene 6000. Genomic DNA samples with a known genotype were used to validate the assay.

Both the probe assay and the HRM assay were found to be able to accurately genotype the DNA samples when compared to sequencing data. However, we found that HRM is a simpler and far more cost-effective way to characterise our DNA samples compared to the TaqMan probes.

We are currently in the process of genotyping over 800 FH patients using HRM real-time PCR.

Aim: The association between low birthweight and cardiovascular disease is amplified by the development of obesity. We explored the effects of postnatal high-fat feeding in dexamethasone-programmed rats, in which prenatal glucocorticoid overexposure is associated with reduced birthweight and adult glucose intolerance.

Methods: Male Wistar rats exposed to dexamethasone (Dex) or vehicle (Veh) during the last week of gestation were weaned onto high-fat (HF) or control diets for 6 months.

Results: Dex-exposed animals were of lower birthweight (Dex 5.34 ± 0.04 vs Veh 6.01 ± 0.07 g; p < 0.001) and showed catch-up growth by 7 weeks. There was no difference in obesity or hyperinsulinaemia between Dex-HF and Veh-HF animals. However, Dex-HF animals had increased hepatic triglyceride content compared with Veh-HF animals (Dex 142 ± 19 vs Veh 92 ± 11 μmol/g liver; p < 0.001).

Conclusions: Antenatal glucocorticoid overexposure in rats does not confer increased sensitivity to high-fat diet induced obesity, but increases susceptibility to fatty liver.
29 **Glucocorticoid-induced inhibition of proliferation and MKP-1 up-regulation in mesenchymal stem cells**

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The chronic administration of glucocorticoids (GCs) results in decreased bone mass and osteoporosis. This is principally due to a decrease in osteoblast numbers. Previously we have studied the effects of GCs on the immortalised preosteoblast cell line MBA 15.4. It was found that GCs increase protein tyrosine phosphatase (PTP) activity, resulting in the switching off of the proliferative ERK pathway and a decrease in mitosis. MKP-1 was found to be the predominant PTP upregulated by GCs in these cells. Furthermore, overexpression of this phosphatase caused a decrease in cellular proliferation, whereas siRNA knock down of expression abrogated some of the anti-proliferative effects of GCs. Consequently, it was hypothesised that if MKP-1 was indeed the conduit for the anti-osteoblastic effects of GCs, a MKP-1-/- homozygous knockout mouse would be resistant to GC-induced osteoporosis. However, it was found that the bones of MKP-1 knockout mice were equally affected by GCs as wild-type animals, implying that MKP-1 activation is not required for the deleterious effects of GCs on bone in vivo. In order to reconcile the disparity between the immortalised MBA 15.4 and in vivo data, the effects of GCs on primary osteoblast precursor cells were studied. These rat mesenchymal stem cells (MSCs) were purified from adipose tissue and were differentiated into an osteoblastic phenotype. Primary cultures were used because, unlike MBA 15.4 cells, the cell cycle is not corrupted.

Cell proliferation and ERK activation were measured in MSCs after administration of the GC dexamethasone. The contribution of the PTPs to decreased mitogenesis was assessed using the inhibitor vanadate, whereas the expression of MKP-1 was measured using quantitative real-time PCR.

It was found that MSC proliferation is highly sensitive to inhibition by GCs. Although the ERK activation profile in MSCs is modulated similarly to that seen in MBA 15.4 cells, the reversal of the anti-proliferative effects of GCs by vanadate was blunted compared to MBA 15.4 cells. However, similarly to MBA 15.4 cells, GC administration also resulted in an increased expression of MKP-1. This implies that PTP activation may not be as essential for the anti-proliferative effects of GCs in MSCs as in immortalised MBA 14.4 cells, even though expression of phosphatases may be increased.

30 **The genetic characterisation of type 1 diabetes in black and white South Africans**

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**Introduction:** Type 1 diabetes (T1D) is the most common and severe chronic disease of childhood with a peak incidence between 11 and 13 years of age. In South Africa, there is sparse information regarding the epidemiology of T1D and it is poorly characterised in the black population.

**Objectives:** Type 1 diabetic patients were screened for GAD65 and IA-2 autoantibodies, their HLA genotypes defined and clinical data collected as the starting point for the development of a T1D registry to determine the prevalence of T1D in the different ethnic groups.

**Results:** We recruited 142 [82 (57.7%) black, 37 (26.1%) white, 18 (12.7%) Indian, 5 (3.5%) coloured] T1D patients, with 20 (14%) diagnosed within the last year. The majority (45%) of patients were diagnosed between 6 to 15 years of age. Interestingly, when patients were divided into ethnic groups, a second peak in the age of onset (> 25 years) was seen in the black population, with 19% black subjects compared to 4% white subjects diagnosed over this age range. Within this group, 75% of the black subjects screened were autoantibody positive. Screening of 40 patients [24 black, 9 white, 4 Indian, 3 coloured] for GAD65 and IA-2 autoantibodies revealed 95% positivity for GAD65 autoantibodies and 27.5% positivity for IA-2 autoantibodies. The majority of patients (83%) had one, or more, of the high risk HLA alleles, namely DR3, DR4, and DQB2.

**Conclusions:** Age of onset of T1D in black subjects differs from that in white subjects, suggesting an ethnic difference in disease aetiology.
Obesity is a multifactorial disease characterised by the accumulation of excess adipose tissue, defined by a BMI ≥ 30kg/m². It can be caused by environmental and genetic factors. Mutations in the melanocortin-4-receptor (MC4R) gene are the most common causes of monogenic obesity with 0.5-1% of obese adults and up to 6% of individuals with severe obesity starting from childhood have been found to have mutations in the MC4R gene. The main aim of this study was to screen black South African females for the presence of MC4R mutations and to determine if these mutations are associated with obesity. One hundred and seventy seven black South African females between the ages of 18 and 60 were recruited. These subjects had body mass indices ranging from 19.0-62.6 kg/m². Conventional and real-time PCR was performed on 69 DNA samples from severely obese individuals (BMI ≥ 35 kg/m²), 4 from obese individuals (30 and < 35 kg/m²), 5 from overweight individuals (25 and < 30 kg/m²) and 3 from lean individuals (18.5 and < 25 kg/m²); to amplify the entire gene and the products were sequenced for mutation analysis. No mutations were found among these subjects. This pilot study shows that mutations in the MC4R gene are not common in obese black South African females and suggests that the higher prevalence of obesity in this population group is not due to a high frequency of MC4R gene mutations.
Identifying single nucleotide polymorphisms in the promoter region of the human tissue non-specific alkaline phosphatase gene (TNSALP)

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Introduction: Alkaline phosphatases (ALPs) are a ubiquitous group of membrane bound glycoproteins that have recently been shown to play a role in adipogenesis in the 3T3-L1 murine preadipocyte cell line and in human preadipocytes. Differences exist in the activity of ALP in extracts from preadipocytes isolated from black and white human subjects, the levels being significantly higher in the black than in the white population. The present study investigated the role that single nucleotide base changes within the promoter region of the ALP gene play in the control of ALP expression in the two ethnic groups.

Methods: DNA was isolated from 6 black females (BMI 33.0±4.6; age 49.7±6.3 years) and 6 white females (BMI 31.5±4.5; age 39.5±11.9 years). Seven sets of overlapping PCR primers were designed to amplify the promoter region of the ALP gene. The PCR products of the gene were sequenced and the results compared against a reference gene for base changes using Sequencher 4.7.

Results: No nucleotide base changes unique to each of the two ethnic groups were identified.

Conclusion: Differences in the ALP activity observed in extracts from human preadipocytes do not seem to be due to changes in the nucleotide base sequence of the promoter region. This suggests that the differences are due to a post-translational modification of the ALP protein, differences in ALP mRNA stability or differences in levels of expression of molecules controlling ALP gene expression.

Klinefelter Syndrome

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Abstract: Klinefelter’s syndrome is the most common genetic cause of human male infertility, but many cases remain undiagnosed because of substantial variation in clinical presentation and insufficient professional awareness of the syndrome itself. Early recognition and hormonal treatment of the disorder can substantially improve quality of life and prevent serious consequences. Testosterone replacement corrects symptoms of androgen deficiency but has no positive effect on infertility. However, nowadays patients with Klinefelter’s syndrome, including the non-mosaic type, need no longer be considered irrevocably infertile, because intracytoplasmic sperm injection offers an opportunity for procreation even when there are no spermatocytes in the ejaculate. In a substantial number of azoospermic patients, spermatocytes can be extracted from testicular biopsy samples, and pregnancies and livebirths have been achieved. The frequency of sex chromosomal hyperploidy and autosomal aneuploidies is higher in spermatocytes from patients with Klinefelter’s syndrome than in those from normal men. Thus, chromosomal errors might in some cases be transmitted to the offspring of men with this syndrome. The genetic implications of the fertilisation procedures, including pretransfer or prenatal genetic assessment, must be explained to patients and their partners.

Klinefelter syndrome (KS) is by far the most prevalent chromosomal aberration in males often causing hypergonadotropic hypogonadism and infertility (1/500 of male births, karyotype 47,XXY). In addition, there is a marked increase of incidence (50% in comparison to the 1970s). In contrast to other human trisomies which are mostly transmitted to the offspring of men with this syndrome. The genetic effects of the parental origin of the extra X-chromosome on the phenotype of Klinefelter men may affect clinical features and associations, e.g. timing of puberty but also well-known aspects of metabolic morbidity. In addition, activation and (skewed) inactivation of the X-chromosome - also in relation to the androgen receptor (AR) CAGn repeat length - play a role.

An overall increased mortality (hazard ratio 1.4) in KS patients is observed, owing to alterations in metabolic functions causing premature vascular damage and insulin resistance. Especially cardiovascular risk and inflammatory status are most likely adversely altered in KS patients. This is suggested by retrospective epidemiological observations but has not been elucidated by prospective and consequently planned studies. In addition, infertility is not omnipresent. Testicular biopsies of prepubertal KS boys have shown in some cases preservation of reduced numbers of germ cells. The testes in the adult KS male are, however, characterised by extensive fibrosis and hyalinisation of the semiferous tubules, and hyperplasia of the interstitium, but the tubules still may show residual foci of spermatogenesis. Reproduction techniques employing microdissected testicular sperm in combination with intracytoplasmic sperm injection techniques has allowed KS males to father children in about 50% of all cases. However, no factor predictive of successful testicular sperm retrieval has been described yet.
Abnormalities in androgen action: When hormones fail to act

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The first report of hormone resistance in humans dates back to 1942 when Albright and colleagues first reported pseudohypoparathyroidism. Since then resistance to many other hormones has been recognised. The androgen resistance syndromes span a clinical spectrum from the complete androgen insensitivity syndrome (CAIS), presenting as phenotypic females, to phenotypic males with azoospermia and/or reduced libido. Intermediate forms of resistance are typified by Reifenstein Syndrome (RS), which is characterised by gynaecomastia +/– or hypoplasias.

CAIS and RS are rare, the incidence estimated at 1:20000 – 1:64000 live births. A lesser degree of androgen resistance, the infertile male syndrome, is thought to be relatively common, but often unrecognised. It manifests as a–or oligo-azoospermia in a phenotypic male. All are X-linked recessive conditions.

These syndromes result from mutations within the coding region of the gene for the androgen receptor (AR), located on the X chromosome at Xq11-12, consisting of eight exons and encoding 919 amino acids. Mutations include stop codons, framehift mutations, insertions, deletions and missence mutations. The androgen receptor, itself, is a nuclear receptor, belonging to the steroid- thyroid-retinoid superfamily of receptors. While the clinical, hormonal (inappropriately high testosterone and LH) and karyotypic profile is usually sufficient for diagnosis, additional investigations include androgen receptor binding studies and molecular genetic techniques.

Defects in ARs are the commonest causes of male pseudohermaphroditism – genetic and gonadal males with impaired masculinisation. By contrast, true hermaphroditism, relatively common in sub-Saharan Africa, is characterised by the presence of both testicular and ovarian tissue.

Examples of androgen resistance syndromes, investigated and managed by the Div. of Endocrinology at Chris Hani Baragwanath Hospital/University of the Witwatersrand will be presented and discussed.

Pharmacogenetics

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Abstract: Variable phenotypes of androgen insensitivity in exist in humans, mainly owing to defective, mutated androgen receptors. A more subtle modulation of androgen effects is related to the CAG repeat polymorphism (CAGn) in exon 1 of the androgen receptor gene: in vitro, transcription of androgen-dependent target genes is attenuated with increasing length of triplets. As a clinically entity, the CAG repeat polymorphism can relate to variations of androgenicity in (apparently) eugonadal men in various tissues and psychological traits: the longer the CAGn, the less prominent is the androgen effect when individuals with similar testosterone concentrations are compared. A strictly defined threshold to hypogonadism is likely to be replaced by a continuum spanned by genetics as well as symptom specificity. In addition, effects of externally applied testosterone can be markedly influenced by the CAGn and respective pharmacogenetic implications are likely influence indications as well as modalities of testosterone treatment of hypogonadal men.

Testosterone (T) and its metabolite dihydro-T exert their effects on gene expression and thus affect maleness via the androgen receptor (AR). A diverse range of clinical conditions starting with complete androgen insensitivity has been correlated with mutations in the AR. Subtle modulations of the transcriptional activity induced by the AR have also been observed and frequently assigned to a polyglutamine stretch of variable length within the N-terminal domain of the receptor. This stretch is encoded by a variable number of CAG-triplets in exon 1 of the AR gene located on the X-chromosome. Longer triplet residues mitigate binding of androgen receptor co-activators and, hence, facilitate decreased androgenicity. Marked hypoandrogenic traits are seen in patients with an elongation of more than 37 CAG repeats; in these patients, irregular processing of the receptor protein leads to spino-bulbar muscular atrophy. Nevertheless, in men with CAG repeat residues of normal length, an influence of the polymorphism on androgen target tissues such as the prostate, spermatogenesis, bone, hair, metabolic parameters and psychological factors has also been demonstrated. It remains to be elucidated whether these insights are important enough to become part of individually useful laboratory assessments in otherwise healthy, eugonadal men. Extending these findings to pharmacogenetic considerations, a possible modulation of androgen effects during T administration has to be considered. This aspect could gain clinical significance especially in older men as these patients are more likely to develop unwanted androgen-related side-effects. With regard to prostate enlargement in over 130 hypogonadal men initiated on testosterone substitution therapy, we recently demonstrated that prostate growth and volume were markedly influenced by the CAG repeat polymorphism. The findings were more pronounced in men older than 40 years and seem to put patients with a repeat chain of 20 or less triplets at an increased risk of developing an enlarged organ.

In Klinefelter patients who have two androgen receptor alleles, the shorter CAGn allele is preferentially inactive. CAGn length is positively associated with body height. Bone density and the relation of arm span to body height are inversely related to CAGn length. Presence of long CAGn is predictive for gynaecomastia and smaller testes, while short CAGn are associated with a stable partnership and professions of long CAGn is predictive for gynaecomastia and smaller testes, while short CAGn are associated with a stable partnership and professions requiring higher standards of education also when corrected for family background. There is a trend for men with longer CAGn to be diagnosed earlier in life. Under testosterone substitution, men with shorter CAGn exhibit a more profound suppression of LH levels, augmented prostate growth and higher haemoglobin concentrations. A significant genotype–phenotype association exists in Klinefelter patients. Androgen effects on appearance and social characteristics are modulated by the AR CAGn polymorphism. Effects of testosterone substitution are pharmacogenetically modified. This finding is magnified by preferential inactivation of the more functional short CAGn allele. In conclusion, these pharmacokinetic findings may provide the basis for individualised testosterone substitution therapy by adjusting the dose to the AR polymorphism.
37 Pathogenesis of the metabolic syndrome – Relationship to diabetes mellitus

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Objective: Glucocorticoids are increasingly thought important in metabolic syndrome pathophysiology and therapy. However, it is a paradox that glucocorticoids stimulate lipolysis acutely but induce obesity chronically. Moreover, consequences for liver fat accumulation are inadequately characterised. We hypothesised that insulin determines the switch from predominant lipolysis to obesity during glucocorticoid excess, and hence the extent of ‘overspill’ liver fat accumulation.

Research design and methods: Male C57BL/6J mice were studied fed or fasted after 3 weeks of normal chow or high fat diets, with vehicle or glucocorticoid treatment and following vehicle or streptozotocin (85mg/kg).

Results: Dexamethasone (1mg/kg/day) reduced adipose tissue mass in mice on normal chow, and shifted liver fat from perivenous to periportal distribution on fasting, without increasing total liver triglycerides. On high fat diet dexamethasone induced substantial expansion of all adipose tissue depots, but still without increasing liver triglycerides. However, when the hyperinsulinaemia induced by dexamethasone and high fat diet was prevented with streptozotocin, dexamethasone-dependent obesity was abolished and substantial liver fat accumulation ensued. This hepatic steatosis appears secondary to enhanced peripheral lipolysis, since plasma free fatty acids increased, while glucocorticoid induction of liver genes involved in lipid synthesis and esterification was abolished by streptozotocin.

Conclusions: Insulin and glucocorticoids are synergistic in enhancing adipose tissue triglyceride storage in vivo. Only in the absence of insulin, eg during starvation or in diabetes, do glucocorticoids induce net lipolysis with spillover of fatty acids to facilitate liver fat accumulation. This has important implications in predicting the effects of dysregulation or inhibition of glucocorticoid action in type 2 diabetes.

38 Essential role of insulin in glucocorticoid-induced obesity and liver fat accumulation

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39 The role played by alkaline phosphatase in lipid droplet formation in different lipid-storing cell types

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Introduction: The alkaline phosphatases (ALPs) comprise a group of membrane bound isoenzymes that function in cellular differentiation and tissue development processes in many species of animals. ALP is found in human preadipocytes and in the 3T3-L1 preadipocyte cell line where it has been shown to play a role in adipogenesis. The current study characterised the role played by ALP in intracellular lipid accumulation in 3T3-L1 and in a human hepatocarcinoma cell line (HepG2).

Methods: Subcellular localisation of ALP was performed by immunocytochemistry. Intracellular lipid accumulation was assessed by the oil red O method. ALP activity and total protein were measured in cell extracts. The expression of the peroxisome proliferator activated receptor gamma (PPARγ) was also studied by quantitative real time PCR.

Results: ALP activity was localised to the lipid droplet membrane in HepG2 cells. Statistically significant differences in ALP activity were observed between day 0 and 4 days post initiation of lipid droplet formation in HepG2 cells (p < 0.05) and in 3T3-L1 cells (p < 0.05). The expression of the PPARγ gene peaked four days after initiation of lipid accumulation after which it declined in both cell lines.

Conclusion: ALP is closely associated with the lipid droplet membrane where it may have a function in lipid aggregation. ALP may be needed in the initial stages of the metabolic conversion of relatively unspecialised mesenchymal cells, into lipid-filled cells in synergy with the activity of PPARγ, and similar processes may also occur during lipid accumulation in hepatocytes.
40 General approach to the diagnosis and management of pituitary disorders

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Abstract: Pituitary disease, in the past was often unrecognised until a patient experienced visual loss or obvious clinical features of hypopituitarism, Cushing's disease or Acromegaly. With current imaging (MRI), performed for a variety of reasons (most commonly headache, trauma), pituitary lesions are being diagnosed earlier than in the past. A pituitary lesion requires a thorough Endocrine evaluation to determine if there is overproduction of a hormone, to determine if loss of pituitary function has occurred and requires hormone replacement(s). Assessment of a patient with a pituitary lesion or clinical issues that suggest a pituitary problem should include: (1) Clinical evaluation including menstrual history in women, symptoms of diminished libido and erectile dysfunction in men, changes in weight (weight loss or gain), fatigue, changes in body features (weight gain, distribution; changes in hand, foot size, symptoms of sleep apnea); (2) Complete hormone assessment including: serum prolactin, IGF-1, GH, Free T4, TSH, ACTH, cortisol, testosterone (men), LH, FSH, alpha subunit levels and 24 hour urine free cortisol in patients with a suspicion of Cushings. The hormone results will determine if a patient requires immediate hormone replacement (i.e., cortisol, thyroid hormone). Symptoms of diabetes insipidus require life-long monitoring and treatment. If the patient has a prolactin producing tumor, the first therapy is medical treatment with a dopamine agonist; approximately 92% of patients have a good response to medical therapy. In patients with other types of pituitary lesions, transsphenoidal resection is required. The most important determinant of the outcome of pituitary surgery is the neurosurgeon’s experience and expertise. It is important to refer a patient to a neurosurgeon who has the necessary experience and expertise. Some tumors cannot be completely resected because of invasion to areas inaccessible to removal – in this situation, adjunctive therapy (radiation therapy) may be indicated. An important aspect of caring for patients with a secretory tumor is control of hormone hypersecretion with medical treatment (somatostatin analogues, GH receptor antagonist [Acromegaly], ketoconazole [Cushing's disease]), dopamine agonist (prolactinoma) until the radiation is effective. If a patient requires radiation therapy, regular Endocrine studies are necessary to diagnose new pituitary hormone deficiency and need for hormone replacement. The most important aspect of caring for patients with pituitary disease is coordinated care among the Endocrinologist, the Neurosurgeon and other physicians involved in the patients’ care. Long term follow up is required for all patients to assess recurrence of the lesion, need for hormone replacement and need for additional treatment. A patient with pituitary disease requires life-long monitoring and treatment.

41 Suppression of the osteoblastic phenotype in mesenchymal stem cells after short-term exposure to minimal adipogenic signals

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Objective: Osteoblasts and adipocytes both arise from multipotential mesenchymal stem cells (MSCs), and recent evidence supports an inverse relationship between adipocyte and osteoblast differentiation in bone. In vitro studies have demonstrated interconversion between relatively mature osteoblasts and adipocytes, indicating considerable phenotypic plasticity in these cells. However, it has been suggested that the adipocytic phenotype selection is dominant in MSCs, with adipocyte differentiation being favoured over osteoblastic development. In order to investigate phenotype selection in MSCs, the effectiveness of conventional osteoblastic and adipocytic differentiation media to induce phenotype-specific characteristics in MSCs was assessed and compared in vitro.

Methods: MSCs were isolated from rat adipose tissue (aMSCs) and exposed to different combinations of adipocyte and osteoblast differentiation constituents. Lipid accumulation was used as a marker of adipocyte differentiation and was measured by Oil Red O staining, whereas increased alkaline phosphatase activity was taken as a marker of an osteoblastic phenotype.

Results: aMSCs exhibited a much more robust response to conventional adipocytic differentiation media than the response to osteoblast differentiation media. Lipid accumulation could be induced in aMSCs by 10- to 40-fold lower concentrations of adipocyte differentiation constituents (insulin, indomethacin, 3-isobutyl-1-methylxanthine and dexamethasone) than those conventionally used. Short-term exposure to minimal adipogenic conditions, although not sufficient to induce adipocytic differentiation, nevertheless significantly suppressed the ability of aMSCs to subsequently acquire an osteoblastic phenotype.

Conclusion: We conclude that short-term exposure of MSCs to adipogenic signals subsequently suppresses the osteoblastic potential of these cells. We hypothesise that short-term exposure of MSCs to adipogenic signals in vivo could have a detrimental effect on osteoblastogenesis, and could contribute to the pathophysiology of several types of osteoporosis.
Insulin resistance and endothelial-dependent microvascular reactivity in South African women: Evidence of association

Aims/Hypothesis: The association between insulin resistance and impaired microvascular reactivity is not completely understood, but has been well-established in obese individuals. There is little data regarding this association in apparently-healthy, non-obese persons, as a possible antecedent to pathophysiology. The primary aim of this study was to investigate endothelial-dependent microvascular reactivity in non-obese women with/without insulin resistance.

Methods: Body fat% (DXA), waist (cm), blood pressure, fasting [glucose], [FFA], insulin resistance (HOMA) were measured in 19 non-obese (BMI ≤ 30 kg/m²) women (aged 20–37 yrs). Forearm microvascular reactivity (incremental area-under-the-curve, AUC) was measured by laser Doppler imager using iontophoresis of acetylcholine (Ach, endothelial-dependent) from 2 sites. Subjects with CV% for repeat measures of > 30% were excluded a priori (Morris & Shore, 1996). Family history, physical activity, dietary intake and socio-demographic variables were also obtained. Data were log-transformed where necessary. Subjects were grouped as insulin sensitive (IS) or insulin resistant (IR) according to the Homeostasis model (HOMA-IR < or ≥ 1.96, respectively, n = 12 vs n = 7).

Results: The IR group had higher body fat% than the IS group (35.2 ± 3.9 vs 27.0 ± 5.0 % fat, P < 0.002). Log AUC for Ach was inversely associated with log HOMA-IR (rho = -0.48, P < 0.05). The IR group had lower endothelial-dependent vasodilation than the IS group (log AUC perfusion units, χ ± SEM); 10.4 ± 0.35 vs 11.4 ± 0.27, P < 0.04 even after adjusting for fat distribution (waist), but not total %fat.

Conclusions: In this small, pilot study, insulin resistance in non-obese women was inversely associated with endothelial-dependent microvascular function. However, these associations were not independent of % fat. More work is needed with a larger sample size and a more sensitive measure of insulin resistance. However, these data provide further evidence of an inverse association between microvascular function and insulin resistance along a continuum, even in persons without diagnosed pathophysiology.

Diagnosis and treatment of testosterone deficiency syndromes

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Abstract: One of the most frequent, but also most underdiagnosed, endocrinopathies is male hypogonadism (testosterone deficiency). Male hypogonadism presents with a clinical picture that is most often associated with typical symptoms, such as disturbances of mood as well as sexual functions. Furtheron, a decrease in muscle mass and strength, an accumulation of body fat and osteopenia/osteoporosis are frequently observed. There are indications that insulin sensitivity is attenuated by androgen deficiency. Especially in older men, symptoms of androgen deficiency may exhibit a differential profile due to accompanying other chronic illnesses. Restoring serum testosterone levels by replacement therapy can markedly mitigate, if not totally relieve, the clinical picture of hypogonadism. New treatment modalities have been introduced during recent years, which include short-acting transdermal or buccal modalities as well as the long-acting depot preparation of testosterone undecanoate. This talk discusses the various modern methods of initiation and surveillance of testosterone substitution therapy.

Understanding the variety of clinical pictures male hypogonadism exhibits is pivotal for diagnosis and putative treatment. There can be disturbances of mood and cognitive abilities as well as sexual functions. Furtheron, a decrease in muscle mass and strength, an accumulation of body fat and osteopenia/osteoporosis as well as anemia might be observed. There are indications that insulin sensitivity is mitigated in a state of androgen deficiency. Especially in older men, symptoms of androgen deficiency may feature a differential profile due to accompanying co-morbidities.

Restoring serum testosterone levels by substitution therapy can markedly attenuate, if not relieve the clinical picture of hypogonadism. New treatment modalities have been introduced, includig short-acting transdermal as well as long-acting depot preparations. Herewith, the diagnostic pathways to describe or exclude male hypogonadism and as well as various options of initiation and surveillance of testosterone substitution therapy are elucidated.

Circumstances of life and food supply in developed countries result in an increasing prevalence of overweight and obesity. Consequently, a disorder of complex pathophysiology involving visceral adipose tissue as an endocrine organ, dyslipidemia, insulin resistance and hypertension emerges: the so-called metabolic syndrome; it leads to the manifestation of diabetes type 2 and cardiovascular disease. In males, testosterone deficiency contributes to the generation of the metabolic syndrome, as demonstrated by epidemiological and interventionnal approaches. Vice versa, hyperinsulinemia is able to attenuate LH-response of Leydig Cells, hence, mitigate testicular testosterone production and creating a vicious circle.

Correspondingly, testosterone substitution in hypogonadal men is able to invalidate the mechanisms of the metabolic syndrome by various pathways. It has reciprocal effects the generation of muscle and visceral fat tissue by exerting influence on the commitment of pluripotent stem cells. In addition, testosterone inhibits further development of pre-adipocytes. Insulin sensitivity of muscle cells is enhanced via beta-cells have been demonstrated. These effects are exerted by androgen receptor-mediated mechanisms. As epidemiological studies indicate, testosterone substitution is especially helpful in preventing or attenuating the metabolic syndrome in aging men with late-onset hypogonadism and Klinefelter patients.
**44 Metabolic phenotyping in the real world**  
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**46 Inadequate glycaemic control in diabetic patients on the medical wards at Groote Schuur Hospital**  
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**Introduction:** Inadequate glycaemic control for diabetics in hospital is common worldwide and is thought largely to be due to the use of regular insulin sliding scales and poor staff training. Thus protocol driven inpatient glycaemic control regimes are currently advocated. The aim of this study was to determine the adequacy of inpatient diabetic glycaemic control on the medical wards at Groote Schuur Hospital.

**Methods:** The names of all people with diabetes admitted to the medical wards over a three month period in 2007 were collected prospectively. After discharge, data was retrieved from their folders (demographic, glycaemic, medical and therapy), and laboratory records were reviewed. The first seven admission days or part thereof were evaluated.

**Results:** 82 of the 98 eligible admissions were suitable for analysis (15 records were incomplete or unobtainable and one patient was excluded having developed Addison’s disease). The patients had a mean age of 57.3 ± 13.3 years. Median length of hospital stay was 8 days (3 to 120). Infection was the commonest reason for admission (26.8%). There were 1842 glucose meter readings equating to 484 patient days. There were 3.8 ± 1 readings per day: 39.2% of early morning glucose readings were in the recommended glucose range of 3.5 to 6.9 mmol/l; 57.6% of random or non-early morning readings were in the recommended range of 3.5 to 9.9 mmol/l. 19 different treatment modalities were identified, the commonest being sliding scale alone (143 patient days, 29.5%). Sliding scale insulin regimes alone or in combination with other glycaemic control therapies were used for 365 patient days (75.4%). There was no significant difference in the number of readings within target ranges and treatment modality used. Sliding scale therapy was significantly associated with severe hyperglycaemia (glucose > 22.2 mmol/l) p < 0.01 vs non sliding scale therapy.

**Conclusion:** This study indicates that inpatient diabetic glycaemic control appears to be suboptimal at Groote Schuur Hospital. The reasons for this include: multiple treatment regimens and frequent use of insulin sliding scales. The introduction of a standardised treatment protocol requires evaluation.

**47 Association of the eNOS and VEGF gene polymorphisms in Type 2 diabetic retinopathy**  
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**Research design and methods:** This study is a retrospective chart review of 230 patients attending the type 2 diabetes clinic at Inkosi Albert Luthuli hospital. Type 2 diabetes patients consisted of 146 patients without retinopathy and 84 patients with retinopathy. 3 polymorphisms of the eNOS gene were determined, T- 786 C within the promotor region, Glu 298 Asp in exon 7 and 27 –bp repeat in intron 4.

**Results:** The eNOS gene polymorphisms were not significantly associated with the presence of diabetic retinopathy or with retinopathy severity.

**Conclusions:** This study suggests no association between the 3 eNOS gene polymorphisms and retinopathy. In addition there is no significant association with the severity of retinopathy and the polymorphisms.
Aim: To investigate the feasibility of a handheld data collection and patient management system and feasibility of a nurse case manager in managing patients (DM) with poor metabolic control.

Setting: A local authority primary health care clinic managed by the Tshwane Metropolitan Council.

Methodology: The pilot study made use of smartphone technology (i-Mate KJAM with a Windows Mobile application), a research assistant and a clinic nurse (nurse case manager). Baseline estimates of lipids and HbA1c were determined. Patients and the nurse case manager were sent automated text messages if their HbA1c or LDL was uncontrolled.

Results: In the period 20 July – 8 August 2007 50 patients were seen, 31 females, 38 (76%) were African, 10 (20%) were Caucasian and 2 (4%) were Indian. The mean age of the group was 54 years (SD 9.4). The number of patients who had LDL > 2.5 mmol or HbA1c > 9% were 36%, 64% respectively (28% had both). It took an average of 7 minutes to enter all the patient details. Entering the visit details took less than two minutes as did entering the results a few days later. The major problem experienced was that of ensuring synchronisation with the database. All the cellphone messages reached the recipients and all except one came for the arranged extra visit.

Conclusions: If synchronisation issues can be resolved this system would allow for valuable data collection for quality control and patient management purposes.

Microalbuminuria (MA) is a strong indicator of incipient nephropathy and systemic vascular damage in diabetic patients. Early detection and accurate measurement of MA is critical for risk stratification and institution of aggressive intervention strategies to delay progression of disease. A negative conventional dipstick test for proteinuria does not rule out MA, a more sensitive method should be used. Laboratory measurement of MA may not be readily available in rural areas and is expensive for screening large diabetic populations. Our aim was to determine whether Immunodip (ID) test for MA is a suitable qualitative, quantitative and cost-effective alternative to standard laboratory testing. [The average cost for one laboratory MA/Cr determination is R130 whereas ID cost R38 per test.] We obtained 49 random spot urine samples from type 1 (n = 19) and type 2 (n = 30) diabetic patients who had 0 - 1+ protein on routine dipstick. ID determination of MA was performed on one half of a random spot urine sample and the remainder sent for laboratory determination. MA value above 19mg/l was regarded as unequivocally positive and values of 12 - 18mg/l threshold positive range.

21 samples were negative for MA on ID. Of the 28 positive on ID, 7 were threshold and 13 strongly positive (UMA > 80mg/l). On laboratory values (MA/Cr > 2.2) 26 samples were negative. Of the 23 positive MA/Cr, 22 were also positive on ID [sensitivity of 96%]. Of the 26 negative MA/Cr, 20 were negative on ID [specificity of 76%]. 3 of the 6 positive on ID and negative on MA/Cr were in the threshold range. Quantitatively there was an excellent correlation of Ma/Cr positive and ID positive samples. (r = 0.84 p<0.00001). Using a CV of 20% for ID values, 46 of the samples accurately matched the laboratory values of microalbumin. Two of the three that did not match were in the threshold range.

ID has an excellent sensitivity (96%) for MA, with a highly significant quantitative correlation to laboratory values. It may be cost effective for routine screening of MA. Threshold values warrant laboratory confirmation.
50 The prevalence of hypertension and associated risk factors in a rural South African community of Zulu descent

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The prevalence of hypertension (HT) and associated risk factors was evaluated in a cross-sectional diabetes epidemiology study in a rural South African Community of Zulu descent in KwaZulu-Natal, selected by random cluster sampling of adults >15yr.

All subjects had demographic, anthropometric and biochemical measurements including a 75g oral glucose tolerance test (OGTT). The criteria of the Seventh Report of the Joint National Committee [JNC 7] were used for classification of blood pressure and the definition of Hypertension (HT) and prehypertension (PreHT).

Of 1021 subjects (M: F; 208: 813) studied, the crude prevalence of HT was 26.4% (M: F; 32.2 vs 25.0%) and of PreHT, 41.6% (M: F; 51.5 vs 38.8%), respectively. The prevalence of HT and PreHT increased with age, both in men and women, with overall peak prevalence in the 45–54 yr age-group for HT and in the > 65 yr age group for PreHT. Of the subjects with HT, 56.3% were discovered during the survey.

When compared with the normal (N) BP group, subjects with HT and preHT were significantly older (p < 0.001), heavier (both total and upper body adiposity) (p < 0.001), had higher waist-height ratio (p < 0.001) and higher plasma glucose, serum lipid and urate levels. The prevalence of sedentary leisure and occupational physical activity was also higher (p < 0.001).

This study has highlighted a high prevalence of HT and any abnormally increased BP, especially in men, and with significant association with modifiable risk factors.

51 Growth hormone replacement in adults

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Abstract: Growth hormone (GH) replacement in GH deficient adults has been shown to improve body composition (decrease in fat mass, increase in muscle mass and bone density), quality of life measures, and in some studies, improvement in muscle strength and exercise ability. In the US, GH replacement was approved by the U.S. Federal Drug Administration in August, 1996. Provision of GH replacement continues to be difficult and problematic (cost of GH and potential for misuse of GH). This may not be the situation in other health care systems as long as appropriate documentation of GH deficiency is provided. Who should be evaluated for GH deficiency? GH production is influenced by factors other than GH – obesity decreases GH secretion, normal aging is associated with a decrease in GH production. Thus appropriate patients to evaluate for GH deficiency are those with a history of pituitary disease (pituitary tumor, pituitary surgery, and/or pituitary radiation). Testing of patients with obesity, chronic fatigue, fibromyalgia or other non specific symptoms is not appropriate and usually leads to difficulties that you don’t want to encounter. How should the diagnosis of GH deficiency be ascertained? In a patient with a history of a pituitary lesion, surgery and/or pituitary radiation and other pituitary hormone deficiencies, a subnormal serum IGF-1 level may be adequate to establish GH deficiency (depending on regulatory and insurance requirements). In patients who have a normal serum IGF-1 level (who may be GH deficient), a stimulation test is necessary to establish the diagnosis. The most rigorous test in insulin induced hypoglycemia (with serial measurement of GH, glucose and cortisol [important if there is a question of ACTH/cortisol reserve]). Insulin induced hypoglycemia is contraindicated in patients with coronary artery disease, seizure disorder or generalised debility. The other most robust test is the GHRH + arginine test. The current diagnosis of GH deficiency is a stimulated GH of less than < 5.0 ng/ml. When beginning GH replacement, a small dose, e.g. 0.2, 0.3 mg/day, should be given to avoid side effects. Six weeks later a serum IGF-1 level should be measured and the GH dose increased according to the result. Women, especially if receiving estrogen therapy, usually require a higher final dose to achieve an optimal IGF-1 level than do men. Measures of the response to GH replacement may include serial quality of life surveys, change in serum lipids, and a bone density (DEXA) study which can also provide information on regional body fat. One caution regarding GH replacement: unrealistic expectations that overstates the benefits of GH therapy (chat rooms, “anti-aging” sites). To date, there is no information regarding changes in life expectancy inpatients receiving GH replacement. This will take at least another 20+ years to determine. GH replacement should be considered as part of a comprehensive program of replacement of deficient hormones. As with any hormone replacement, regular monitoring and clinical assessment is needed to determine optimal dose and avoidance of side effects.
The aim of this study was to determine the patterns of change in body fat and metabolic parameters in a South African cohort on a first line ART regimen containing stavudine. Fasting lipogram, blood glucose and insulin levels, CD4 cell count, viral load, BMI, waist-to-hip ratio (WHR), and skinfold thickness at the triceps, scapula and iliac crest were measured before starting ART in 42 (27 female) subjects. Repeat measurements were performed at four monthly intervals for 2 years. Lipodystrophy was diagnosed using patient perception and assessment by a physician. At baseline, subjects who went on to develop lipodystrophy (LD group) were fatter and had higher skinfold thickness at all 3 sites and higher insulin levels than subjects who never developed lipodystrophy (NLD group). The WHR increased to a greater extent whilst hip circumference and tricep skinfolds fell more significantly in the LD than NLD group. Triglyceride and cholesterol levels increased significantly in both groups whilst lactate and glucose levels increased more and insulin levels increased less in the LD than the NLD group. Neither viral load nor CD4 count differed between the groups during the study. Viral load correlated positively with insulin levels at baseline. Thus, lipodystrophy in the South African population is characterised by a higher BMI before initiation of ART and lipoatrophy of the arms and hips, lipohypertrophy of the waist and increased lactate production. When compared to the NLD group, the LD subjects display attenuated insulin secretory output in response to a higher weight gain.

**Aims:** Reports from the developed world have suggested that antiretroviral therapy (ART) may have detrimental effects on glucose tolerance. However, no studies confirming this have been reported from sub-Saharan Africa, which bears the burden of the HIV-AIDS epidemic. The aim of the present study was therefore to measure glucose levels in subjects receiving ART in Johannesburg, South Africa.

**Methods:** Glucose levels were measured using a portable Hemocue blood glucose monitor in 331 HIV-positive, ART-naïve subjects (ART- group) and 310 HIV-positive subjects receiving a first-line ART regimen that includes stavudine (ART+ group). Subjects were asked when they had last eaten and were then classified as fasted or non-fasted.

**Results** (data given as median [interquartile range]): Fasting glucose levels were not significantly different between the ART- (4.3 [1.0]; n = 117) and ART+ (4.4 [1.1]; n = 122) groups. However, the non-fasted levels were higher in the ART+ (5.0 [1.6]; n = 213 vs 5.4 [1.6]; n = 187; p < 0.01) subjects. In the ART+ group, non-fasted glucose levels correlated with age (r = 0.16, p < 0.05), ART duration (r = 0.15, p < 0.05) and BMI (r = -0.15, p < 0.05) whilst in the ART-group they correlated only with age (r = 0.19, p < 0.01).

**Discussion:** Stavudine-containing ART increases postprandial but not fasting glucose levels. This suggests that when screening ART+ subjects for glucose intolerance, a full OGTT may be necessary. Also, subjects receiving this ART regimen display a negative relationship between BMI and glucose levels suggesting that glucose intolerance is related directly or indirectly to lipoatrophy.
Prevalence of dysglycaemia in HIV-positive Xhosa-speaking South Africans on antiretroviral therapy

Background: Antiretroviral therapy (ART) dramatically improves life expectancy, but at the cost of developing metabolic complications including insulin resistance, diabetes, dyslipidaemia and lipodystrophy. Most data on these complications are from patients in industrialised countries on protease inhibitors, and may not be applicable to developing countries that are using cheaper non-protease inhibitor-based regimens as first-line therapy.

Objective: To determine the prevalence of dysglycaemia in South African HIV-positive adults who are ART-naïve or on 1st-line ART

Methods: Cross-sectional study in an ambulatory HIV-infected cohort in Cape Town. Subjects were randomly selected from the clinic list at a Community Health Centre and underwent a field worker-administered questionnaire, an oral glucose tolerance test (OGTT) and anthropometry. Subjects were either ART-naïve or on 1st-line ART regimen (stavudine, lamivudine and efavirenz or nevirapine)

Results: There were 727 subjects [405 on ART-age 35 (30–41) years; 320 (79%) females and 322 ART-naïve-age 32 (27–37) years; 246 (76%) females]. 21 (3%) had diabetes (11 ART-naïve; 10 on ART) and 165 (23%) had pre-diabetes (64 ART-naïve; 101 on ART). As a group, subjects on ART are more overweight [BMI 26 (23–30) kg/m² vs 24 (21–29) kg/m², p<0.001] and have greater centralisation of fat [waist circumference 86 (78–95) cm vs 80 (74–89) cm, p=0.0001] but are not more insulin resistant [HOMA-IR 1.2 (0.7–2.2) vs 1.0 (0.6–1.7), p= 0.1] than the ART-naïve subjects.

Dysglycaemic subjects from both groups (ART-naïve; ART) had a similar BMI [25 (22–31) kg/m² vs 27 (24–32) kg/m², p = 0.15] and CD4 counts [339 (171–539) cells vs 372 (258–486) cells, p = 0.21]. Patients on ART had a higher waist circumference [80 (76–95) cm vs 89 (81–95) cm, p < 0.01). The 2 hour post-load glucose value was higher in the ART-naïve subjects [7.3 (6.5–7.7) mmol/L vs 6.8 (6.0–8.1 mmol/L, p = 0.04). HOMA [1.3 (0.8–2.7) vs 1.8 (0.9–3.7), p = 0.16] and the insulinogenic index [13.3 (6.7–25.3) vs 14.5 (6.2–29.3), p = 0.27] were similar in both groups.

Conclusions: There is a similarly high prevalence of dysglycaemia in both ART-naïve and ART subjects despite patients on ART being more overweight and having greater centralisation of fat.

Size at birth, weight gain in infancy and childhood and adult diabetes in five low and middle income country cohorts: When does weight gain matter?

Objective: Promoting catch-up growth in malnourished children has health benefits, but recent evidence suggests that accelerated child weight gain increases adult chronic disease risk. We aimed to determine how birth weight (BW) and weight gain to mid-childhood relate to diabetes (DM) and impaired fasting glucose (IFG) in young adults.

Methods: We pooled data from birth cohorts in Brazil, Guatemala, India, the Philippines and South Africa. We used conditional weight (CW), a residual of current weight regressed on prior weights, to represent deviations from expected weight gain from 0−24 months, 24−48 months, and 48 mo to adulthood. Adult glucose and risk of IFG and DM were modeled before and after adjusting for confounders. Interactions of CWs with small size for gestational age (SGA) at birth were also tested.

Results: After adjustment for confounders (age, sex, site, percentage body fat, socio-economic status, maternal educational level, and waist circumference) we found that neither birth weight nor CW gain at any age was significantly associated with IFG, but birth weight and CW between birth and 24 mo was positively and significantly associated with adult diabetes (p<0.05).

Conclusion: greater birth weight and faster infant weight gain poses a higher risk for adult diabetes than weight gains at other ages.
Introduction: Little is known about the effects of age on the proinsulin-processing efficiency of human beta cells. The current study therefore compared surrogate markers of proinsulin-processing efficiency between children and adults.

Methods: Fasting glucose, insulin (I), proinsulin (PI) and des-31,32 proinsulin (desPI) levels were measured in 122 (62 males) 7-year-old children and 42 (17 males) adults below and 41 (15 males) adults above the age of 38. Insulin resistance was assessed using HOMA and percentage levels of insulin ([I/[PI+desPI+I]]x100), PI and desPI were used as markers of PI-processing efficiency.

Results (Data is median [interquartile range]): Fasting PI levels were lower in the older (1.60 [1.70]; p=0.01) and the younger (1.75 [2.50]; p = 0.07) adults than the children (2.85 [1.70]) whilst desPI levels were higher in the older (3.70 [5.00]) than younger (1.65 [3.20]; p = 0.006) adults but were not significantly different from the children (2.10 [3.80]). Similar trends were noted for percentage levels of both prohormones. Multiple regression analyses demonstrated that age, independently of gender, BMI and HOMA was a determinant of fasting PI and desPI and percentage desPI levels.

Conclusions: Increasing age, independently of insulin resistance causes higher conversion of PI to insulin but at older ages this occurs in the face of reduced conversion of desPI to insulin. This suggests that the processing of desPI to insulin is the first section of the PI processing pathway to become compromised in the face of the higher metabolic demands placed on the beta cell by increasing age and insulin resistance.

Objective: The Dawn Youth programme recognises and acknowledges the importance of psychological and sociological management in the overall care and treatment of the diabetic child. A programme to evaluate the problems and concerns of South African diabetic youth were undertaken.

Method: 27 Diabetic children aged 12 to 18 years (13 boys and 14 girls) were interviewed and 27 interviews with the parents of the diabetic children were conducted. The discussion was done in their home language. The discussions were audio taped and the tapes transcribed and translated back into English. Content analysis was done once all transcripts were received.

Results: In terms of day-to-day adjustment, parents and children appear to accept the discipline of regular testing and injecting. The most difficult aspect of the condition and the one producing the most anxiety is eating correctly. Children don’t want to feel different from their peers, but their condition, often very publicly illustrates their ‘differences’ on a daily basis. Feelings of depression occurred when children and parents dwelt on the unrelenting nature of managing diabetes. Children rely on their parents, particularly their mothers, for emotional and physical support. For some parents there was an added financial burden. The children have to maintain a healthy diet and parents are faced with additional expenses in terms of doctor’s visits, hospital treatment and the child’s monthly insulin requirements. Financial stresses are responsible for family arguments. Parents, children and teachers need more information about the condition, diet and treatment. Children want this information given to them verbally rather than in print.

Conclusion: Educating diabetic patients and their family should in future address the aspects that make these children feel different from their peers. In South Africa the financial burden in the lower economic group should be addressed.
The role of statin and ACE inhibitor treatment in adolescents with childhood-onset type 1 diabetes

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Abstract: The incidence of childhood-onset type 1 diabetes (T1DM) has doubled over the last 20 years, and has risen particularly steeply in children under the age of 5 yrs. Despite advances in treatment, its prognosis remains generally poor. Although life expectancy has increased by several years, reflecting the increased longevity in the general population, the life expectancy of a child aged 10 years with T1DM is shortened on average by 17 years, and this figure has remained unchanged over the last four decades. By the age of 20-39 years the standardized mortality rate for coronary artery is increased 10-fold in men and 40-fold in women. In the second decade after diagnosis diabetic nephropathy accounts for about 60% of deaths, but by the third decade, cardiovascular disease (CVD) accounts for two thirds of all deaths. The Diabetes Control and Complications Trial (DCCT) demonstrated that maintaining good glycaemic control can prevent both micro and macrovascular complications. However, achieving glycaemic goals during puberty is difficult and Hb1c levels are invariably higher than the level of 7.5% recommended for prevention of complications.

Adolescence may be a critical period in determining the future risk of nephropathy and CVD since glycaemic control inevitably deteriorates and puberty is an independent risk factor for the development of microalbuminuria, which is an early risk marker for diabetic nephropathy and CVD. Microalbuminuria may be found in 12-16% of adolescents. Its development is also associated with hyperlipidaemia, elevated arterial blood pressure and decline in renal function, suggesting a generalised endotheliopathy. Flow mediated dilatation, an established marker of endothelial function, may be abnormal and carotid artery intimal medial thickness (cIMT), a marker of early atherosclerosis, may be increased in adolescents with T1D.

Clinical guidelines recommend treatment from early adulthood with ACE inhibitors (ACEIs) and statins for patients at increased risk of diabetic nephropathy and CVD. However, there is no consensus on the use of these drugs in adolescence. A few small studies confirm that ACEIs reduce albumin excretion in adolescents with T1D and may improve renal pathology, but there have been no formal randomised controlled trials. Statin therapy reduces progression of subclinical atherosclerosis (cIMT) in adolescents with familial hypercholesterolaemia, but its use in adolescents with T1DM has not been evaluated. Early intervention in adolescents at high risk of microalbuminuria with ACEI and statin therapy may provide cardio-renal protection and lead to long-term improvements in prognosis. This hypothesis is being tested in the Adolescent Diabetes Intervention Trial (AdDIT) which is a randomised double blind placebo controlled 2x2 factorial multinational trial of a statin, ACEI and combination therapy in 500 adolescents at high risk of developing microalbuminuria.