Thursday, 19 April 2012: Oral presentations

TO1. Postmenopausal bone loss: an osteoimmunological perspective
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TO2. Bone programming
Lisa Micklesfield, John Pettifor
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Early growth has been associated with adult bone mass and fracture risk. Traditionally, birthweight has been used as a proxy for intrauterine growth, and is a significant predictor of postnatal, childhood, and adult bone density. More recently, results of a study from the South Hampton Women’s Survey show that early intrauterine growth, measured using high-resolution ultrasound, determines bone mass at four years of age, while later intrauterine growth is more closely associated with bone mass at birth. Growth during the first years of life is important for skeletal development, and birth to Twenty data have shown an association between weight and height at one year, and dual energy X-ray absorptiometry (DXA) scan bone mineral content in children aged 10 years. Findings from other cohort studies report similar findings between birthweight and growth in infancy, and bone mass later. To date, most evidence has been obtained using a DXA scan, which is known to be dependent on size. Peripheral quantitative computed tomography (pQCT) measures appendicular volumetric bone density, and is therefore not size-dependent, as well as bone geometry and trabecular bone mass. Results from most pQCT studies report a positive association between birthweight and bone size and strength, independent of current body size. However, bone mineral density appears to be associated with current weight and height more. This presentation will review the current literature investigating these relationships.

TO3. Bone mass and fractures in black and white South African women
Magda Conradie, Stephen Hough
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Ethnic differences in bone mass and fracture risk in South African adult black and white women will be reviewed. Generally, it is accepted that the shared genetic phenotype of black populations in America and on the African continent protect them against osteoporosis and consequent fragility fractures. It is also accepted that black populations in Africa will have similar patterns of bone gain and loss to African Americans. Studies in South Africa contest this belief. Exposure to adverse environmental factors may negatively impact on ultimate achievement of optimal bone mineral density (BMD), even in genetically protected black populations. Higher BMD values and lower fracture rates at all skeletal sites have been extensively documented in African-American females. Studies in South Africa, although limited, have consistently noted site-specific differences in bone mass and fracture risk in both pre- and postmenopausal black and white females. Vertebral BMD are either lower or similar in blacks, compared with whites, with recently documented similar vertebral fracture rates in black and white females respectively (11.5 vs. 8.1%). A five-year longitudinal study found new morphometric vertebral deformities in a high percentage of black women over the age of 60 years (38%), BMD at the proximal femur is higher in South African black females. Recent data on South African hip fractures are not available. Adverse environmental factors in South African black females include low dietary calcium intake, limited physical activity (especially in the elderly), and frequent use of injectable contraception. Findings highlight the need to better define the role of clinical risk factors, to document hip fracture prevalence, and to develop local bone mass reference data that are appropriate for our black population.

TO4. Site-specific differences in bone mineral density in black and white premenopausal South African women
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Background: There is a paucity of data on the relative contribution of body composition, lifestyle factors, and socio-economic status unique to different ethnic groups in South Africa, to bone mineral density (BMD). We examined differences in femoral neck (FN), total hip (TH) and lumbar spine (LS) BMD between black and white premenopausal South African women, and the associations between BMD and body composition, lifestyle factors, and SES, in these two ethnic groups.

Method: BMD and body composition were measured in 240 black (27±7; 18-45 years) and 187 white (31±8; 18-45 years) women, using dual-energy X-ray absorptiometry. Questionnaires were administered to examine SES, physical activity, and dietary intake.

Results: After co-varying for age, FN and TH were higher in black than white women (FN 0.882±0.128 vs. 0.827± 0.116 g/cm², p-value <0.001; TH 0.970±0.130 vs. 0.943± 0.124 g/cm², p-value = 0.018). When adjusting for ethnic differences in body composition, LS was higher in white, than black, women. In black women, fat-free soft tissue mass, SES, and injectable contraceptive use, explained 33-42% of the variance in BMD at the hip sites, and 22% of the LS. In white women, fat-free soft tissue mass and leisure activity explained 24-30% of the variance in BMD at the hip sites, whereas fat mass, leisure activity, and oral contraceptive use, explained 11% of the variance at the LS.

Conclusion: FN and TH BMD were higher, but LS BMD was lower in black, than white, South African women, with body composition, lifestyle, and SES factors, contributing differently to BMD in these women.
TO6. Association of body mass index with fracture risk and bone mass in urban South African children: the Birth to Twenty cohort
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Worldwide prevalence of childhood obesity is increasing. This study aims to investigate the association of body mass index (BMI) with fracture risk and bone mass. Using the Bone Health cohort of the Birth to Twenty longitudinal study, we retrospectively obtained information of lifetime fractures until age 15 years, in 533 subjects. Whole body bone mineral content (BMC), bone area (BA), fat mass (FM) and lean mass (LM) [measured by dual energy X-ray absorptiometry (DXA) scans], physical activity, and anthropometric data, were obtained at ages 10 and 15 years. Non-fracturing black females were used as the control group. Individual anthropometric measurements [height for age Z score (HAZ) and BMI for age Z score (BAZ)] were calculated using the World Health Organization Anthroplus® software. White males who fractured were significantly taller (10 years, p-value < 0.01), more physically active (15 years, p-value < 0.05) and had higher LM (10 years, p-value = 0.01; 15 years, p-value < 0.001), while white females who fractured were fatter (10 years, p-value = 0.05 and 15 years, p-value < 0.05), than their non-fracturing peers. Overweight or obese white females had a greater number of fractures by the age of 15 years. At the age of 10 years, obese subjects had a higher BA and BMC at most sites, and fracturing obese black males had a lower BMC Z score at the whole body, hip, and spine, compared to their non-fracturing obese peers. Increased adiposity in white females is associated with increased fracture risk. This association is not evident in black females, despite an increasing prevalence of overweight or obesity in both groups that needs further elucidation.

TO7. Demographic profile and risk factors for osteoporotic hip fractures in the elderly in the Ethekwini municipality, KwaZulu-Natal
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Background: The aim was to determine the demographic profile and risk factors for osteoporotic hip fractures in the public sector in Ethekwini.

Method: Consecutive subjects aged ≥ 60 years, with minimal trauma hip fractures, were prospectively enrolled from five public sector hospitals. Demographic details were documented, and a questionnaire for risk factors, administered.

Results: In the 277 enrolled subjects, the mean age was 75.8 ± 9.1 years, with a female:male ratio of 2.8:1. Men were significantly younger than women [71.7 ± 9.3 years vs. 77.4 ± 8.6 years, p-value < 0.0001]. Indian subjects comprised 51.3%; African subjects, 32.1%; white subjects, 14.1%; and mixed ancestry subjects, 2.5%. Of those who completed the questionnaire (n = 200), hypertension was present in 112 (56%), diabetes mellitus in 56 (26.6%), arthritis in 55 (26.6%), and an underlying malignancy in 16 (8%). Forty-seven (23.5%) were smokers, 28 (14%) consumed alcohol weekly, 39 (19.5%) were below 57 kg, 72 (34%) had prior falls, and 14 (7%) gave a maternal history of falls or fractures. Despite a previous fragility fracture in 56 subjects (28%), only two subjects received specific treatment.

Conclusion: This study is the first to report hip fractures in all ethnic groups in South Africa, and suggests that the Indian population may be at high risk. In contrast to developed countries, hip fractures appear to occur at a younger age, especially in men. This study underscores the need to include osteoporosis in the healthcare package. A limitation of the study is the possible disproportionate representation of the ethnic groups due to differences in utilisation of public-sector hospitals.

The study was supported by an unrestricted educational grant from Servier Laboratories (SA).
Method: In a longitudinal study, subjects aged 60 years and over with minimal trauma hip fractures, were reviewed at three months to assess functional outcome and mortality.

Results: Two hundred patients were prospectively enrolled. The mean age was 74.2 ± 8.8 years (range 60-113 years), with a female:male ratio of 2.6:1. Surgery was performed on 186 subjects (93%), with 14 (7%) being unfit for it. The average length of stay was 21.6 days (range 4-120 days), and average time to surgery was 10.4 days (range 1-37 days). At three months, 35 subjects (17.5%) had died, and of the 117 subjects reviewed, 27 (23.5%) were able to ambulant independently, 64 (54.7%) required help, 26 (22.3%) were bed-bound, and 106 (90.5%) were unable to complete at least one instrumental activity of daily living (IADL). The quality of life (QOL) scale and Oswestry disability index showed a twofold decline, and the patient global assessment (visual analogue scale) worsened from 0.9 to 5. Apart from a history of arthritis, there were no other predictors of mortality.

Conclusion: The early mortality and morbidity in this study is higher than that reported internationally, and may be due to the significant delay before surgery, and lack of dedicated orthogeriatric facilities. Urgent healthcare reform is required to improve the management of osteoporosis and fragility fractures.

This study was supported by an unrestricted educational grant from Servier Laboratories (SA).

TO10. The anatomical basis of cortical porosity in children

CM Schnitzler, JM Mesquita

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Debate I: Bone mineral density measurement is a very useful tool to monitor the response to therapy in osteoporosis

Graham Ellis (for), and Stephen Hough (against)

TO11. T cells: unexpected players in the mechanism of action of parathyroid hormone

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TO12. Endocrine cross-talk between bone and fat: emerging new roles for well-known players

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Both osteoblasts and bone marrow adipocytes originate from a common mesenchymal stromal cell (MSC). In healthy individuals, a delicate balance is maintained between osteoblastic and adipogenic differentiation of MSCs, which ensures the preservation of bone architecture. Disturbance of this balance can skew MSC differentiation towards adipogenesis at the expense of osteoblastogenesis, resulting in decreased osteoblastic bone formation, and increased marrow adiposity. In addition, mature bone and fat tissue also regulate each other’s function in a reciprocal manner, through endocrine cross-talk. This physiological system, labelled the bone-adipose axis, is essential for the maintenance of skeletal integrity and energy homeostasis, and involves the actions of well-known hormones, such as insulin, leptin, and osteocalcin. While the traditional roles of these hormones are well described, recent studies have highlighted potential new roles for them in modulating the mechanisms by which mature adipocytes effect bone biology, and conversely, in the way that osteoblast products such as osteocalcin, modulate adipocyte function and energy homeostasis. This review will focus on the endocrine cross-talk between bone and fat tissue, including the clinical implications thereof, with regard to conditions such as obesity, lipodystrophy, diabetes, and the way in which pharmaceutical agents, such as glucocorticoids, thiazolidinediones, and antiretroviral drugs, impact on the skeleton.
TO13. Expression of the tumour suppressor PDCD4 during osteoblastic differentiation of adipose-derived stromal cells

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**Background:** The use of mesenchymal stromal cells (MSCs) has been cited as a putative therapeutic option for tissue regeneration in the future. Adipose tissue is an abundant source of these cells, which have the propensity to be differentiated into an osteoblastic, chondrocytic, adipocytic, or myoblastic phenotype, for possible regenerative therapy of bone, cartilage, fat, and muscle. However, for successful therapeutic use, the cell cycle must be precisely regulated to avoid aberrant cell function, such as uncontrolled proliferation or premature death. The expression of programmed cell death 4 (PDCD4) has been associated with the control of differentiation and proliferation in neoplastic and immortalised cells. However, the role for PDCD4 in the regulation of these cellular fates in primary MSCs had yet to be assessed. The aim was to examine the expression of PDCD4 in primary subcutaneous and visceral adipose-derived stromal cells of rats (ADSCs) during differentiation into osteoblasts.

**Method:** ADSCs were differentiated into mature osteoblasts, and proliferation measured using tritiated thymidine incorporation after 0, 3, 7, 14, 21, and 28 days of differentiation. The state of differentiation was determined by Alizarin Red S staining of mineralised nodules, and real-time quantitative polymerase chain reaction (QRT-PRC) analyses of the bone markers, MSX2 and Runx2. PDCD4 mRNA expression, during differentiation, was measured by QRT-PRC. PDCD4 protein expression was measured by Western Blot analysis.

**Results:** Subcutaneous ADSCs, but not visceral ADSCs, differentiate into osteoblasts after incubation in osteogenic media, as seen by calcified nodule formation and expression of bone markers. Preliminary data indicate that PDCD4 mRNA expression correlates with the state of differentiation, increasing during subcutaneous ADSC osteogenesis, but remaining low in non-differentiating visceral ADSCs. The proliferation profile of both cell types was similar.

**Conclusion:** Consequently, the tumour suppressor, PDCD4, is more closely associated with an increase in osteoblastic differentiation, rather than a decrease in proliferation in ADSCs.

TO14. Sodium orthovanadate stimulates osteoblast proliferation, but inhibits osteoblast function in vitro and in vivo

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**Background:** We have previously shown that vanadate can stimulate extracellular signal-regulated kinase activity and proliferation in culture-naive rat adipose-derived stromal cells (ADSCs), and also stimulates osteoblast proliferation in rats in vivo. We have also shown that ADSCs from rat subcutaneous adipose tissue can undergo osteoblast differentiation in vitro, but the effects of vanadate on the osteoblastic differentiation of ADSCs have not been investigated. Consequently, we wished to compare the effects of vanadate on osteoblast proliferation, differentiation, and function, between these in vitro and in vivo systems.

**Method:** For in vitro studies, ADSCs were isolated from the inguinal adipose tissue of rats, expanded in number, and treated with osteoblast differentiation media (OM: standard culture media supplemented with dexamethasone, ascorbic acid, and glycerol-2-phosphate) in the presence and absence of vanadate for 28 days. The deposition of calcified matrix, as a marker of mature osteoblast function, was quantified by means of Alizarin Red S staining, and normalised to relative cell density, which was measured using crystal violet stain. For in vivo studies, rats were administered vanadate via the drinking water for nine weeks, after which time time spaced tetracycline labelling was used to quantify bone deposition in the femur. Bone mineral density (BMD), bone formation rate (BFR), and surfaces covered by osteoblasts and osteoclasts, were also measured.

**Results:** In the in vitro studies, vanadate stimulated the proliferation of differentiating osteoblasts, but inhibited the formation of calcified matrix. This lack of increased function with increased osteoblast number was paralleled in in vivo data showing that vanadate increased osteoblast surfaces in rat femora, while no concomitant increase in BFR, or BMD, was observed.

**Conclusion:** Vanadate induced an increase in osteoblast numbers in vitro in rat ADSCs, as well as in vivo in rats, yet concomitantly decreased osteoblast activity. Further investigation examining osteoblastic marker expression is required to find whether this is due to inhibition of differentiation.
TO16. Human immunodeficiency virus and bone
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The improved pharmacotherapy of patients with human immunodeficiency virus (HIV)/acquired immune deficiency syndrome (AIDS) has significantly reduced mortality, converting this disease into a chronic disorder that requires long-term treatment. As individuals live longer and are subjected to the chronic sequelae of both the disease and its treatment, a number of complications have emerged, including metabolic bone disorders, such as osteoporosis, osteomalacia, osteonecrosis, and immune reconstitution inflammatory syndrome-induced hypercalcaemia.

It has been suggested that more than 65% of patients with HIV have a low bone mineral density (BMD), and that the odds ratio for osteoporosis and fracture are 3.7 and 2.5 respectively. Yet the underlying pathogenesis, clinical relevance, and most appropriate management of this disorder, remains unclear. Some ascribe the low BMD largely to the low body mass which typically accompanies HIV/AIDS.

Others implicate:
- The disease (pro-inflammatory cytokines which osteoclastogenesis, malnutrition which osteoblastic bone formation, or even direct infection of osteoblasts (OB) by the HIV virus and hOB apoptosis);
- Associated osteoporosis risk factors (alcohol, smoking, hypogonadism, and hypovitaminosis D); and or
- The deleterious effects of HIV treatment on bone.

The latter may involve RANKL-mediated increase in osteocastic bone resorption by some protease inhibitors, but more likely to result from the effects of antiretroviral drugs on osteoprogenitor cells, with an increase in adipogenesis, at the expense of osteoblastogenesis. An inverse relationship between lipohypertrophy or metabolic syndrome and BMD has been reported by some, but not all, researchers. Recent meta-analyses show that bisphosphonates increase BMD, but fracture data will have to await further study.

TO17. Bone health and body composition in HIV-positive and -negative urban black South African women
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Background: Human immunodeficiency virus (HIV) infection and antiretroviral drugs (ARVs) are associated with low bone mineral density (BMD). The purpose of this study was to consider bone density and body composition (BC) in HIV-positive, urban women.

Method: Two hundred and forty-seven premenopausal [mean ± standard deviation (SD) age 32.1 ± 7.24 years], black women were recruited in Soweto, and underwent baseline dual energy X-ray absorptiometry (DXA) scans, and other assessments. Group 1: HIV-negative control (n = 98); Group 2: HIV-positive, preserved cluster of differentiation 4 (CD4) (mean CD4: 413 ± 91; n = 74); Group 3: HIV-positive, low CD4 prior to ARV initiation, (mean CD4: 161 ± 70; n = 75).

Results: Mean values ± SD in groups 1, 2 and 3 respectively, for height (m) were similar (p-value > 0.05). Weight (kg) significantly (p-value < 0.02) differed, with group 3 being the lightest (69.7 ± 17.0, 72.0 ± 17.4, and 62.3 ± 15.2 respectively). No significant differences in BMD at the hip, lumbar spine, and whole body (p-value > 0.05) were found with and without adjustment (weight, height, and age), and no difference in fat/lean ratio (p-value > 0.05). Previous fractures were reported in 23.4%, 25.7% and 13.3%, respectively. After full adjustment for bone area, weight, height, and age, there were no significant BMD differences at any site.

Conclusion: HIV-positive women with low CD4 counts are significantly lighter than HIV-positive women with preserved CD4 counts and HIV-negative women, but have no significant difference in BMD and fat or lean measures. Currently, the subjects are being followed-up longitudinally to assess the effects of ARV exposure.

TO18. Prevalence and predictors of low bone mineral density in HIV-positive South Africans on antiretroviral therapy
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Background: Human immunodeficiency virus (HIV) positive men and women from developed countries have reduced bone mineral density (BMD). In these patients, antiretroviral therapy (ART) does not appear to play a significant role. Traditional risk factors are more prominent. The prevalence and predictors of low BMD in HIV-positive patients on ART in sub-Saharan Africa are unknown. The objective was to determine the prevalence and predictors of low BMD in HIV-positive patients.

Method: The method was a cross-sectional study in an ambulatory HIV-infected cohort in Cape Town which examined the metabolic complications of ART. A randomly selected sub-sample of these patients underwent BMD assessment, using dual-energy-X-ray absorptiometry (DXA) scans. Only patients < 50 years old were included, and a low BMD was defined according to the NOFSA guidelines as a Z-score < -2.0.

Results: DXA scanning was performed in 422 patients who were ART-naïve (n = 190); ART-reg1 (on non-nucleoside reverse transcriptase inhibitor-based ART), (n = 145); ART-reg2 (on protease inhibitor-based ART), (n = 87); randomly selected from 1 019 patients (ART-naïve 436, ART SB3) in the parent study. A low BMD was detected in 52 (27%) ART-naïve patients, 45 (31%) ART-reg1 patients, and 27 (31%) ART-reg2 patients. Of the 124 patients with a low BMD, 121 (99%) had a low BMD at the spine and, 21 (15%) patients had a low BMD at the hip. Patients with a low BMD had a lower body mass index (BMI) [22 (22.32) vs. 24 (21.27) kg/m²; p-value < 0.0001], but all other measures of body composition (waist circumference, waist:hip ratio, abdominal skinfold thickness, and calf skinfold thickness) were not significantly different. There was no difference between the groups with respect to time on ART, height, cluster of differentiation 4 count, age, smoking, alcohol use, and vitamin D status. However, on multivariate logistic regression analysis, low BMI, ART exposure, and male sex, were all independently associated with low BMD at the hip; and male sex, low BMI, and smoking, were all independently associated with low BMD at the spine.

Conclusion: ART exposure was only associated with a low BMD at the hip, and smoking was only associated with a low BMD at the spine, whereas male gender and low BMI were associated with a low BMD at both sites. Interestingly, vitamin D status was not associated with a low BMD.
FO1. Androgens and bone
Roger Bouillon
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FO2. Non-union and delayed union in osteoporotic fractures: is there a place for anti-osteoporosis medication?
Stanley Lipschitz
The Osteoporosis Clinic, Rosebank, Johannesburg

FO3. Fragility fractures and the bisphosphonates
Mac Lukhele
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Bisphosphonates have a relatively good safety record, and are generally tolerated by patients. Usually, gastrointestinal side-effects have been overcome by the development of long-acting bisphosphonates, together with intravenous administered ones. Patients can also develop flu-like symptoms, which usually resolve. Rare complications, such as renal dysfunction and jaw osteonecrosis, have been described.

In the past six years, there have been several cases of patients who developed atypical fragility fractures after taking bisphosphonates for a long time.

The characteristics of these atypical fragility fractures are that:
- They are associated with minor trauma.
- They are located subtrochanteric, or on the shaft.
- They are transverse.
- There is associated cortical thickening, with beaking of the cortex.
- The patient often has pre-injury thigh pain.

The pathophysiology of atypical subtrochanteric fractures, following long-term usage of bisphosphonates, is not known. Several possible mechanisms that work either alone, or together, have been suggested. Bisphosphonates may affect bone mineralisation density distribution by slowing bone turnover, which leads to more homogenous bone, which increases the risk of crack and fracture. Reduced bone turnover also increases the accumulation of microdamage, as cracks are not repaired. This reduces bone durability, thereby increasing susceptibility to more cracks. Although it has not been replicated in any studies, bisphosphonates were reported to prevent and reduce collagen maturation in that way, decreasing bone durability.

The potential link of bisphosphonates, with atypical subtrochanteric fracture of the femur, has become one of the controversial orthopaedic topics of the times. The first report on the atypical fractures was by Odvina in 2005, where he identified atypical fragility fracture in patients who had been on oral bisphosphonates. This was followed up by several case reports, case-control studies, epidemiology studies, and review of phase III trial subjects. To date, there is no consistent high-level evidence on the link between the long-term use of bisphosphonates and atypical fragility fractures. The available evidence does not suggest that the well-known benefits of bisphosphonate treatment are outweighed by the risk of these rare atypical subtrochanteric fractures. The US Food and Drug Administration has recommended extensive discussion with patients, and continuous drug usage, with strict surveillance. Regarding atypical fractures associated with long-term bisphosphonates use, the American Society of Bone and Mineral Research committee has made several recommendations pertaining to medical and surgical treatment strategies.
FO4. Calcium homeostasis during pregnancy and lactation
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Pregnancy and lactation place considerable demands on maternal calcium homeostasis. It is estimated that the growing foetus requires an average of 100 mg calcium daily, spread over the full nine months, while lactation imposes further stress of some 300 mg daily for the duration of lactation. These increased calcium demands have to be met by increased maternal intestinal calcium absorption, reduced renal calcium excretion, or increased bone resorption. Based on these increased requirements, it has been customary to recommend increased maternal calcium intake, during both pregnancy and lactation. However, are these recommendations necessary, or based on scientific evidence?

A number of studies have investigated the influence of calcium supplementation, both during pregnancy and lactation, on the degree of bone loss that occurs during these periods, and the rate of recovery following weaning. There is no convincing evidence that calcium supplementation ameliorates the degree of bone loss, or increases the rate of recovery during weaning. Furthermore, supplementation has no effect on breast milk calcium concentrations during lactation. However, a few studies suggest that during pregnancy, calcium supplementation may influence foetal, or neonatal, bone mass.

In conclusion, bone loss that occurs during pregnancy and lactation recovers completely following weaning, even in mothers whose habitual calcium intakes are well below the levels recommended in a number of developed countries. There is no evidence that calcium supplementation influences maternal bone loss or recovery. Thus, it is not recommended as a routine supplement during this period of calcium stress.

FO5. The association between vitamin D status and body composition, serum lipids and HOMA-IR in urban 12-year-old South African children
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Background: The aim was to determine the association between plasma 25-hydroxyvitamin D [25(OH)D], and body composition, lipid profiles, and homeostatic model assessment in insulin resistance (HOMA-IR) in urban South African children.

Method: The method was a cross-sectional study of 261 children, [black children, n = 197; and white children, n = 64], with a mean age of 12.7 years, who formed the Bone Health sub-cohort of the Birth to Twenty cohort. The evaluation included weight and height, body composition by dual-energy-X-ray absorptiometry (DXA) scan, serum 25(OH)D [Diasorin Liaison®], lipids and glucose (RX Randox Daytona®) and insulin (Immulate 1000®).

Results: Both ethnic groups were vitamin D-replete. White children had greater 25(OH)D and total lean tissue/height, and lower insulin and total fat/height than their peer. In black children, 25(OH)D correlated negatively with high-density lipoprotein (HDL) cholesterol (r = -0.17), and in black females, with triglycerides (r = -0.3). There were no significant correlation with anthropometry, body composition, or other lipid variables. In white children, 25(OH)D correlated negatively with total cholesterol (r = -0.3), triglycerides (r = -0.4), BMI (r = -0.3), and total lean tissue/height (r = -0.4). In white female subjects only, 25(OH)D correlated negatively with HDL-cholesterol (r = -0.3), and HOMA-IR (r = -0.4).

Conclusion: The correlations of 25(OH)D with anthropometric variables, body composition, lipids, and HOMA-IR, differ between ethnic and gender groups. This may be due to differences in fat mass distribution between the ethnic and gender groups. The authors had no conflict of interests.

FO6. The association between early life factors and bone mass and size in 13-year-old urban South African children
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Background: To determine if early growth is associated with bone mass and size measured using peripheral quantitative computed tomography (pQCT) at 13 years of age.

Method: We examined the association between size [weight, height and body mass index (BMI)] at two years of age, current height, fat and lean mass, and bone parameters in black boys (n = 170), and girls (n = 150), at 13 years of age.

Results: In boys, BMI at two years was associated with metaphyseal (4%) tibia total area and trabecular density, before and after adjusting for current size. Height at two years was associated with diaphyseal (38%) tibia total area, but not after adjusting for current size or puberty. In girls, metaphyseal (4%) radius total area was associated with weight at two years, but not after adjusting for current size, and then puberty. Weight at two years was inversely associated with 38% tibia total area in girls, before and after adjusting for current body size, and pubertal development.

Conclusion: pQCT-derived trabecular bone density was associated with BMI at two years, independent of current body size and pubertal status in boys, while height at two years influenced diaphyseal size, probably through its effect on current body size. In black girls, who were more pubertally advanced than boys, current body size adjustments removed the effect of weight at two years on metaphyseal and diaphyseal size. Pubertal growth may mask the independent influence of early growth on bone density and size.
FO7. Sex and ethnic differences in skeletal maturation during adolescence
John Pettifor,1 Nicola Hawley,1 2 Noel Cameron,1 2 Shane Norris1
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Skeletal maturation during puberty plays a major role in determining bone mass and size accrual during adolescence, thus an understanding of sex and ethnic differences in the tempo of skeletal development is important when interpreting bone mass measurements during this period. The aim of this study was to determine the pattern of skeletal maturation in a longitudinal cohort of black and white boys and girls living in Johannesburg.

Skeletal maturity was assessed annually from hand-wrist radiographs of children \(n \approx 475\) in the Bone Health sub-cohort of the Birth to Twenty cohort in Johannesburg from the age of 9 to 17 years, using the Tanner and Whitehouse III (TW3) RUS technique, and a computerised Greulich and Pyle method using BoneXpert 9. In girls, menarcheal age was determined by questionnaire.

Age of menarche was similar in black and white girls (mean 12.4 and 12.5 years respectively), and black and white girls’ skeletal maturation advanced at similar rates through puberty. In black boys, skeletal maturity diverged from that of white boys from the age of 12 years, so that by 14 years, they were approximately 12 months behind, and remained so over the next three years.

Menarcheal age in black girls has shown marked secular trends over the last 50 years, with a reduction of 3.5 years, while less marked changes have occurred in white girls (0.6 years in 27 years). Black and white girls have shown a similar timing and rate of skeletal maturation during puberty. However, in black boys, skeletal maturation is delayed. These patterns should be taken into consideration when assessing bone mass measurements during adolescence.

Debate II: Kyphoplasty is an effective and safe way in which to manage the patient with symptomatic osteoporosis
Mac Lukhele (for), and Stan Lipschitz (against)

FO8. Meet the expert - bisphosphonates: when and how to stop
Steven R Cummings
Professor of Medicine and Epidemiology; Director, San Francisco Coordinating Center, CPMC Research Institute, University College of San Francisco, USA

FO9. Novel treatments to manage osteoporosis
Steven Cummings
Professor of Medicine and Epidemiology; Director, San Francisco Coordinating Center, CPMC Research Institute, University College of San Francisco, USA; and University of California, San Francisco, USA

Several new treatments for osteoporosis are being developed that work using novel biological mechanisms, and which may have advantages over existing therapies. Denosumab has not yet been approved for use in South Africa, but it works via the receptor activator of the RANK pathway. Twice yearly, subcutaneous injections achieve maximum reduction in bone resorption, and improve compliance with treatment, and reduce the risk of all types of fractures, at least as effectively as bisphosphonates.

Odanacatib inhibits cathepsin K, reduces bone resorption more than formation, and appears to steadily increase bone mineral density (BMD), and perhaps add cortical bone. It is hoped that odanacatib might reduce non-spine fracture risk more than current therapies. Results of a pivotal anti-fracture trial should be available within the year.

Antisclerostin antibodies block sclerostin’s inhibition of osteoblastic bone formation. They dramatically increase bone formation, and decrease bone resorption. This therapy has the potential to “cure” osteoporosis. Anti-fracture trials will begin in 2012.

Daily intermittent nitroglycerin may work via osteocytes, including inhibition of sclerostin production. In a two-year trial, treatment increased bone formation, decreased resorption, and increased cortical bone width by 15-25% in the tibia and radius, more than has been observed using teriparatide, or any other therapy. Because it is generic and widely available, it will be difficult to prove its anti-fracture effects in a large expensive trial.

FO10. The placebo effect: is it real or placebo?
Graham Ellis
Mediclinic Vergelegen, Somerset West

While there is widespread belief by medical practitioners that the “placebo effect” exists, the explanations for its existence and the magnitude of the effect are controversial, and difficult to measure. This uncertainty has spawned the burgeoning $60 billion-per-annum “alternative health” industry, in which 95% of alternative therapies have been ascribed to the placebo effect.

It is recognised that placebos have real physical effects, particularly on pain, mood, and insomnia. These effects are attributed to expectancy, whereby the anticipation of an effect will lead to a specific outcome, and conditioning, whereby the placebo effect is a conditioned response.

The placebo controlled, double-blind clinical trial has become the “gold standard” in the assessment of the efficacy of new therapeutic agents. The number of new therapeutic agents that make it through Phase II and III clinical trials is declining, and since 2007, approximately 50% of these agents have failed, due to their inability to prove any therapeutic advantage over placebo. There is evidence that the placebo effect in clinical trials is increasing.

The response that is seen in the placebo arm of a clinical trial is not always due to the placebo effect. Statistical regression to the mean predicts that patients selected for an abnormality will tend to improve. Many of the improvements attributed to the placebo effect may be no more than statistical regression, and many of the effects attributed to placebos may be no more than a statistical artifact. I ask: is the placebo effect a real, perceived, or statistical, effect?

Bob Millar
Edinburgh, UK
FO12. Menopausal hormone therapy in the management of osteoporosis 10 years after the Women’s Health Initiative study

Mike Davey
Westville Hospital, Kwazulu-Natal

The publication of the Women’s Health Initiative (WHI) study in 2002, called into doubt the use of hormone therapy for the management of menopausal problems. Specifically, the original publication concluded that the use of estrogen and progestin increased the risk of coronary heart disease death and non-fatal myocardial infarction, the primary end-points of this study. With reference to osteoporosis, the WHI reported a reduction in both vertebral and non-vertebral fractures, with the use of estrogen and progestin.

In the ensuing 10 years, the WHI has published more material. The original conclusion of increased risk of cardiac events has been modified to “no decrease in the risk of these events”. Re-analyses of this, and other studies, have suggested that there may be a decrease in overall cardiac events, and a decrease in overall mortality if hormone therapy is initiated within 10 years of the onset of menopause, giving rise to the “window of opportunity theory”.

Different types of hormones from those used in the WHI study, lower doses of hormones, and alternative modes of delivery, may further improve the risk:benefit ratio of hormone therapy.

Given the evidence that has emerged in the 10 years since the initial WHI publication, with appropriate individualisation of therapy, menopausal hormone therapy should still be considered as an available option when making treatment decisions for the prevention of bone loss, and decreasing fracture risk, in the recently menopausal patient.

FO13. Vitamin D is a multifunctional hormone

Roger Bouillon
Professor of Medicine, Laboratory for Experimental Medicine and Endocrinology, Katholieke Universiteit Leuven, Belgium

The vitamin D endocrine system is essential for calcium and bone homeostasis. Absence of a functional vitamin D receptor (VDR) or cytochrome P27B1 (CYP27B1) creates a severe rachitic bone and growth plate phenotype in humans and mice, as in severe vitamin D deficiency. The intestine is the key target for VDR, as a high-calcium intake or selective VDR rescue in the intestine restores a normal bone and growth plate phenotype. Selective absence of VDR in osteoblasts does not create a bone phenotype when calcium intake is normal.

Tissue-specific deletions of VDR or CYP27B1 have now better defined the role of vitamin D in different tissues. The implications for humans are multiple. Rickets is still endemic in different parts of the world, and milder forms of vitamin D deficiency are present in more than a billion people worldwide, so that appropriate large-scale strategies are needed to correct this situation.

VDR is ubiquitously expressed, and about three per cent of the mouse or human genome is regulated by D-endo. The native immune defense system is activated by the vitamin D endocrine system, but VDR or vitamin D deficiency leads to increased sensitivity to autoimmune diseases, such as inflammatory bowel disease or autoimmune diabetes, after exposure to predisposing factors. VDR-deficient mice do not have a spontaneous increase in cancer, but are more prone to oncogen, chemocarcinogen, or UVB-induced tumours. A wealth of observational studies in men also links a poor vitamin D nutritional status to increased risk of all major cancers. The vitamin D endocrine system also relates to the cardiovascular system, as VDR or CYP27B1 KO mice develop high renin hypertension, cardiac hypertrophy, and increased thrombogenicity. Observational studies in men also link poor vitamin D status to all aspects of the metabolic syndrome, and increased risk of cardiovascular diseases. The muscle development of VDR KO mice is delayed, and their fertility is impaired.

Whether the same spectrum of activity is also operational in humans has not yet been established, but vitamin D deficiency is frequently associated with an increased prevalence of expected diseases, on the basis of the VDR KO phenotype. Prospective and intervention studies will be presented to define the spectrum of activities, and optimal vitamin D status for global health.
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SAO1. Jackson revisited: the myth of pre-diabetes
Edwin Gale
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SAO2. Glycated serum albumin, plasma fibronectin and urinary type IV collagen as markers of incipient nephropathy in African and Indian subjects with type 1 diabetes in KwaZulu-Natal
Anban Naidoo, Nicola Rodda, Sedeshan Govender, Suresha Maharaj, Imran Paruk, Fraser Pite, Ayeshka Motala
University of KwaZulu-Natal

SAO3. The prevalence of newly diagnosed diabetes, IGT, and IFG in a population-based survey, and in an HIV-positive cohort in Cape Town
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Division of Diabetic Medicine and Endocrinology
Division of Pharmacology
Human Biology, University of Cape Town, Biostatistics and CDL Units MRC

Background: There is growing concern that exposure to antiretroviral therapy (ART) will exacerbate the current rising prevalence of dysglycaemia. This is particularly pertinent to South Africa, which in global terms, has the greatest number of human immunodeficiency virus (HIV) positive people. The objective was to compare the prevalence of newly diagnosed diabetes, impaired glucose tolerance (IGT) and impaired fasting glucose (IFG) in the urban black population of Cape Town, and in a cohort of HIV-positive subjects from the same community.

Method: Two samples of similar age were studied, namely a cohort of HIV-positive patients, who were ART-naïve (n = 393) on non-nucleoside reverse transcriptase inhibitor-based ART (ART-Reg1) (n = 439), or protease inhibitor-based ART (ART-Reg2) (n = 108), attending a primary care HIV clinic, and a randomly selected cross-sectional sample (n = 880), from the same Cape Town townships, of unknown HIV status, who attend the primary care clinics. Demographic and anthropometric data were collected from all the patients, who also underwent oral glucose tolerance tests. The latest World Health Organization criteria were used to define categories of dysglycaemia. Logistic regression analysis assessed the independent effects of determinants on dysglycaemia (diabetes and IGT and IFG).

Results: The mean and standard deviation (SD) ages and body mass index (BMI) were: naive: 33.6 (8.7), 25.9 (6.2); ART-Reg1: 36.1 (8.9), 26.8 (5.8); ART-Reg2: 36.7 (8.3), 27.5 (6); and cross-sectional 39.9 (10.0), 29.2 (8.4) years and kg/m² respectively.

Prevalence and (95% CI) diabetes, IGT and IFG are listed in the Table I.

| Table I: Prevalence and (95% CI) diabetes, impaired glucose tolerance and impaired fasting glucose |
|---|---|---|---|
| | Diabetes | IGT | IFG |
| ART-naïve | 3.0 (1.3, 4.7) | 4.3 (2.3, 6.3) | 14.2 (10.8, 17.7) |
| ART-Reg1 | 2.3 (0.9, 3.7) | 2.6 (1.0, 3.9) | 21.1 (17.4, 25.0) |
| ART-Reg2 | 5.6 (0.1, 9.8) | 12.0 (5.9, 18.2) | 19.4 (11.9, 26.9) |
| Cross-sectional sample | 4.9 (3.5, 6.3) | 11.6 (7.4, 15.7) | 13.5 (8.7, 23.3) |

a = impaired glucose tolerance, b = impaired fasting glucose, c = antiretroviral therapy

On preliminary logistic regression analysis, using ART-naïve as a reference group, age, male gender, BMI > 30 kg/m² and ART-Reg2 were positively associated with dysglycaemia, and being assumed HIV negative, i.e. the participants from the community survey, was protective.

Conclusion: Previously undiagnosed dysglycaemia is common in this community, especially in subjects on regimen 2.

SAO4. Ethnic differences in ectopic fat and associations with insulin sensitivity in black and white South African women
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University of Washington, USA

Ectopic fat deposition in muscle and liver is an important factor that links obesity to insulin resistance, but these associations may vary by ethnicity. Therefore, we examined ethnic differences in ectopic fat deposition and its association with insulin sensitivity, in obese black and white South African women. Body composition (dual energy X-ray absorptiometry), liver and muscle (proton-magnetic resonance spectroscopy), and insulin sensitivity (euglycaemic hyperinsulinaemic clamp), were measured in 16 obese black, and 16 obese white, premenopausal South African women. Black and white women were matched for age (36 ± 5 vs. 37 ± 4 years, p-value = 0.670); body mass index (BMI) (37.8 ± 4.9 vs. 35.2 ± 3.6 kg/m², p-value = 0.097); and insulin sensitivity (M/I: 6.7 ± 3.8 vs. 6.8 ± 3.2 mg/min/kg lean body mass/mU/l, p-value = 0.872). Black women had less liver fat (2.1 ± 1.8 vs. 7.8 ± 9.4%, p-value = 0.037), but greater extramyocellular (EMCL): 1 236 ± 765 vs. 748 ± 491 AU, p-value = 0.029), but not intramyocellular (IMCL) fat than white woman (IMCL: 1 082 ± 670 vs. 751 ± 319 AU, p-value = 0.298). Liver fat correlated with M/I in white (r = -0.61, p-value = 0.026), but not black women (r = -0.17, p-value = 0.536). There were no associations between IMCL and M/I in black (r = -0.26, p-value = 0.369) or white women (r = -0.04, p-value = 0.885), whereas the association between EMCL and M/I differed by ethnicity (p-value = 0.031), such that EMCL was positively associated with M/I in white (r = 0.52, p-value = 0.045), but not black women (r = -0.30, p-value = 0.300). The associations between ectopic fat deposition and M/I in white women were not independent of body fat distribution, with trunk or leg fat being the most significant (r = -0.70, p-value = 0.002) correlate of M/I. In contrast, M/I was more closely correlated with absolute fat mass in black women (body fat (kg): r = -0.52, p-value = 0.039). In conclusion, ectopic fat deposition and the association with insulin sensitivity, differs between black and white women.
**Sa05. Physical activity is positively associated with a lowered metabolic risk in black South African women**

K Dickie, S Chantrill, LK Micklesfield, EV Lambert, J Evans, CL Jennings, Y Joffe, JH Goedecke

UCT/MRC Research Unit for Exercise Science and Sports Medicine, Department of Human Biology, University of Cape Town

**Background:** The objective was to compare body composition and metabolic risk outcomes between sufficiently and insufficiently active black South African women.

**Method:** Physical activity (minutes per week) was estimated using the validated Global Physical Activity Questionnaire (GPAQ). Body composition (dual-energy X-ray absorptiometry and computerised tomography), blood pressure, fasting glucose, insulin and lipid levels, were measured in 231 black South African women (26 ± 7 years).

**Results:** Based on the GPAQ analysis guide cut-offs [World Health Organization (WHO), 2010], 61.1% (95% CI: 54.4-67.4%) of the women were considered active (n = 141), whereas 38.9% (95% CI: 32.6-45.6%) were considered insufficiently active (n = 90). Body mass index [24.9 (22.2-33.8) vs. 33.9 (25.4-38.7) kg/m², p-value = 0.001]; body fat [35 (28.6-43.7) vs. 42.2 (35.4-46.3%), p-value = 0.001]; and fasting serum insulin levels [7.9 (5-14) vs. 9.8 (5.8-16.9) mU/l, p-value = 0.04] were significantly lower, whereas high-density lipoprotein (HDL) cholesterol levels were higher [1.3 (1.1-1.6) vs. 1.2 (1.1-1.6) mmol/l, p-value = 0.017] in the sufficiently active, compared to the insufficiently active group, respectively.

**Conclusion:** Women who meet the WHO criteria for physical activity had lower body fat and fasting insulin levels, and higher HDL cholesterol values, than those who did not meet the criteria. The promotion of increased daily physical activity among black South African women should be encouraged to reduce metabolic risk.

**Sa06. Somatostatin analogues as the first-line therapy in acromegaly**

Annamaria Colao

Department of Molecular and Clinical Endocrinology and Oncology, Federico II University of Naples, Italy

Currently, therapy based on glucagon-like peptide-1 (GLP-1) is one of the most promising treatments for type 2 diabetes. Because GLP-1 is rapidly degraded by dipeptidyl-peptidase-4 (DPP-4), research has focused on DPP-4 inhibitors to raise levels of GLP-1 which are attenuated in type 2 diabetes. We tested whether treatment of obese, pre-diabetic rats with cardiovascular pathology, with a DPP-4 inhibitor (PFK275-055) was cardioprotective.

Obesity was effected in diet-induced obese (DIO) Wistar rats for 12 weeks, after which half of the control-fed and DIO rats were treated orally with 10mg/kg/day PFK275-055. After four weeks of treatment, in conjunction with the obesity-inducing diet, animals were sacrificed, the blood collected, the body weight and intraperitoneal (IP) fat weight recorded, pancreata harvested, and isolated hearts perfused (Langendorff perfusion: infarct development after regional ischaemia, recovery after low-flow ischaemia). The kinase profile was determined in the reperfusion phase. Ventricular myocytes were prepared (standard collagenase perfusion) to determine insulin sensitivity via (1H)-2-deoxyglucose accumulation.

GLP-1 levels were attenuated in DIO, and restored by treatment. Insulin levels were 49% higher in DIO, and lowered by treatment. DIO suppressed pancreatic beta vs. alpha cell ratio, and treatment partially restored this. There were no effects on weight, IP fat or blood glucose levels. DIO animals: 47.7 ± 4.6% infarct of area at risk vs. control = 30.0 ±3.7 and DIO treated = 29.8 ± 3.1; p-value < 0.05, n = 6/group. The ratio of phosphorylation or total PKB/Akt and extracellular signal-regulated kinase 42 (ERK42) was attenuated in DIO, and improved after treatment. Cardiomyocytes did not show insulin sensitisation.

Treatment of pre-diabetic animals with a DPP-4 inhibitor was cardioprotective, improved glucose homeostasis and RISK pathway profile on reperfusion after ischaemia.

**Sa08. Raising the bar: liraglutide (glucagon-like peptide-1 analogues) and composite end-points**

MAK Omar

Centre for Diabetes and Endocrinology, Overport, Durban

**Background:** Cardiovascular disease (CVD) is the commonest cause of mortality in subjects with Type 2 diabetes. Other well-established CVD risk factors e.g. obesity, hypertension and dyslipidaemia often co-exist with diabetes. Hypoglycaemia is now also recognised as a CVD risk factor.

**Method:** Data from the Lead MT programme were analysed to evaluate the effects of liraglutide, a GLP-1 analogue, and other anti hyperglycaemic agents, on glycaemic control and certain CVD endpoints. The Lead TM programme, comprising 6 phase 3 clinical trials involving over 4000 Type 2 diabetic subjects compared liraglutide as monotherapy and as combination therapy with other agents, viz: metformin, glimepiride, rosiglitazone, insulin glargine and exenatide. Composite end-point evaluation was based on meta-analysis using logistic regression across Lead studies 1-6.

**Results:** A decrease in HBAIC associated with loss of weight was significantly more common in those on liraglutide (78%) and exenatide (72%) compared to the other treatment groups. Composite end-point (1) comprising HBAIC < 7%, + no weight gain + no confirmed hypoglycaemia was more common in the liraglutide group (OR 2.0-10.3) compared to the other groups. Composite end-point (2) comprising HBAIC < 7%, systolic BP < 130mmHg and no weight gain was also more common in the liraglutide group.

**Conclusion:** Data from the Lead studies have shown that liraglutide not only improves glycaemic control but has a beneficial effect on certain CVD composite end-points.

**Sa09. The Bernard Pimstone Memorial Lecture: manipulating GPCRs to treat endocrine diseases**

Robert Millar

Edinburgh, United Kingdom

**Sa10. Treatment of type 1 diabetes: biologics to bionics**

David Nathan

MGH Diabetes Center, Harvard Medical School, Boston, USA
Saturday 21 April 2012: Poster presentations

SaP1. tissue-nonspecific alkaline phosphatase inhibition impairs lipid accumulation in rat adipose-derived stromal cells

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1Stellenbosch University
2University of Witwatersrand

Tissue-nonspecific alkaline phosphatase (TNAP) is found in many cell types throughout the body, including bone, liver, kidney, neural and adipose tissue. TNAP has an established function in bone mineralisation, where it serves to hydrolyse inorganic pyrophosphate (Ppi) into inorganic phosphate (Pi), which, in combination with Ca2+ ions, forms the hydroxyapatite crystals present in mineralised bone. TNAP also serves as a marker of osteoblastic differentiation in preosteoblastic cells. However, previous results obtained in immortalised 3T3-L1 pre-adipocytes have shown that TNAP is also involved in adipogenesis, surprisingly. Therefore, we questioned whether TNAP activity was required for lipid accumulation in primary adipose-derived mesenchymal stromal cells (ADSCs), and if any possible association between TNAP activity and adipogenesis was dependent on the depot from which the cells were obtained. Consequently, ADSCs from the inguinal subcutaneous and visceral perirenal depots were cultured in standard adipogenic differentiation medium, in the presence and absence of the TNAP-specific inhibitors, levamisole, histidine and L-homoarginine. In order to determine whether blocking TNAP would have an effect on adipogenesis, Cells from the subcutaneous and visceral depots were compared, as preadipocytes from these depots have previously been found to have different adipogenic potential. Lipid accumulation was used as an indicator of adipogenesis, and measured by staining with Oil Red O. Preliminary results indicate that lipid accumulation in rat ADSCs, from both visceral and subcutaneous depots, was similarly impaired in the presence of each of the three TNAP inhibitors, with a slight additive effect on the inhibition of lipid accumulation, observed when the inhibitors were used together. The obtained results indicate that TNAP may play a role in adipogenesis in ADSCs.

SaP2. Glucocorticoid receptor-α mRNA is downregulated in gluteal adipose tissue of black South African women and associates, with increased metabolic risk

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Increased capacity for glucocorticoid regeneration in subcutaneous adipose tissue (SAT) by 11β-hydroxysteroid dehydrogenase-1 (11HSD1) is associated with obesity and associated risk factors. We hypothesised that downregulation of SAT 11HSD1 and/or glucocorticoid receptor-α (GRα) may explain differences in body fat distribution and metabolic risk between black and white women. The study aimed to compare the expression of 11HSD1 and GRα, and glucocorticoid-responsive genes in gluteal SAT depots, and determine their relationships with body composition and metabolic risk factors in South African women. Body fat (DXA) and distribution (computerised tomography), insulin sensitivity (S, intravenous glucose tolerance test), and the expression of 11HSD1, GRα, peroxisome proliferator-activated receptor γ (PPARγ), adiponectin, CD68 and tumour necrosis factor α (TNFα), were measured in gluteal SAT of 56 normal-weight and obese black and white premenopausal South African women. 11HSD1 expression was increased with obesity in both black and white women (p-value < 0.001), but did not differ by ethnicity. In contrast, GRα mRNA levels were significantly lower in both normal weight and obese black, compared to white women (0.86 ± 0.25 vs. 1.31 ± 0.65 AU, and 0.52 ± 0.21 vs. 0.91 ± 0.26 AU, respectively, p-value < 0.01). Lower GRα expression in black women was associated with increased CD68 (r = -0.64, p-value < 0.001) and TNFα (r = -0.39, p-value < 0.01), reduced PPARγ (r = 0.84, p-value < 0.001) and adiponectin mRNA levels (r = 0.47, p-value < 0.001), as well as increased fat mass (r = 0.61, p-value = 0.001) and serum triglycerides (r = -0.43, p-value = 0.022), and reduced high-density lipoprotein-cholesterol (r = 0.48, p-value = 0.010) and S (r = 0.47, p-value = 0.016). In conclusion, expression of GRα is downregulated in gluteal SAT of black South African women, and associates with reduced adipogenic capacity and increased metabolic risk factors.

SaP3. The efficacy of Prosopis glandulosa as an anti-diabetic treatment in rat models of diabetes and insulin resistance

Cindy George, Barbara Huisamen
Stellenbosch University

Background: In recognition of the increased incidence of diabetes mellitus, untested agents are flooding the market. Diavite™ (pods of Prosopis glandulosa) is marketed as a glucose-stabilising supplement. The aim of this study was to determine the efficacy of P. glandulosa as an anti-diabetic agent.

Method: Male Wistar rats were rendered type 1 diabetic with streptozotocin (STZ) and insulin-resistant by diet. Half the animals were placed on P. glandulosa treatment (100 mg/kg/day) for eight weeks, and the remaining animals served as controls. At the time of sacrifice, blood was collected for glucose and insulin level determination, the pancreata of the STZ rats were harvested for histological analysis, and cardiomyocytes and skeletal muscle strips prepared for insulin sensitivity determination.

Results: In the type 1 diabetic model, P. glandulosa ingestion resulted in significant increased insulin levels (p-value < 0.001), accompanied by decreased glucose levels (p-value < 0.05). Additionally, P. glandulosa ingestion resulted in increased small β-cells (p-value < 0.001) in the pancreata. Treatment also partially prevented the weight loss observed after STZ injection. In the insulin resistant model, P. glandulosa ingestion resulted in increased basal (p-value < 0.01) and insulin-stimulated (p-value < 0.05) glucose uptake in cardiomyocytes. It also increased insulin sensitivity (p-value < 0.05) in skeletal muscle from control animals.

Conclusion: This study showed that P. glandulosa treatment moderately lowers glucose levels in different animal models of diabetes, stimulates insulin secretion, leads to the formation of small β-cells, and improves insulin sensitivity of skeletal muscle strips and cardiomyocytes.
SaP4. Evaluation of novel therapeutic interventions to limit myocardial glucose toxicity

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This study focused on delineating mechanisms underlying hyperglycaemia-induced reactive oxygen species (ROS) production in heart cells. Here, hyperglycaemia (HG) enhances flux via the hexosamine biosynthetic pathway (HBP), polyol pathway, protein kinase C (PKC) pathway, and advanced glycation end-products (AGE), while in parallel, increasing mitochondrial ROS generation. However, elevated pentose phosphate pathway (PPP) flux is associated with favorable outcomes. We hypothesised that increased PPP flux decreases ROS levels, thereby attenuating the damaging effects of HG on the heart. H9C2 rat cardiac-derived myoblasts were cultured with 25 mM glucose (hyperglycaemia) for 24 hours vs. 5.5 mM glucose (controls). Pathway inhibitors were administered during the last hour of HG: 40 µM DON (HBP), 10 µM zopolrestat (polyol pathway), 5 µM chelerythrine (PKC), 100 µM aminoguanidine (AGE), 250 µM 4-OHCA (mitochondrial anti-oxidant), 50 and 100 µM benfotiamine (increase PPP flux), Cells were stained with a mitochondrial-specific ROS dye, and assessed by flow cytometry. HG increased mitochondrial ROS (p-value < 0.05 vs. control), while 4-OHCA reduced it (p-value < 0.001 vs. HG). ROS levels were attenuated by 100 µM benfotiamine and chelerythrine treatment (18%, p-value < 0.05 vs. HG, and 26%, p-value < 0.001 vs. HG), respectively. Our data implicate the PKC pathway in oxidative stress generation under HG conditions, while PPP activation blunted ROS production. We propose that benfotiamine (vitamin B derivative) offers unique therapeutic potential for diabetic patients by attenuating the damaging effects of hyperglycaemia.

SaP5. Cardioprotective and antihypertensive effects of Prosopis glandulosa in a rat model of pre-diabetes

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Department of Biomedical Sciences, Division Medical Physiology

Background: Obesity and type 2 diabetes present with two debilitating complications, hypertension and heart disease. Currently, in South Africa, the dried and ground pods of Prosopis glandulosa are marketed as a food supplement with anti-hypertensive properties. We determined the efficacy of P. glandulosa as an anti-hypertensive agent, and its myocardial protective ability.

Method: Male Wistar rats were rendered pre-diabetic through diet-induced obesity, or hypertensive through a high-fat diet. Diet-induced obese (DIO) animals were treated with P. glandulosa, 100 mg/kg/day, for eight weeks, and compared to age-matched controls. Hearts were perfused ex vivo to determine infarction size. Biometric parameters were determined at the time of sacrifice. CIRKO mice were similarly treated with P. glandulosa, and infarction size determined. High-fat diet animals were treated from day one of the change in diet, or from weeks 12-16, using captopril (50mg/kg/day) as a positive control. Blood pressure was monitored weekly.

Results: With regard to the DIO rats and CIRKO mice, P. glandulosa ingestion significantly reduced infarction size after ischaemia or reperfusion. Proteins of the PI-3-Kinase/PKB/Akt survival pathway were affected in a manner supporting cardioprotection. Regarding the high-fat diet model, P. glandulosa treatment both prevented and corrected the development of hypertension, and this was also reflected in the alleviation of water retention.

Conclusion: P. glandulosa is cardioprotective and infarction-sparing, as well as anti-hypertensive, without affecting the body weight or the intraperitoneal fat depots of the animals. Changes in the PI-3-Kinase/PKB/Akt pathway may be causal to protection. Results indicated water retention, possibly coupled to vasoconstriction, in the high-fat animals, while ingestion of P. glandulosa alleviated both. Treatment of pre-diabetes, type 2 diabetes, or hypertension, with P. glandulosa may have immense beneficial health effects.

SaP6. Management of in-patients with diabetes who are able to eat meals: an audit before and after the implementation of a standardised in-patient management protocol

DG van Zyl, P Rheeder
University of Pretoria

Background: This study attempted to implement a structured in-patient management protocol, to assess if glucose control in hospital would be improved.

Method: This was a quasi-experimental study, with a before and after design. An audit of glycaemic control was carried out before and after a physician and nurse-training programme, and after the introduction of a standardised in-patient management protocol.

Results: The first audit included records of 164 patients, and the second audit, 199 patients. Of these, 150 records from audit one, and 183 records from audit two, were eligible for inclusion in the study. On the first full day of hospitalisation, the mean blood glucose was significantly higher in the second audit (1.72 mmol/l higher) [p-value < 0.001]. Mostly, this could be attributed to patients who were admitted to Internal Medicine, in whom the average blood glucose was 2.07 mmol/l higher (p-value < 0.001). A significant improvement in mean blood glucose was seen from day 1-7 within audit two (-1.88 mmol/l, p-value < 0.001). Within audit one, this change was not significant [-0.88 mmol/l, p-value = 0.33]. Despite the higher mean blood glucose on day one, the proportion of patients who achieved a mean daily blood glucose of less than 10 mmol/l during hospital admission was very similar (43% vs. 43.7%, p-value = 0.97). The number of hypoglycaemic events (blood glucose less than 4 mmol/l per day of hospitalisation) increased significantly during audit two (19.6 vs. 17.2 events per 100 patient days, p-value = 0.048). After adjustment for age, diabetes-related admission or not and known with diabetes before admission or not mean blood glucose values was still higher in audit two than in audit one over time.

Conclusion: This study found no evidence that implementation of a standardised management protocol reduces hyperglycaemia and achieves earlier target blood glucose levels, in comparison to a free unstructured approach in in-patient glycaemic management.
SaP7. Autoimmune polyglandular syndrome type 1 in a 12-year-old Ugandan girl: a case report from a resource-limited setting

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Autoimmune polyglandular syndrome type 1 (APS 1) is an extremely rare, and frequently devastating, childhood disorder. A clinical diagnosis of APS 1 classically requires the presence of two of the three cardinal components, namely chronic mucocutaneous candidiasis, autoimmune hypoparathyroidism, and autoimmune adrenal failure. Few case reports have been published among African patients.

A 12-year-old female patient was referred to the dermatology unit with a six-year history of a generalised and intensely itchy skin rash that was initially responsive to topical steroid therapy, but later refractory, and a three-year history of progressive abnormal growths on the face and scalp associated with a deformity of the nails, oral sores, mild dysphagia, and odynophagia. A physical examination revealed extensive facial and scalp growths with alopecia, extensive oral thrush and angular cheilitis. There were generalised, scaly and well demarcated skin lesions on the hands and feet, with markedly thickened nails that had a distorted appearance. An endocrine screen revealed reduced parathyroid hormone (PTH) levels of 6 pg/ml, and a corrected mild asymptomatic hypocalcaemia of 8.4 mg/dl. On screening, no other autoimmune condition was detected.

A diagnosis of APS 1 was made, based on the presence of mucocutaneous candidiasis and hypoparathyroidism. Long-term endocrine monitoring in such patients is mandatory for early recognition of any autoimmune condition that may develop later.

SaP8. Screening for and management of diabetic retinopathy at primary healthcare clinics in Tshwane

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Background: Globally, diabetic retinopathy is the fifth leading cause of preventable blindness. Screening for diabetic retinopathy was undertaken as part of a larger screening study for complications linked to diabetes in the Tshwane district. The current prevalence of diabetic retinopathy at primary care level in South Africa is not known, and this study aims to provide an estimate.

Method: Non-mydriatic retinal fundus photographs was taken and evaluated by the head of the Ophthalmology Department of the University of Pretoria. A Canon CR-1® retinal camera, with a Canon EOS-40D digital camera® linked to a computer, was used in a mobile clinic. A standard retinopathy grading scheme was used. Patients were grouped into three categories, namely follow-up in one year’s time, referral to a hospital eye clinic for further management (of other non-diabetic eye problems), or referral to the mobile unit for laser therapy (Nd:Yag Yc-1800®).

Results: A total of 374 patients were screened during the first round of the study. Of those, 76.2% (n = 285) were to be evaluated again in one year’s time, 17.4% (n = 65) were referred to the closest hospital eye clinic to manage other eye problems, and 6.4% (n = 24) were lasered on the mobile unit for diabetic retinopathy.

Conclusion: This study has shown a higher-than-expected referable diabetic retinopathy prevalence rate among primary care diabetic patients. In a world-first event, 24 patients received laser photocoagulation surgery at the mobile unit within a week of being identified with referable diabetic retinopathy.

SaP9. The elusive insulinoma: a case study

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A 25-year-old male presented with a three-year history of symptomatic fasting and post-prandial hypoglycaemic episodes. A 12-hour fast was performed, during which the patient developed severe hypoglycaemia. Blood samples taken at the time revealed a serum glucose of 1.2mmol/l, insulin of 11.0μIU/l, C-peptide of 4.6 μU/l and cortisol of 182μmol/l. He fulfilled Whipple’s criteria, as his symptoms resolved with the administration of intravenous glucose. An abdominal magnetic resonance imaging, PET computed tomography scan, as well as transthoracic, transoesophageal sonography, failed to localise the tumour. A selective arterial calcium stimulation test was performed, which yielded a significant spike in insulin secretion in the proximal splenic artery at 20, 40, and 60 seconds. This localised the insulinoma preoperatively to the body or early tail region of the pancreas.

This case study highlights the challenges in the preoperative localisation of insulinomas. Their elusiveness stems from their small size, and also the lack of the availability and expertise in relevant radiological investigations, which carry a much higher sensitivity than other non-invasive localisation modalities. By developing these skills, and utilising different preoperative localisation techniques, improved surgical outcomes for patients can be expected.

SaP10. Primary aldosteronism: a case study

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A 60-year-old women presented with severe hypokalaemia (serum potassium of 1.7 mmol/l) and hypertension. Her antihypertensive medication consisted of hydrochlorothiazide 12.5 mg daily, and Adalat XL 30 mg daily.

An elevated serum aldosterone concentration (729 pmol/l) and suppressed renin levels (3 μIU/l), followed by a positive saline infusion test, suggested the diagnosis of an aldosterone secreting tumour. An abdominal computed tomography scan revealed a left adrenal mass (1.7 x 1.5 x 0.5 cm, Hounsfield unit = 65). The results of an adrenal vein sampling localised the aldosterone secreting tumour to the left adrenal gland (Table I).

<table>
<thead>
<tr>
<th>Table I:</th>
<th>Aldosterone (pmol/l)</th>
<th>Renin (μIU/l)</th>
<th>Cortisol (nmol/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left adrenal vein</td>
<td>&gt; 3 300</td>
<td>4.3</td>
<td>&gt; 2 069</td>
</tr>
<tr>
<td>Right adrenal vein</td>
<td>1 739</td>
<td>2.4</td>
<td>367</td>
</tr>
</tbody>
</table>

Primary aldosteronism is an uncommon, but underdiagnosed, cause of hypertension, which should be considered in all patients presenting with hypertension and hypokalaemia. Appropriate use of screening, diagnostic and imaging allows for improved localisation and appropriate management.
SaP11. Hyperthyroidism due to suppurative thyroiditis caused by Nocardia brasiliensis
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Acute thyroiditis is an extremely rare complication of Nocardia infection. We report a patient with hyperthyroidism, due to suppurative thyroiditis caused by Nocardia brasiliensis. A 38-year-old black male patient presented with features of thyrotoxicosis, sepsis, and airway obstruction. He had no evidence of underlying thyroid disease, but was severely immunocompromised as a result of advanced acquired immune deficiency syndrome (AIDS). He had previously been diagnosed with Nocardiosis of the lungs, and had nocardial abscesses on his anterior chest wall.

Investigations revealed thyrotoxicosis with a FT3 of 43.2 pmol/l, and a suppressed thyroid stimulating hormone (TSH) of less than 0.01 mIU/l. Serum thyroid anti-thyroid peroxidase and anti-thyroglobulin antibodies were negative. A computed tomography scan showed a large abscess in the anterior neck involving the left lobe and isthmus, as well as inhomogeneous changes of the right lobe of the thyroid gland. The radioisotopic thyroid scan showed the absent uptake of tracer, in keeping with thyroiditis.

While the initial presentation was that of hyperthyroidism, destruction of the gland later resulted in hypothyroidism, necessitating thyroid hormone supplementation. The mechanism of the hyperthyroidism can be explained by the release of pre-synthesised and stored thyroid hormone into the circulation, as a result of inflammation and disruption of the thyroid follicles. The failure to return to the euthyroid state can be attributed to the fact that much of the gland was destroyed by the abscess, and the functioning of the remaining gland was disrupted by an extensive inflammatory process.

This is the first documented case of hyperthyroidism in a patient with acute suppurative thyroiditis caused by Nocardia.

SaP12. Late presentation of a pituitary anomaly
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1Division of Endocrinology, Department of Medicine, Faculty of Health Sciences, Stellenbosch University
2Division of Endocrinology, Department of Medicine, Faculty of Health Sciences, Stellenbosch University

Congenital abnormalities of the pituitary gland should be considered in patients presenting with anterior hypopituitarism. We report two cases, a 24-year-old male and a 16-year-old female, who presented with short stature and delayed secondary sexual development. Hormonal studies showed multiple pituitary hormone abnormalities in both. In both cases, magnetic resonance imaging (MRI) showed an ectopic posterior pituitary (EPP). EPP is an unusual anomaly of the pituitary gland, and the exact aetiology of this entity is unknown. Two hypotheses are described in the literature. The first is that of pituitary stalk transection during a traumatic birth. The second is an embryonic abnormality, or defect, in pituitary gland development. Mutations in several genes have been associated with the development of this anomaly. On MRI, the posterior pituitary bright spot is ectopic, and often at the level of the median eminence. The presence of an ectopic posterior pituitary is associated with both anatomical and functional abnormalities of the anterior pituitary gland. Hypopituitarism may manifest as isolated growth hormone deficiency, or multiple anterior pituitary hormone deficiencies. In both our cases, multiple anterior pituitary hormone deficiencies were present.

SaP13. Human immunodeficiency virus and hypoglycaemia
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We describe a patient with human immunodeficiency virus (HIV) disease on treatment, complicated by Kaposi’s sarcoma, presenting with true hypoglycaemia, and postulate a unique cause for the hypoglycaemia.

HIV/acquired immune deficiency syndrome is associated with various potential causes of hypoglycaemia, including immune dysregulation, the propensity to develop various tumours, malnutrition, and organ failure, drug therapy, and endocrinopathies like Addison’s disease. Anti-diabetic agents and drugs, such as pentamidine, were excluded as causes of hypoglycaemia in our patient. Antiretroviral drugs have never been shown to cause hypoglycaemia. Our patient was well nourished, without evidence of organ failure or endocrinopathy.

Endogenous hyperinsulinaemic hypoglycaemia secondary to an insulinoma needed to be excluded. Serum fasting insulin levels in our patient were low to borderline elevated, but C-peptide values were low. Imaging of the abdomen revealed no evidence of a pancreatic or any other tumour. Non-islet cell tumour-induced hypoglycaemia has not been described in HIV-associated Kaposi’s sarcoma.

Auto-immune causes of hypoglycaemia usually result from antibodies directed at either the insulin molecule or the cell-surface insulin receptor, and have usually been described in the setting of other autoimmune disorders, such as systemic lupus erythematosus. Our patient’s life-threatening hypoglycaemia responded to immunosuppressive therapy, and slowly resolved, so that no immunosuppression was later required. To our knowledge, autoimmune hypoglycaemia, secondary to the immune dysregulation of HIV, has not been described before.

SaP14. Pulmonary hypertension and thyrotoxicosis
Marii Conradoie, Coenie Koegelenberg, Brynne Ascott-Evans, Magda Conradoie, Stephen Hough,1
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2Division of Pulmonology, Department of Medicine, Faculty of Health Sciences, Stellenbosch University

Background: Thyrotoxic heart disease, classically left-ventricular failure, and atrial fibrillation, leads to increased morbidity and mortality. Less well appreciated is the fact that hyperthyroidism may also be associated with pulmonary arterial hypertension (PAH) and right-heart failure. We describe three patients who presented with thyrotoxicosis and features of PAH, in whom other causes of PAH had been excluded. We also examined the reversibility of the pulmonary hypertension upon restoration of the euthyroid state. Possible aetiologies for the considered PAH included a high output state causing endothelial injury, increased metabolism of vasoconstricting substances, vasoospasm, hypercoagulability, and most interestingly, an autoimmune cause.

Results: The age of the patients, one male and two females, ranged from 44-72 years. All patients had clinical features of PAH. The mean FT3 was 87.3pmol/l (43-155 pmol/l) and mean PAP on echocardiography was 56 mmHg (50-64 mmHg) (normal < 30 mmHg). Other possible causes of PAH were excluded on special investigations. PAH normalised in all three cases, when the patients were rendered euthyroid. Thyroid stimulating hormone (TSH) receptor antibodies were measured in two of the three cases, and were found to be strongly positive (mean titre 51.72).

Conclusion: Thyrotoxicosis should be recognised as a reversible cause of PAH. The exact prevalence, pathophysiology, and clinical significance of this association is not clearly defined. Other causes of pulmonary hypertension, especially pulmonary embolism, need to be excluded. Reversibility of the pulmonary hypertension is usually achieved upon restoration of the euthyroid state.
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Accord Metformin is indicated for type 2 (non-insulin dependent) diabetes mellitus when diet has failed and especially if the patient is overweight.¹

Get the balance right
SaP15. Antidiabetic medicine utilisation in South Africa using the World Health Organization ATC/Defined daily Dose Methodology
Shelley McGee
Sanofi-Aventis Pharmaceuticals

Background: The objective was to evaluate the utilisation trends of antidiabetic medicine in South Africa.

Method: The consumption of antidiabetic medicines in South Africa generally, and in the traditional private and public sectors, was analysed in terms of the World Health Organization (WHO) ATC-defined daily dose (DDD) method, between 2008-2010. Data was extracted from the South African IMS national sales database.

Results: Between 2008-2010, antidiabetic consumption in the country rose by 67%, driven mainly by increases in utilisation in the public sector. Consumption in the private sector rose to 47.32 DDD/1 000 population per day, based on the privately insured market. The consumption of antidiabetic agents, excluding insulin oral antidiabetics in the private sector rose by 7.4%, while in the case of insulin analogues, the increase was 13.8%. Sulphonylureas were the most commonly used class in both sectors; and gliclazide and metformin, the most used medicines. In 2010, utilisation of antidiabetic agents in South Africa stood at 30.12 DDDs/1 000 population per day, which is below national comparable figures for several other countries.

Conclusion: The consumption of antidiabetic agents has been steadily increasing in both public and private sectors in South Africa, in line with expectations regarding increasing disease burden. The overall country levels of consumption are lower than would be expected, and warrant further scrutiny. Utilisation levels in the state sector, adjusted for population served, remain low, relative to the private sector and international benchmarks.

SaP16. Hypoglycaemia due to a pituitary syphilitic gumma
Jo Skelton, Cecile Kanyama, Sally Candy, Peter Raubenheimer
University of Cape Town

Hypopituitarism, due to syphilis, is well described in old texts, but there are no case reports of this condition in adults in the magnetic resonance imaging (MRI) era. We present the first case of a pituitary syphilitic gumma seen on MRI.

A 47-year-old, previously well woman presented with severe hypoglycaemia, against a background of three weeks of malaise, weight loss, and postural dizziness. Clinically, she was wasted, with a body mass index of 14, a blood pressure of 80/60 mm Hg, patchy alopecia, and an extensive, reddish-brown, papular, scaly, non-pruritic rash covering most of the body, including the palms and soles.

Investigations were consistent with anterior panhypopituitarism, and she responded well to hormone replacement, with recurrent hypoglycaemia resolving. She regained her weight, appetite, and strength.

Plasma RPR was positive at 1 a titre of 1:16, and cerebrospinal fluid (CSF) was also RPR and TPHA positive. Pituitary MRI showed abnormal hypoglycaemia, with a mass lesion in the pituitary gland with central hypodensity. This mass, and the surrounding bony abnormality, significantly improved after treatment with intravenous and intramuscular penicillin.

SaP17. Early cortisol responses to depot synthetic adrenocorticotropic hormone testing in patients with suspected secondary adrenal insufficiency
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Division of Endocrinology, University of Stellenbosch and Tygerberg Hospital

Background: Synthetic adrenocorticotropic hormone (ACTH) is widely used in testing for primary and secondary adrenal insufficiency. Various formulations are available internationally, including convenient short-acting ACTH, where cortisol is measured at baseline, and after one hour. In South Africa, only a synthetic depot preparation is readily available, requiring repeated sampling for up to eight hours. In this pilot study, we evaluated the adequacy of the cortisol responses at time intervals less than eight hours after injection of this long-acting depot preparation of ACTH in patients with suspected secondary adrenal failure, in an attempt to validate a shorter duration of testing.

Method: Patients with suspected secondary adrenal insufficiency with 8 AM cortisol levels below 300 nmol/l received an intramuscular depot synthetic ACTH preparation of 1000 μg. Cortisol levels were evaluated at baseline, one, two, six, and eight hours post-injection. Standard statistical methods were used to correlate levels attained at one and two hours, with those at eight hours.

Results: Twelve patients were enrolled. Mean cortisol levels at baseline were 197.4 nmol/l (range 100-280). Eleven of the 12 (91.7%) achieved cortisol levels in excess of 800 nmol/l (mean of 961.9) at eight hours. All of these 11 subjects had cortisol levels above 500 nmol/l at one hour, and above 600 at two hours.

Conclusion: This pilot study suggests that the one- and two-hour cortisol responses, after intramuscular injection of the synthetic depot ACTH preparation, correlate well with those achieved at eight hours, in patients suspected of having pituitary insufficiency. If validated by larger patient numbers, local ACTH testing will become simpler, far cheaper, and more convenient.

SaP18. Quality of care is suboptimal at the Groote Schuur Hospital Diabetes Clinic. Division of Endocrinology and Diabetes, University of Cape Town: the case for intervention
B Kamanga, I L Ross, N S Levitt
Division of Endocrinology, Department of Medicine, University of Cape Town

Background: People with diabetes do not frequently receive standardised care, even in tertiary institutions.

The objective was to determine the adequacy of care at the Groote Schuur Hospital diabetes clinic.

Method: A retrospective folder review of people with diabetes attending between 1 August-31 December 2011 was conducted. Optimal care was defined as an annual examination for peripheral neuropathy, retinopathy, proteinuria or microalbuminuria, serum creatinine, lipid profile, routine haemoglobin A1C (HbA1C), and the appropriate use of aspirin and statins.

Results: On preliminary analysis of the 274 evaluated folders, 171 were of women (62.4%). The median interquartile range ages at diagnosis and review were 38 (28-47) and 53 (50-63) years respectively, while disease duration was 13 (8-20) years. The proportions of type 1, type 2, and other, were 70.1%, 24.8%, and 5.1%, respectively. The median HbA1C was 8.8 (7.5-11.5) g/dl vs. 8.6 (7.5-9.7) g/dl, and proportions of patients with HbA1C ≤ 7% (20%) vs. 20%, did not differ between the initial visit and final review, despite the majority (90%) conducting home blood glucose monitoring. At final review, 77.6% had hypertension, of whom 53.8% had blood pressure > 130/80 mmHg. Optimal care was found in 51.7% of cases.

Conclusion: The inadequate adherence to standard practice guidelines, and low level of glycaemic control achieved in this clinic, points to the urgent need for a multi-faceted intervention.
**SaP19. McCune-Albright syndrome: a case of the runaway G protein**

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McCune-Albright syndrome (MAS) is an extremely rare disorder (1:500 000 population), characterised by fibrous dysplasia, pigmented skin lesions, and endocrine abnormalities.

We present a case of a young, black female, who presented with a right-sided tuberculous pleural effusion. In addition, she was short (height 135 cm), and had menstruated from the age of five years. A prothrombinase of her right forehead was noted, as well as a solitary café-au-lait patch on her left thigh. No other deformities were noted, and she had normal secondary sexual development, with no virilisation.

Her oestradial levels were markedly raised, at 1 390 and 3 150 pmol/l. The rest of her hormonal profile was normal. A computed tomography scan of the abdomen and pelvis demonstrated a large left cystic ovarian mass. X-ray imaging of the pelvis and long bones demonstrated various lytic lesions. A skull X-ray showed sclerosis, with obliteration of the frontal and sphenoid sinuses, and a dense base of skull. There were no indications for any active management at this stage.

MAS results from an early post-zygotic somatic mutation, whereby a gain-of-function mutation at amino acid 201 of the alpha-subunit of the heterotrimeric G-protein, results in unabated activity of adenylate-cyclase, leading to skeletal abnormalities, pigmented skin patches, and hyperfunction of various endocrine organs, most commonly the ovary.

**SaP20. Non-islet cell tumour-induced hypoglycaemia**

V Nicolau, R Shires, KRL Huddle
Division of Endocrinology, Chris Hani Baragwanath Academic Hospital, and University of the Witwatersrand, Johannesburg

Hypoglycaemia is a rare manifestation of neoplastic disease, most often due to overproduction of an incompletely processed form of insulin-like growth factor II (IGF II).

A 30-year-old Malawian man presented in coma with a plasma glucose level of 1.9 mmol/l. He recovered consciousness following administration of 50% dextrose water. There was no history of diabetes or exposure to hypoglycaemic medications or toxins. A moderately enlarged liver was the only significant clinical abnormality.

Laboratory investigations directed at determining the cause of the hypoglycaemia demonstrated an appropriate suppression of C-peptide (level 0.2 ng/ml) and insulin (level 2 pmol/l) during a hypoglycaemic event (plasma glucose 2.1 mmol/l). A disproportionately elevated ratio of IGF II/I confirmed the diagnosis of non-islet cell tumour-induced hypoglycaemia (NICTH). The a-fetoprotein was markedly elevated at 10 278 µg/l (N 0-7). Sonar and computed tomography imaging of the liver revealed numerous lesions throughout the liver, in keeping with hepatocellular carcinoma (HCC). Histopathology confirmed a poorly differentiated HCC.

The recurrent hypoglycaemic events responded to steroid therapy. Palliative care was instituted in view of the advanced stage of the malignancy.

NICTH is an uncommon, but serious, complication of malignancy. The hypoglycaemia is mediated by tumoral overproduction of incompletely processed IGF II, which in turn stimulates insulin receptors, resulting in increased glucose utilisation and hypoglycaemia. Surgical removal of the tumour (where feasible) reverses the metabolic derangements. Therapies such as glucocorticoids, growth hormone, or combinations thereof, may alleviate symptoms.
Su3. Cross-talk between cyclic AMP and cyclic GMP during adipogenesis in adipose-derived stromal cells
H Sadie-van Gijzen, FS Hough, WF Ferris
Division of Endocrinology, Department of Medicine, Stellenbosch University

Background: Naïve stromal cells isolated from adipose tissue [adipose-derived mesenchymal stromal cells (ADSCs)] can be used as a model system to study adipocyte differentiation in vitro. Adipogenesis can be induced by adipocyte differentiation media (AM), which consists of standard culture media, supplemented with isobutylmethylxanthine (IBMX), insulin, indomethacin and dexamethasone. IBMX, a nonspecific phosphodiesterase inhibitor, which inhibits the degradation of cyclic nucleotides [both cyclic AMP and cyclic GMP] is indispensable for the AM-mediated induction of adipogenesis in ADSCs, suggesting that intracellular signaling pathways, activated by cyclic nucleotides, are essential for adipogenesis in ADSCs. We wished to assess the individual contribution of cAMP and cGMP to adipogenesis.

Method: ADSCs were isolated from rat adipose tissue from subcutaneous (scADSCs) and perirenal visceral (pvADSCs) adipose depots, and maintained in culture. Adipocyte differentiation was induced in these cells by treating the cells with AM for seven days. In an effort to delineate the pathways involved in adipogenesis in ADSCs, the IBMX in AM was replaced with either cAMP or cGMP, or with theophylline, another nonspecific phosphodiesterase inhibitor. Adipogenesis was quantified by measuring intracellular lipid accumulation by means of Oil Red O staining.

Results: Within the context of AM, IBMX and theophylline were equally effective at inducing adipogenesis in scADSCs and pvADSCs, confirming that phosphodiesterase inhibition was involved in the differentiation of these cells into adipocytes. Both cAMP and cGMP, as well as a combination of the two, stimulated lipid accumulation in the presence of AM depleted of IBMX, suggesting that cAMP and cGMP induced adipogenesis via a similar pathway.

Conclusion: The induction of adipogenesis in cultured ADSCs requires either a cAMP- or a cGMP-activated pathway. Therefore, convergence occurs between cAMP and cGMP signalling.

Su4. Associations between interleukin-6 gene polymorphisms and obesity and serum lipids, and their interaction with dietary fat intake in black and South African white women
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2Biostatistics Unit
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4Department of Statistics, University of Western Cape, Cape Town

The objective of the study was to explore the associations between polymorphisms within the interleukin (IL) 6 gene, obesity and serum lipids outcomes, as well as their interaction with dietary fat intake in black and white South African women. Body composition, fasting lipids, and dietary intake were measured in 108 normal-weight and 124 obese black, and 89 normal-weight and 63 obese white women, who were also genotyped for the IL-6-174 G > C, IVS3+281 G > T and IVS4+869 A > G polymorphisms. The genotype frequency distributions were all significantly different between ethnic groups, with the minor -174 C and IVS3+281 T allele frequencies being higher in white, than black women (40% vs. 1%, and 41% vs. 27%, respectively, in normal weight women). In black women, the IVS4+869 AG+GG genotype was associated with greater body mass index (BMI) compared to AA (p-value = 0.018). In black women, dietary fat intake (percentage energy) modulated the relationship between BMI and the IVS4+869 polymorphism (recessive model, p-value = 0.009). With increasing fat intake, BMI decreased for GG, and increased for AA+AG genotypes.

White women with the IVS3+281 GG genotype had higher triglyceride concentrations than those with GT+TT genotype (dominant model, p-value = 0.008), and we detected an interaction between IVS3+281 and n-3 PUFA intake (percentage energy) on total cholesterol: high-density lipoprotein cholesterol ratio (total cholesterol:HDL cholesterol) (recessive model, p-value = 0.004), such that with increasing n-3 PUFA intake, total cholesterol:HDL cholesterol decreased only in those with the TT, and not the TG+GG genotype. In conclusion, we showed that polymorphisms within the IL-6 gene were associated with body composition in black women, and with serum lipids in white women, and that both total intake, and the quality of dietary fat, interacted with the IL-6 polymorphisms on obesity and serum lipids.

Su5. Metabolic surgery: baseline patient profile and three-year outcome data
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2University of Pretoria

Background: Baseline patient profiling, biochemical, morbidity and mortality outcome after bariatric surgery.

Method:
1. Fifty baseline variables expressed as percentage (%) of total patient population (data not shown), inclusive of dietary and social history, major and minor co-morbidities.
2. Biochemical and clinical outcomes: (mean +/- SEM) p-value* < 0.05; p-value** < 0.01 (unpaired t-test). Parameters:
Baseline: (n = 607); 3 months (n = 533); 1 year (n = 354); 2 years (n = 201); 3 years (n = 193).
Weight (kg): 127 ± 1.4; 101 ± 1.2**; 93 ± 1.1**; 88 ± 2.0**; 83.1 ± 3.4**.
Body mass index: 44.6 ± 0.4; 36 ± 0.4*; 32 ± 1.1**; 30.7 ± 0.6**; 32.6 ± 0.6**.
Waist (cm): 123 ± 1.0; 103 ± 1.0**; 91 ± 1.0**; 106 ± 1.2**; 113 ± 2.2**.
Neck (cm): 43.5 ± 0.3; 39 ± 0.5*; 37 ± 0.3*; 36 ± 0.5**; 37 ± 0.6**.
Systolic blood pressure (mmHg): 147 ± 1.0; 130 ± 0.8*; 132 ± 1.0*; 133 ± 1.5*; 132 ± 2.3**.

Diatolic blood pressure (mmHg): 89 ± 2.0; 80 ± 0.6*; 79 ± 0.8*; 81 ± 0.9; 80 ± 1.7**.
Co-morbids: diseases: 6 ± 0.1; 1 ± 0.4**; 0.4 ± 0.7**; 0.5 ± 0.8**; 0.6 ± 0.1**.
F-glucose (mmol/l): 6.8 ± 0.1; 5.3 ± 0.1*; 4.9 ± 0.05*; 4.8 ± 0.1**; 4.9 ± 0.2**.
F-TG (mmol/l): 1.8 ± 0.05; 1.4 ± 0.0; 1.2 ± 0.4; 1.1 ± 0.05*; 1.2 ± 0.1*.
F-HDL mmol/l: 1.0 ± 0.02; 1.1 ± 0.04*; 1.7 ± 0.14; 1.6 ± 0.05*; 1.6 ± 0.08.
F-LDL mmol/l: 3.3 ± 0.05; 2.2 ± 0.04; 2.5 ± 0.14*; 2.5 ± 0.08*; 2.5 ± 0.1*.
ALT (U/l): 31 ± 0.9; 28 ± 0.9*; 25 ± 0.9*; 24 ± 1.2**; 22 ± 1.4*.
AST (U/l): 25 ± 0.5; 24 ± 0.5; 23 ± 0.6; 23 ± 0.8; 21 ± 1.4.
GGT (U/l): 38 ± 2.1; 32 ± 1.1; 24 ± 2.0*; 19 ± 1.6**; 21 ± 2.0*.
U/A (mmol/l): 0.44 ± 0.06; 0.5 ± 0.05*; 0.48 ± 0.02; 0.29 ± 0.02**; 0.28 ± 0.03**.
CRP (mg/l): 16 ± 0.6; 6 ± 0.2*; 5 ± 0.2*; 5 ± 0.2*; 5 ± 0.5*.
3. Mortality: Surgical (0%), medical (0.1%).
4. Morbidity: Surgical: major (4.6%); minor (6.1%); medical: major (3.1%); minor (5.2%).

Conclusion: Bariatric surgery is a modern day solution for obesity with high disease resolution, and very low mortality.
**Su6. Management of functional GEP-NET tumours**
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**Su7. The South African Addison’s study: an updated review**
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**Background:** We aimed to address a number of unanswered research questions in Addison’s disease: investigate whether autoimmunity is the predominant cause of Addison’s disease in South Africa and if a human leukocyte (HLA) DQ antigen association exists; the extent to which lipids, lipoproteins and biochemical markers of cardiovascular disease are abnormal; the degree to which replacement doses of hydrocortisone are supra-physiological; the impact of glucocorticoid receptor (GCR) polymorphisms on risk factors, markers of cardiovascular disease, and replacement doses of hydrocortisone.

**Method:** A national database of patients with Addison’s disease was compiled from primary care referral centres and private practices. One hundred and forty-eight patients [97 of European descent (white), 34 of mixed ancestry, 5 Asian and 12 Africans] were matched, with controls for gender and ethnicity. Anthropometric data were elicited using questionnaires. Demographic and clinical data were elicited using questionnaires. Anthropometric data were recorded, and blood was drawn. The causes of Addison’s disease were investigated using a specific algorithm. Lipids, lipoproteins, and markers of cardiovascular disease, were assessed. Salivary cortisol day curves were evaluated in 31 patients with Addison’s disease on usual hydrocortisone doses, and in control subjects. The role of the GCR polymorphisms was explored to determine its influence on metabolic parameters and hydrocortisone dose.

**Results:** Fifty-one per cent of patients with Addison’s disease were autoimmune in origin. Either 21-hydroxylase or adrenocortical autoantibodies were present in 50% of the cohort, while 23% had both. None of the Asian or black patients had detectable evidence of autoimmune disease. Overall, 8% had tuberculosis, 4% had adrenal leukoencephalodystrophy, 1% had adrenocorticotropic hormone (ACTH) resistance syndrome, and 6% had X-linked adrenal hypoplasia. HLA DQB1*0201 predominated in the autoimmune group. Almost 50% had hypertriglyceridaemia, 65% had hypercholesterolaemia, about 75% had low-high density lipoprotein (HDL) cholesterol, and 75% had elevated low-density lipoprotein (LDL) cholesterol. Highly sensitive C-reactive protein (hs-CRP) was increased in both white and mixed ancestry patients, compared to controls. The Framingham risk of > 20% in 10 years was found in 36% of the cohort. The patients with Addison’s disease had significantly higher first and second peak salivary cortisol concentrations, and median and interquartile range (IQR) salivary cortisol area under the curve (AUC) than the controls’ endogenous cortisol profiles. The AUC correlated with the peak salivary cortisol concentrations in patients, \( r = 0.87; p\text{-value} = 0.0001 \) and controls \( r = 0.74; p\text{-value} = 0.0001 \). The GCR ER22/23EK heterozygous polymorphism was associated with an elevated body mass index (BMI) in patients \( 29.4 \) vs. \( 24.7 \) kg/m\(^2\); p-value = 0.02) and healthy controls \( 26.3 \) vs. \( 24.2 \) kg/m\(^2\); p-value < 0.0001), but with a lower HDL cholesterol in patients, than controls. Neither the BcII nor the N363S polymorphisms were associated with any significant alteration in the metabolic traits examined.

**Conclusion:** Enhanced awareness of this highly treatable condition is warranted. Autoimmunity predominated in patients mostly of European descent (white), but was not found in any of the Asian or black patients. A low threshold is required for screening, intervention, and follow-up of all patients for cardiovascular risk factors, given the atherogenic profiles of the patients in this study. The supra-physiological concentrations of salivary cortisol on hydrocortisone replacement should prompt clinicians to screen patients for side-effects. The association between the ER22/23EK polymorphism and elevated BMI in both patients and controls requires confirmation in a large sample.

**Su8. Hypothalamic-pituitary-adrenal axis suppression in children at Cape Town allergy units: prevalence and predictive factors**
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**Background:** Generally, hypothalamic-pituitary-adrenal axis suppression (HPAS) is thought to be rare in children treated with corticosteroids (CS), since HPAS may be partially masked by recovering hypothalamic-pituitary-adrenal axis (HPA) function. The objective was to determine the prevalence and predictive factors for HPAS in children treated with CS at the allergy clinics in Cape Town.

**Method:** One hundred and forty-three asthmatic children, 5-18 years old, on inhaled CS (ICS) with additional CS were recruited. Clinical features compatible with HPAS were documented. Daily and cumulative CS dose, adherence, asthma score, and lung functions, were recorded. A Metapyrone test was performed if the 08:00 hour cortisol (C) was > 83 nmol/l. Spearman correlation coefficients (r) were calculated between the post-metyrapone (PMTP) adrenocorticotropic hormone (ACTH), 11-deoxycortisol (11DOC), 11DOC+C, and each variable. A multiple linear regression model of rACTH, and a logistic regression model for HPAS, were developed.

**Results:** The prevalence was as follows. All HPAS 65.1 (56.5-72.9)%; low (PMTP 11DOC, 11DOC+cortisol) 32.3 (23.7-40.9)%; low (PMTP ACTH, 11DOC, 11DOC+cortisol) 16.3 (9.3-23.3)%; hypocortisolism 6.1 (1.8-10.5)%; Gastrointestinal tract symptoms in hypocortisolastic children were associated with HPAS in 2/8 (p-value = 0.016). Log daily NS/m\(^2\) was associated with HPAS [OR = 3.7 (1.1-13.6)]. Daily ICS+nasal steroid dose (NS)/m\(^2\) correlated with ACTH (r = -0.29; p-value < 0.001), BMI (p-value = 0.048), poor adherence to ICS (p-value < 0.001) and NS (p-value = 0.002) were predictive to rACTH.

**Conclusion:** About two thirds of asthmatic children on CS may have a degree of HPAS. In one third, the adrenals may still be suppressed, while hypothalamic-pituitary function may have recovered. Predictive factors for HPAS are comorbid NS use, BMI, adherence to ICS and NS.
Su9. Radioactive iodine in the management of thyrotoxicosis at Inkosi Albert Luthuli Central Hospital, Durban
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The use and outcomes of radioactive iodine (RAI) therapy in the definitive management of thyrotoxicosis at Inkosi Albert Luthuli Central Hospital (IALCH), KwaZulu-Natal, was evaluated in a retrospective study. The clinical records of all new patients with thyrotoxicosis, referred in a four-year period between 1 January 2003 and 31 December 2006, were analysed. Response to RAI was monitored using biochemical parameters, namely, thyroid stimulating hormone and free T4 levels. Rates of euthyroidism (cure), hypothyroidism and hyperthyroidism (treatment failure) were evaluated. Patients were followed-up for at least two years, or until the onset of hypothyroidism. The follow-up period was until 31 December 2007.

One hundred and fourteen patients (37.7%), of a cohort of 302 new thyrotoxic patients treated with RAI, met the inclusion criteria. Ninety-six patients (84.2%) had Graves' disease, while 18 had toxic nodular disease. At two-year follow-up, 91 patients (79.8%) were hypothyroid, 10 (8.8%) were euthyroid, and 13 (11.4%) were hyperthyroid. The mean initial dose of 8.5 ± 1.4 mCi and the mean cumulative dose was 11.0 ± 5.5 mCi. The average time to achieve euthyroidism was 5.9 months, and 10.1 months to become hypothyroid. Thirty-one patients (27.2%) remained persistently hyperthyroid after one dose of RAI. Patients with Graves’ disease (88.5%) were more likely to become hypothyroid (p-value < 0.001), while 38.9% of patients with toxic nodular disease remained hyperthyroid (p-value = 0.001). Baseline TFT values were significant in terms of outcomes correlated with the prescribed RAI dose. i.e. low dose (< 8 mCi) vs. intermediate dose (8-9 mCi) vs. high dose (> 9 mCi) [thyroid stimulating hormone p-value = 0.05, FT4 p-value = 0.003; FT3 p-value = 0.001]. The majority of patients became hypothyroid over time, in keeping with reported data. In the public health sector, where early access to RAI is vital, follow-up is a major problem, early cure is essential to minimise the morbidity of thyrotoxicosis, and this may be achieved with an initial high dose of RAI.

Su10. The prevalence of subclinical hypothyroidism among patients with diabetes mellitus at the Kalafong Hospital Diabetes Clinic
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Background: The purpose of this study was to determine the prevalence of subclinical hypothyroidism among patients with diabetes mellitus in a South African setting, at the Kalafong Diabetic Clinic.

Method: In this cross-sectional study, 563 patients with diabetes mellitus (type 1, type 2, or unknown), following up at the Kalafong Hospital diabetes clinic, were evaluated with thyroid stimulating hormone (TSH) levels. Patients with TSH levels > 5.66 IU/ml (upper reference limit of the Kalafong National Health Laboratory Service Laboratory) subsequently underwent repeat thyroid function evaluation, including T4 level, to determine the prevalence of subclinical hypothyroidism. Within the group of patients evaluated, a comparison was made between those who had a normal TSH level, and those with subclinical hypothyroidism, evaluating the presence of macro- or microalbuminuria, elevated low-density lipoprotein (LDL) level, presence of retinopathy, and haemoglobin A1c (HbA1c) as a marker of control.

Results: A total of 563 patients met the inclusion criteria for this study, and underwent TSH evaluation. The prevalence of subclinical hypothyroidism was found to be 0.9% in the study population, and 1.6% in a subgroup of patients with type 2 diabetes mellitus. The group of patients in whom subclinical hypothyroidism was diagnosed was too small to make inferences about the risk of diabetic retinopathy, nephropathy and hyperlipidaemia, in comparison with the remainder of the patients.

Conclusion: The prevalence of subclinical hypothyroidism, in this South African population of patients suffering from diabetes, was significantly lower than the prevalence stated in the literature. This holds true for both the general population, and populations of patients with diabetes mellitus. To our knowledge, there is no data available for the prevalence of subclinical hypothyroidism in the general population in South Africa, for comparison with the study group. The finding of a significantly lower prevalence of subclinical hypothyroidism in a South African group of patients may reflect the inappropriate use of biochemical reference ranges determined in a Western population. Further studies are required to establish the normal reference range for TSH in the South African population, as well as the prevalence of subclinical hypothyroidism in this population.

Su11. Baseline characteristics of diabetes patients screened for complications at primary healthcare clinics in Tshwane
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Background: Managing diabetes complications and conducting complication screening at primary care level, is often problematic. Innovative approaches involving multiple partners were investigated.

Method: A cluster-randomised control trial consisting of intervention (6 clinics, n = 326), and control (6 clinics, n = 273) groups, was set up in the Tshwane district. Baseline characteristics of both levels of care and patients characteristics will be reported.

Results: Sixty-eight per cent were female. The mean age was 58.1 years [standard deviation (SD) 10.50; 10.9% were current smokers; 70% were self-reported type 2 diabetics; and the mean body mass index (BMI) was 30.7 (SD 6.8)]. Complication screening was monitored for the year preceding the study. It was found that only 23.4% of patients had haemoglobin A1c (HbA1c) tests carried out; 25.9% had lipids conducted; 21% had serum-creatinine tests carried out; and 8% had their eyes, and 6.3% had their feet, screened respectively. This study found that 28% of patients had a HbA1c of more than 10% [n = 168], mean low-density lipoprotein (LDL) cholesterol of 2.8 mmol/l (SD 0.9), and mean serum creatinine of 72.8 umol/l (SD 41.8). During feet screening, it was found that 25% of the screened patients had monofilament testing absent in either the left or right foot, or both, and 11.4% had vibration sense absent in either the left or right foot, or both. The mean systolic blood pressure was 145 mm Hg (SD 23.9), and the mean diastolic blood pressure was 86 mm Hg (SD 13.1). Of male patients (intervention, n = 92), 35.9% (n = 33) reported severe erectile dysfunction.

Conclusion: This study confirms that complication screening for diabetes’s sub-optimal at primary care level, and new models need to be developed and implemented.

Su12. Treating type 2 diabetes with insulin: pouring oil on the flames?
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