Diagnosis and treatment of diabetic ketoacidosis

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Diabetic ketoacidosis (DKA) is the most serious acute metabolic complication of diabetes. DKA is responsible for more than 500 000 hospital days per year at an estimated annual direct medical expenses and indirect cost of US$2.4 billion in the United States. DKA is characterized by the triad of uncontrolled hyperglycaemia, metabolic acidosis and increased total body ketone concentration. These metabolic derangements result from the combination of absolute or relative insulin deficiency, and an increase in counter-regulatory hormones (glucagon, cortisol, catecholamines and growth hormone). Most patients with DKA have autoimmune type 1 diabetes mellitus. However, patients with type 2 diabetes are also at risk during the catabolic stress of acute illnesses such as trauma, surgery or infection. Successful treatment of DKA and HHS requires correction of dehydration, hyperglycemia, and electrolyte imbalances, identification of co-morbid precipitating events, and above all, frequent patient monitoring. The mainstay of DKA treatment involves the administration of regular insulin via continuous intravenous (IV) infusion, or by frequent subcutaneous (SC) or intramuscular (IM) injections. Randomised controlled studies in patients with DKA have shown that low-dose insulin therapy is effective, regardless of the administration route. However, continuous IV infusion of regular insulin in obese patients with DKA, including acute intravenous insulin infusion and transition to subcutaneous insulin, have reduced hospital morbidity and mortality in patients with DKA.

The prevalence and relationship with waist circumference of metabolic syndrome and related disorders in an urban population of African females

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Background: The prevalence of obesity is high in urban African females. Therefore, the aim of the study was to measure the prevalence of obesity-related disorders in such a population, and to determine the appropriate waist circumference cut-points for use in the diagnosis of the metabolic syndrome.

Method: Anthropometric data were collected from 1 251 mothers/caregivers of children participating in the Birth to 20 study. Fasting lipid, glucose and insulin levels were taken from 474-609 subjects. Waist cut-points were derived using the receiver operating characteristic (ROC) curve analysis.

Results: The median age (IQR) of the cohort was 40.0 (10.6) years. The prevalence of obesity, type 2 diabetes and metabolic syndrome, were 50.1%, 14.3% and 42.1%, respectively. The most prevalent components of the metabolic syndrome in this population were abdominal obesity (waist ≥ 80cm) at 69.3% and low high-density lipoproteins (HDL) (< 1.3mmol/L) levels at 70.1%. ROC curve analysis demonstrated that the optimal waist cut-off point for diagnosing subjects with three of four metabolic syndrome components was 91.5 cm, while optimal cut-points for hypertension (systolic blood pressure ≥ 130 and/or diastolic blood pressure ≥ 85 mmHg), dysglycaemia (glucose ≥ 5.6mM) and low HDL were 90.1cm, 88.4cm and 87.6cm, respectively.

Conclusion: These data demonstrate a very high prevalence of obesity and related metabolic disorders in an urban population of middle-aged African females and indicate that the waist cut-off point (≥ 80cm) currently used for diagnosing metabolic syndrome in sub-Saharan African females is inappropriate, and should be increased. Confirmatory studies in other African cohorts are required.
a hyperchloraeic metabolic acidosis. Ringers lactate (RL) is an alternative, but is associated with hyperkalemia. The objective was to compare the effects of these two fluids during treatment and the biochemical parameters in Type 1 diabetics admitted with DKA.

Method: Patients admitted with DKA were enrolled in a non-randomised intervention study between November 2008–November 2010. Patients were allocated to either NS or RL infusion on diagnosis

Results: Thirty-seven patients, with 40 admissions for DKA, were enrolled. Fifty-five per cent of patients received NS as the initial fluid. Between the two groups, there were no differences in mean age, gender distribution, the duration of diabetes, or number of previous DKA episodes. There was no overall difference in time to resolution of DKA between the two fluid groups (Chi-squared 6.830, p-value = 0.655). There were no significant differences between groups with regard to the occurrence of sodium, potassium, chloride or acid-base abnormalities.

Conclusion: There were no differences in patients receiving NS or RL, either in time to resolution of DKA, or with regard to the occurrence of electrolyte disturbances.

4 Measured glomerular filtration rate (mGFR) and estimated glomerular filtration rate (eGFR) in patients with diabetes mellitus at the Inkosi Albert Luthuli Hospital diabetes clinic, Durban

Background: This study was undertaken to evaluate measured (m) and estimated (e) glomerular filtration rate (GFR) in patients with type 1 and type 2 diabetes or diabetes mellitus in the diabetes clinic at Inkosi Albert Luthuli Hospital (ALCH), Durban, to determine its usefulness and correlation with mGFR.

Method: This was a retrospective chart review of 435 South African Indian (I) (n = 251) and African (A) (n = 184). Information was recorded on the first visit, and on the most recent visit for demographic, anthropometric, and biochemical test measurements. True (measured) GFR (mGFR) was determined by the isotope Cr-EDTA method. For eGFR, the Cockcroft-Gault (eGFR CG) and modification of diet in renal disease (eGFR MDRD) equations were used.

Results: There were 71 patients with type 1 diabetes mellitus (A: I; 44:27) and 364 with type 2 diabetes mellitus (A: I; 157:207). For type 1 diabetes mellitus (M:F; 37:34), mean age was 29.8 ±12.6 years, and diabetes duration 14.5 ±9.3 years. At first visit, the mean (ml/min/1.73m²) mGFR was 105.0 ±29.2, eGFR CG 125.4 ±39.6 and eGFR MDRD, 117.1 ±37.9 (p-value < 0.001). The values recorded at the most recent visit were 84.9 ±30.2, 109.0 ±59.5 and 86.1 ±33, respectively (p-value < 0.001). Good correlation was only found between latest visit mGFR and eGFR MDRD, both in type 1 diabetes mellitus (r 0.50; p-value 0.18; contraindications (CI): 13.2-2.5) and type 2 diabetes mellitus (r 0.80; p-value 0.28; CI: 3.5-0.99). Independent risk factors associated with mGFR included eGFR MDRD, age and proteinuria (type 1 and type 2 diabetes mellitus); body mass index, serum creatinine, plasma glucose (type 1 diabetes mellitus); retinopathy and African ethnicity (type 2 diabetes mellitus).

Conclusion: In this study, in diabetes subjects with a wide range of renal function, eGFR overestimated GFR and there was poor correlation between mGFR and eGFR, except with latest eGFR MDRD.

10:15: Tea/Coffee

10:15-12:00: Oral Presentations

5 Thyroid disease and pregnancy

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The thyroid plays an important role during pregnancy, both in the mother and developing foetus. Severe thyroid disease during pregnancy puts both at great risk. Even mild thyroid disease may affect foetal development. A complete understanding of the role of the thyroid in normal pregnancy is important for the management of thyroid disease during pregnancy. This presentation will review the full spectrum of thyroid disorders in pregnancy and their management.

6 Low prevalence of thyroid microsomal and thyroglobulin antibodies in thyroid disease patients presenting at Nelson Mandela Academic Hospital, Eastern Cape

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Background: To determine the prevalence and determinants of thyroid antibodies in patients presenting with thyroid disease at Nelson Mandela Academic Hospital, Mthatha, Eastern Cape Province.

Method: The method used was a retrospective review of medical records. Prevalence of thyroid microsomal and thyroglobulin antibodies were determined in 120 patients with Toxic Graves’ disease (n = 56), toxic nodular goitre (n = 16), spontaneous primary hypothyroidism (n = 18) and non-toxic goitre (n = 30). Univariate analysis was undertaken to ascertain determinants of thyroid microsomal positivity.

Results: The 120 patients, who were all black Africans, comprised 114 females and six males. Prevalence of microsomal antibody positivity in various thyroid diseases were Toxic Graves (23.2%, n = 13/56), toxic nodular goitre (0%, n = 0/16), spontaneous primary hypothyroidism (16.7%, n = 3/18) and non-toxic goitre (10%, n = 3/30).
Results: Associations with metabolic derangements were evaluated.

Two of which are known to be sensitising.

Two single nucleotide polymorphisms, one polymorphism inducing a degree of cortisol resistance, N363S. Bcl polymorphism occurred more frequently in whites than in any of the other ethnic groups, but was not associated with any metabolic derangement. The ER22/23EK polymorphism was associated with lower low-density lipoprotein (LDL) cholesterol in controls vs. the wild type. The overall effect of the GCR polymorphisms was to increase the BMI in healthy control subjects and patients harbouring the ER22/23EK polymorphism, which was in contrast to what was expected. No associations between any of the polymorphisms and obesity, and an increased risk of type 2 diabetes mellitus.

Conclusion: This study shows that thyroid microsomal antibody testing is of limited diagnostic value in evaluating thyroid disease in our setting, particularly in those with short- or long-term disease duration. Thyroglobulin antibody testing is virtually of no diagnostic use in our patient population.

The prevalence of Bcl polymorphism occurred more frequently in whites than in any of the other ethnic groups, but was not associated with any metabolic derangement. The ER22/23EK polymorphism was associated with an increased BMI in both patients (29.4 vs 24.7 kg/m²; p-value < 0.02) and control subjects (26.3 vs 24.2 kg/m²; p-value < 0.001) compared with wild type. This heterozygous polymorphism was associated with lower low-density lipoprotein (LDL) cholesterol in controls vs. the wild type (3.46 mmol/L vs 3.93 mmol/L; p-value = 0.02). The N363S was not associated with any metabolic derangement.

Conclusion: The effect of glucocorticoid receptor polymorphisms on the sensitivity to cortisol in Addison’s disease

Background: There is uncertainty as to whether GCR polymorphisms play a role in the development of glucocorticoid-related side-effects in individuals receiving hydrocortisone replacement for Addison’s disease.

Method: One hundred-and-forty-seven Addison’s patients were age, gender, ethnicity and body mass index (BMI) matched with 147 control subjects. Genotyping was performed using polymerase chain reaction (PCR) for three single nucleotide polymorphisms, 147 control subjects. Genotyping was performed using polymerase chain reaction (PCR) for three single nucleotide polymorphisms.

Results: The prevalence of Bcl polymorphism occurred more frequently in whites than in any of the other ethnic groups, but was not associated with any metabolic derangement. The ER22/23EK polymorphism was associated with an increased BMI in both patients (29.4 vs 24.7 kg/m²; p-value < 0.02) and control subjects (26.3 vs 24.2 kg/m²; p-value < 0.001) compared with wild type. This heterozygous polymorphism was associated with lower low-density lipoprotein (LDL) cholesterol in controls vs. the wild type (3.46 mmol/L vs 3.93 mmol/L; p-value = 0.02). The N363S was not associated with any metabolic derangement.

Conclusion: The overall effect of the GCR polymorphisms was to increase the BMI in healthy control subjects and patients harbouring the ER22/23EK polymorphism, which was in contrast to what was expected. No associations between any of the polymorphisms and hydrocortisone doses were found, albeit that doses are prescribed on an empiric basis.

The prevalence and clinical significance of acanthosis nigricans in women of mixed ancestry

Background: Acanthosis nigricans (AN) is associated with insulin resistance, obesity, and an increased risk of type 2 diabetes mellitus...
(T2DM). AN has an ethnic predisposition and is described as rare, although in selected patient groups, the prevalence reportedly ranged from 5-50%. This may be due to an increased prevalence of obesity/T2DM in these populations, but may also simply represent a normal phenotype.

The aim of the study was to determine the prevalence of AN in women of mixed ancestry attending general dermatology and medicine clinics at Tygerberg Hospital, and to ascertain whether, in this population, the prevalence of AN is associated with obesity, blood pressure, and/or blood glucose/haemoglobin A1c (HBA1c) levels.

Method: Females of mixed ancestry, aged 30-70 years were randomly recruited. Subjects with known malignancies, alcoholism and chronic glucocorticoid use were excluded. The presence and distribution of AN, blood pressure, body mass index (BMI), and glucose/HBA1c were determined.

Results: Data on the first 120 patients showed that 27.5% (n = 33) had AN. Those with AN had a significantly higher mean BMI, when compared with those without (36.6% vs. 30.6%; p-value < 0.001), but there was no association between AN and random blood glucose/HBA1c or blood pressure.

Conclusion: AN is very common (27.5%) in our mixed ancestry population, and is associated with an increased BMI, but not glucose/HBA1c levels. Further studies are needed to determine its clinical relevance.

12 An unusual case of primary hyperparathyroidism
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Primary hyperparathyroidism is a common disease among the elderly, and affects mainly females. In modern times, diagnosis is often made early. Presently, osteitis fibrosa cystic occurs in less than 10% of patients.

A 27-year-old male presented with a spontaneous fracture of the right tibia. A hard non-tender mass over the proximal tibia was detected, which, on the X-ray, showed a large expansile lytic mass. His initial results revealed his Alkaline phosphatase was 369U/L (N 53-128U/L) and corrected calcium was 4.68mmol/L (N 2.15-2.50mmol/L). A three-phase Tc-99m methylene diphosphonate (MDP) bone scan showed intense uptake over the proximal tibia, left distal femur and mandible. An magnetic resonance imaging (MRI) study suggested giant cell tumors of the right tibia and distal left femur. A bone biopsy of the mass confirmed a giant cell tumour. Despite therapy, he had persistent hypercalcaemia. His parathyroid hormone level was 90.7pmol/L (N 1.2-8.5pmol/L). A Tc-99m MiIBI scan showed marked uptake over the left cervical area. Therefore, the giant cell tumors were assessed as brown tumours of hyperparathyroidism. The patient underwent parathyroidectomy and a large benign parathyroid adenoma was excised.

Culture of the bone biopsy specimen displayed mycobacterial growth. He had no clinical, biochemical, or radiological evidence of active tuberculosis. To our knowledge, this is the first reported case of tuberculosis within a brown tumour, and as such, this may represent an unusual site of latent tuberculosis.

13 The anthropometric determinants of insulin resistance change with increasing body mass index
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Background: Visceral adipose tissue mass, which is thought to be a principal determinant of insulin resistance, increases in parallel with rising body mass index (BMI). Therefore, the aim of this study was to determine whether a proxy measure of visceral adipose mass and waist circumference, has a stronger influence on insulin resistance in overweight and obese, rather than on lean subjects.

Method: Anthropometry and fasting insulin and glucose levels were measured in 243 (133 females) non-diabetic, Indian subjects. Pearson correlation and backward, stepwise regression analyses were performed to determine the relationship between insulin resistance (HOMA) and anthropometric variables in lean (n = 147) and overweight/obese (n = 96) subjects.

Results: In the total cohort, HOMA correlated with BMI (b = 0.41, p-value < 0.0001) independently of waist circumference (b = 0.28, p-value = 0.003). However, in lean subjects, BMI (b = 0.31, p-value = 0.0001) was the principal determinant of HOMA, while in overweight/obese subjects, waist circumference (b = 0.30, p = 0.003) was the strongest correlate of insulin resistance.

Conclusion: This study demonstrates that in lean subjects, BMI is the major determinant of insulin resistance, while in overweight and obese subjects, waist circumference predominates. When examining the relationship between anthropometric variables and insulin resistance, lean, overweight and obese subject groups should be examined separately. In studies where such groups are combined, the relationship between simple anthropometric measures and insulin resistance will be influenced by the ratio of lean: overweight: obese individuals.

14 Adrenocortical carcinoma in a child
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Adrenocortical carcinomas are rare, comprising 0.2% of childhood cancers. We report on a child with adrenocortical carcinoma with cushingoid features and virilisation. A four-year-and ten-month female child presented with convulsions, hypertentation and a right-sided hypochondral mass. The patient had features of Cushings syndrome and prominent virilisation. The urinary cortisol concentration was greater than 2 069 nmol/l, with a serum adrenocorticotropic hormone (ACTH) which was suppressed (< 5 ng/l). The serum testosterone and dehydroepiandrosterone (DHEA) were elevated (testosterone > 55 nmol/L and DHEA > 27 umol/L). Both serum aldosterone and renin were elevated.

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(1 182 pmol/l and 263 mIU/l respectively). The bone age was advanced at 10 years. Computed tomography (CT) of the abdomen confirmed the presence of a mass with calcifications arising from the right adrenal gland. A large mass adherent to the right kidney was found and removed during surgery. The entire tumour measuring 170 x 125 x 85, and the right kidney, were removed. Apart from the renal involvement, there was no evidence of further dissemination of the tumour. Histology confirmed the presence of a low-grade adrenal carcinoma. However, there was evidence of lymphovascular invasion and breaching of the adrenal capsule by the tumour. The hormonal studies normalised postoperatively. Although the tumour was completely excised, given the generally grave prognosis of adrenocortical tumours and high risk for recurrence, chemotherapy was initiated. Mitotane, cisplatinum, doxyrubicin and etoposide were given. The presence of virilisation in childhood Cushing’s syndrome indicates a possible adrenocortical carcinoma diagnosis.

15 Leukocyte O-GlcNAcylation: a novel tool for the early detection of type 2 diabetes mellitus?

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Hyperglycaemia increases flux through the hexosamine biosynthetic pathway (HBP), resulting in greater O-GlcNAcylation of target proteins (a post-translational modification). The HBP usually acts as a “fuel sensor” under normal conditions, i.e. sensing nutrient availability and repartitioning fuel substrates into suitable storage depots. However, chronic activated HBP flux is maladaptive and may contribute to pathophysiologic phenotypes (insulin resistance and cardiovascular diseases). Since O-GlcNac protein sites are found in leukocytes, it was hypothesised that increased O-GlcNAcylation of leukocyte proteins in the pre-diabetic milieu represents a novel diagnostic tool for earlier detection of type 2 diabetes. Subjects were recruited at the Stellenbosch University campus (35-65 years old) and categorised by fasting blood glucose levels (normal, pre-diabetic, diabetic, and ADA criteria). Subsequently, a second blood sample was collected for leukocyte isolation and the degree of O-GlcNAcylation evaluated by flow cytometry, immunoblotting and fluorescence microscopy. The outcome of the subject recruitment was not as expected, and sufficient characterisation into the three glucose groups (refer above) was unsuccessful. However, when we analysed individuals within the normal range for fasting glucose levels (4-5.4 mmol/L), we found that O-GlcNAcylation of leukocyte proteins changed in parallel with increasing fasting glucose levels. Our data show early promise for a potential future method that may help improve the detection and management of type 2 diabetes by assessing the degree of leukocyte protein O-GlcNAcylation.

16 A functioning malignant insulinoma in a patient with human immunodeficiency virus infection

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A 30-year-old human immunodeficiency virus (HIV) positive female, presented at her local hospital in the third trimester of pregnancy with episodes of severe, symptomatic hypoglycaemia. She had commenced antiretroviral therapy in the early stages of the pregnancy as per the National HIV Mother to Child Prevention Programme. Her baby was delivered by emergent Caesarean section and she was referred to our department in the postpartum period for further investigation. Apart from the history of HIV infection, past medical and family history did not contribute to a diagnosis. General examination revealed the presence of acanthosis nigricans. Abdominal examination was significant only for a contracted, postpartum uterus. Fasting serum glucose was 1.6 mg/dl with symptoms of adrenergic stimulation and neuroglycopaenia. The concomitant insulin level was 30 mU/l, with an inappropriately low C-peptide level. Symptoms resolved transiently with the administration of intravenous dextrose, completing Whipple’s triad. Screening for sulphonylureas was negative. An abdominal CT scan showed a contrast-enhancing mass in the head of the pancreas, with multiple ring-enhancing lesions in the liver. The presence of liver metastases was confirmed by octreotide scan. Histology obtained at liver biopsy confirmed the presence of a malignant neuroendocrine tumour, and diagnosis of a functioning, malignant insulinoma was made. The symptoms responded favourably to the administration of subcutaneous octreotide. To the best of our knowledge, this is the first case of a functioning malignant neuroendocrine tumour described in the setting of HIV.

17 Characteristics of children presenting with newly diagnosed type 1 diabetes

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Background: The clinical presentation of Type 1 diabetes in children can be acute or insidious, and symptoms may be subtle and frequently misinterpreted. Presentation with diabetic ketoacidosis (DKA) may be associated with significant morbidity and mortality in the paediatric population. This study set out to determine the characteristics of those children presenting with DKA on diagnosis at the paediatric endocrine service at Inkosi Albert Luthuli Central Hospital (IALCH), and to determine the frequency of missed diagnoses in the month prior to diagnosis.

Method: A retrospective study was carried out at IALCH. The study sample included all children presenting with an initial diagnosis of type 1 diabetes diagnosed from January 2008–June 2010. Children presenting with DKA were compared to those who presented without DKA.

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Results: During the period under review, 63 children presented with type 1 diabetes. Forty-four of 63 patients (64%) presented with DKA at diagnosis. The median duration of symptoms preceding diagnosis in the DKA group was two weeks versus four weeks in the non-DKA group (p-value = 0.002). Twenty-seven of the 42 patients (64%) who presented to health care facilities in the month preceding diagnosis were misdiagnosed.

Conclusion: Patients who presented with DKA had a shorter duration of symptoms than the non-DKA group. This implies that there is an unacceptable rate of missed diagnoses of type 1 diabetes in both the private and public sector.

The contribution of carbon atoms derived from dietary fructose to lipid synthesis in humans

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Background: Excessive dietary fructose intake has been shown to raise serum triglyceride levels in human subjects, but the exact mechanism by which this occurs is uncertain. Therefore, the aim of this study was to determine whether fructose acts as a substrate for lipogenesis.

Method: A 50 g-fructose load, spiked with 50 mg of 13C-fructose was given orally to seven fasting, female volunteers. Breath and blood samples were collected at baseline, and at 0.5, 1.3 and 6 hours after fructose ingestion. Subjects were then asked to consume 10g of fructose spiked with 50 mg of 13C-fructose, twice per day for four weeks. Blood samples were collected weekly, and two weeks after the final dosing. Insulin, glucose, triglycerides and total, high-density lipoprotein, and low-density lipoprotein cholesterol levels were measured. Lipid fractions were also isolated from blood samples via thin layer chromatography and the 13C content of each fraction was measured via isotope ratio mass spectrometry.

Results: The 13C content of the total lipid fraction rose significantly (p-value < 0.05) above the baseline value by 3.95 ±2.82%, 3.62 ±2.55%, 7.67 ±7.94%, 9.03 ±5.57%, 10.4 ±6.93% and 8.11 ±5.31%, at the three- and six- hour time points, and at the one-, two-, three- and four-week time points, respectively. The 13C content of serum free fatty acids (FFAs) was significantly lower than the baseline level at six of the nine time points (p-value < 0.05).

Conclusion: Fructose contributes carbon atoms for lipid synthesis in humans, but leads to a reduction in serum FFA levels. This may be due to increased hepatic FFA uptake for incorporation into triglycerides.
present study, we isolated scADSCs and vADSCs from rats with diet-induced visceral obesity and insulin resistance, to investigate the effects of systemic insulin resistance on the insulin response of cultured ADSCs.

**Method:** Adult male Wistar rats were fed either standard laboratory lean food, or a highly palatable diet which induced excessive energy intake (DIO) for 16 weeks. This diet resulted in visceral obesity, dyslipidaemia and insulin resistance. Paired subcutaneous and visceral adipose tissue samples were harvested from lean and DIO rats, and ADSCs isolated, providing cells from lean subcutaneous (LS) and lean visceral (LV), and DIO subcutaneous (DS) and DIO visceral (DV) depots. The cultured cells were treated with AM (standard culture media supplemented with insulin, indomethacin, isobutylmethylxanthine and dexamethasone) and the effects of systemic insulin resistance on the insulin response of differentiating LS and DS cells, or between differentiating LV and DV cells.

**Results:** All four cell-types accumulated small intracellular lipid droplets of the same size in response to AM treatment. LV and DV cells displayed a stronger adipogenic response to AM than LS and DS cells, but cells from DIO rats accumulated lipid to the same extent as cells from lean rats. Insulin alone was not lipogenic in naive cells, but was more lipogenic in differentiating LV and DV cells, and more mitogenic (proliferative) in differentiating LS and DS cells. There was no difference in the magnitude of the insulin response between differentiating LS and DS cells, or between differentiating LV and DV cells.

**Conclusion:** Diet-induced insulin resistance in donor animals may not persist in cultured ADSCs. This suggests that in vivo insulin resistance is conferred by circulating factors, and that the effects of these factors on intracellular signalling are reversible.

Vanadate stimulates osteoblast proliferation both in vitro and in vivo, yet fails to increase bone formation or bone mineral density in the rat

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**Background:** Glucocorticoid (GC) induced osteoporosis results largely from diminished numbers of functional osteoblasts. We have previously reported that GCs inhibit mitogen-induced proliferation of preosteoblasts in vitro by upregulating protein tyrosine phosphatase (PTP) expression and consequently reducing mitogenic Erk activity. Inhibition of PTP activity with vanadate was found to abrogate the actions of GCs both in vitro, in immortalised MBA 15.4 cells, by restoring Erk activity and preosteoblast proliferation, and in vivo, in rats, by re-establishing normal bone formation, bone mineral density and bone strength. However, during our recent investigations on mesenchymal stromal cells, the precursor cells of osteoblasts, we found that vanadate alone stimulates Erk activity and proliferation in these primary cells. Therefore, we hypothesised that vanadate could not only abrogate the actions of GCs in vivo, but might also enhance osteoblast numbers and increase bone mineral density in the absence of GCs.

**Method:** Adipose derivedstromal cells (ADSCs) were made synchronous by incubation overnight in one per cent foetal bovine serum (FBS). Western blotting was used to determine Erk activity after the addition of vanadate. Cellular proliferation was then measured by tritiated thymidine incorporation. For the in vivo studies, rats (n = 10) were fed vanadate in the drinking water (0.5 mg/ml) for nine weeks, after which femur bone mineral density (BMD), bone formation rate (BFR), bone surfaces covered by osteoblasts, osteoclast surfaces and eroded surfaces (ES) were measured by quantitative histomorphometry, following time-spaced tetracycline labelling.

**Results:** Vanadate caused a rapid activation of Erk and increased proliferation in ADSCs. This translated to increased osteoblast surfaces (87%, p-value < 0.005) in vivo, but no statistical differences in BFR or the other histomorphometric parameters were measured. Although vanadate increased osteoblast numbers in vivo, there was no apparent stimulation of bone formation, or increase in BMD.

**Conclusion:** Since neither osteoclast activity nor numbers were affected by vanadate, it would appear that the vanadate-induced increase in osteoblast numbers is accompanied by a proportional decrease in activity. The effects of vanadate, not only on osteoblast numbers, but also on osteoblast function, therefore warrant further investigation.

14:45: Tea/Coffee

15:15-16:30: Oral Presentations

22 Hypoglycaemia in type 1 diabetes: inevitable or avoidable?

Amiel SA

23 The influence of diabetic patients’ knowledge, attitude, and practices regarding diet, lifestyle and their diabetes on glycaemic control and complications: a cross-sectional study

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**Background:** To quantitatively assess the knowledge, attitudes and practices (KAP) of patients at Maluti Adventist Hospital (MAH) towards a diabetic diet and healthy lifestyle, and how these variables impact on long-and short-term glycaemic control and complications.

**Method:** One-hundred-and-fifty diabetic patients were recruited from MAH from May-June 2009. Social, demographic and KAP information was obtained through a structured questionnaire. Patients underwent a physical examination, during which the following was taken: anthropometric measurements, resting electrocardiogram (ECG), dipstick urinalysis and measurement of haemoglobin A1c (HbA1c).

**Results:** The sample comprised 150 patients (121 female), with a mean age of 58.2 years. The mean body mass index (BMI) of the
study population was 30.4 kg/m², while 49.7% was obese (BMI ≥ 30 kg/m²). 94.7% of patients were taking an oral hypoglycaemic agent (OHA). Eighty-five per cent experienced coexisting hypertension, 34.4% demonstrated evidence of diabetic eye complications, while 56.7% had a BP > 130/80 mmHg. Forty-six per cent and 57.5% of patients respectively had poor short- and long-term glycaemic control. Peripheral neuropathy was present in 43.3% of patients, while 6.7% had 2+ dipstick positive proteinuria. Patients portrayed a number of resting ECG abnormalities, particularly S-T changes (29.7%), and arrhythmias (28.3%). Overall, patients portrayed relatively good KAP, with 94.6%, 98.7%, 74.8% obtaining > 40% of knowledge, attitude and practice scores respectively. Generally, better KAP scores were associated with poor HBA1c. Due to the limited sample size and/or infrequent occurrence of the complications in this study, the relationship between KAP and DM complications was not statistically significant.

**Conclusion:** Despite demonstrating favourable KAP, this did not necessarily translate into better short- and long-term glycaemic control in this group of patients.

**Exploring novel ways to blunt hyperglycaemia-induced contractile dysfunction**

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**Background:** Previous studies have reported that the prevalence of higher blood glucose levels during, and after an ischemic insult, amplifies the risk of future cardiovascular disease events. We concur, having discovered that hyperglycemia triggers oxidative stress, thereby resulting in a greater flux of glucose through alternate metabolic pathways [e.g. the hexoseamine biosynthetic pathway (HBP)], leading to increased myocardial apoptosis. Since benfotiamine (vitamin B-derivative) can decrease HBP flux, we hypothesised that it attenuates cardiac cell death, and thus improves contractile dysfunction in response to ischemia-reperfusion.

**Method:** We employed an isolated heart perfusion system (Langendorff). Rat hearts were mounted and perfused for 90 minutes with 22 mM and 33 mM glucose (hyperglycemia) respectively. Controls (11 mM glucose, normoglycemia). Subsequently, hearts were subjected to 30 minutes of global ischemia, followed by 60 minutes of reperfusion, to assess functional recovery. To evaluate the cardioprotective effects of benfotiamine, three doses (25, 50, and 100 µM) were administered immediately after reperfusion.

**Results:** Our data show that functional recovery of heart function was significantly blunted (vs. controls) under hyperglycemic conditions, following ischemia-reperfusion. However, benfotiamine treatment blunted the damaging effects of hyperglycemia, and significantly improved the heart’s functional recovery in response to ischemia-reperfusion.

**Conclusion:** Our study demonstrates that benfotiamine is a promising cardioprotective agent that may ultimately benefit pre- and full-blown diabetic patients suffering from cardiovascular disease complications.

**16:30: SEMDSA Annual General Meeting**

**17:30: SEMDSA Awards Committee Meeting**

**Sunday 10 April 2011**

**8:30-10:00: Oral Presentations**

**25 Why can’t we stop eating? Emerging evidence from neuroimaging studies for appetite dysregulation in metabolic syndrome**

Amiel SA

**26 Parathyroid hormone replacement treatment in hypoparathyroidism**

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Hypoparathyroidism (HypoPT) is the only major hormone deficiency disease that is not usually treated with the missing hormone. Bovine parathyroid hormone (PTH) has been purified and used as experimental treatment, dating back to 1928, by Fuller Albright. However, treatment was abolished mainly because of antibody formation and costs. The recent approval of fully humanised truncated parathyroid hormone [Teriparatide, PTH (1-34)] and intact parathyroid hormone [Preotact, PTH (1-84)] for treatment of osteoporosis, has made the PTH drugs more accessible, and thereby made clinical trials with PTH replacement treatment (PTH-RT) of HypoPT feasible.

Recent clinical trials have shown that, compared with conventional treatment, treatment with PTH (1-34) and PTH (1-84) can stabilise plasma calcium, normalise plasma phosphate and reduce urine excretion of calcium. It seems that, compared with conventional treatment of 1α-hydroxylated vitamin D metabolites and calcium supplements, some patients experience an improved quality of life when treated with PTH.

Moreover, the very low bone turnover normally present during conventional treatment is increased in response to PTH-RT. A normalisation of bone remodelling might enable repairing of micro cracks, and thereby increase bone strength. Despite an increased bone turnover, bone mineral density (BMD) does not seem to decrease in response to PTH-RT. PTH-RT seems to exert bone anabolic effects in patients with HypoPT (similar to the way in which osteoporosis patients being treated with PTH are affected), thereby increasing bone mass. Further studies should aim to confirm these potentially advantageous PTH-RT effects. Long-term beneficial and adverse treatment effects should also be determined. There is a need for studies on how PTH is best administrated in order to obtain a steady level with plasma calcium concentrations within the normal range. Finally, more should be known about the epidemiology of HypoPT, and the clinical consequences of the disease and its treatment.

**10:00: Tea/Coffee**
The association between hyperglycaemia in hospitalised patients, with or without diabetes, and increased risk of complications and mortality is well established.1-4 This association is observed for both admission glucose and mean blood glucose levels during the hospital stay. Although most randomised controlled trials (RCTs), investigating the impact of treating hyperglycaemia on clinical outcomes, have been performed on critically ill patients strong observational data support the importance of hyperglycaemia management among patients who are not critically ill, and who have been admitted for general medicine and surgery. In such patients, hyperglycaemia is associated with a prolonged hospital stay, increased incidence of infections, and more disability after hospital discharge and death.1, 5

Recent RCT in general surgery patients with type 2 diabetes mellitus, indicated that glycaemic control results in a reduction in the risk of infection (relative risk 0.47, 95% contraindications, 0.28-0.79) and a trend for increased risk of hypoglycaemia (relative risk 1.4, 95% contraindications, 0.86-2.27).6,7 The American Association of Clinical Endocrinologists (AACE) and American Diabetes Association (ADA) Practice Guideline recommends pre-meal glucose of < 140 mg/dl (7.8 mmol/l) and a random blood glucose (BG) of < 180 mg/dl (10.0 mmol/l) for the majority of patients who are not critically ill, and who are being treated with insulin.1 To avoid hypoglycaemia (BG < 70 mg/dl), the total basal and prandial insulin dose should be reduced if BG levels fall between 70 and 100 mg/dl. This lecture will review consensus recommendations for the management of hyperglycaemia in hospitalised patients in non-critical care settings. The central goal is to provide practical, achievable, and safe glycaemic goals, and to describe protocols needed to facilitate glycaemic control in the non-ICU setting.

Haemoglobin A1c in the diagnosis of diabetes: a balanced view
Motala AA

Genetic defects of the GH–IGF-1 axis in intrauterine growth retardation
Pfäffle R

Perioperative management of patients with diabetes.
Umpierrez GE
Low-density lipoprotein receptor mutations in familial hypercholesterolaemia at the Groote Schuur Hospital Lipid Clinic, Cape Town

Brice BC, Wolmarans KH, Blom DJ, Jones S, Solomon GAE, Ratanjee BD, Barron JK, Cowie PLE, Jooste RJ, Marais AD
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Background: To review the occurrence of low-density lipoprotein (LDL) mutations in subjects presenting at a referral clinic with the heterozygous familial hypercholesterolemia (FH) phenotype.

Method: Following clinical evaluation for premature coronary disease, tendon xanthomata and LDL cholesterol > 5mmol/L, deoxyribonucleic acid (DNA) from consenting subjects was analysed by polymerase chain reaction, single-strand conformational polymorphism and heteroduplex formation on gels, and high resolution melting, confirmed by restriction enzyme analysis and sequencing. To date, all exons except 11, 13, 15, 17 and 18 have been screened. Large insertion/deletion mutations would not be detected.

Results: The cohort comprised 1 624 mostly unrelated individuals: blacks < 1%, Indians 1%, mixed ancestry 45% and whites 53%. A total of 57 different LDL receptor mutations were identified in 977 subjects: 10 in exon 4; 8 in exon 9; 6 in exons 3, 6, 7 and 8; and 4 in exons 5 and 14 with 3, 2, 1; and 1 in exons 2, 1, 12 and 16. The most common mutations were D206E (357), V408M (190), D154N (49), D200G and del197 (38). LDL receptor mutations were identified in 66% whites, 32% mixed ancestry, 1% Indian and < 1% of black subjects. Though founder effects were evident, in the main, mutations were not exclusive to the different ethnic groups, with the exception of exon 7 and 8 2.5 kb deletion in mixed ancestry, and N384K, Indians.

Conclusion: Though FH should be diagnosed clinically, genetic confirmation is possible with differing success rates in different groups. More research is required to define the full range of mutations that would be appropriate for a local diagnostic set.

Evaluation of efficacy and safety of lapaquistat when coadministered with high-dose statin therapy in subjects with primary hypercholesterolaemia: the Cape Town experience

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Background: Patients with the heterozygous familial hypercholesterolaemia (heFH) phenotype represent a primary hyperlipidaemia, with an increased risk of coronary artery disease. Treatment with statins is effective in lowering cholesterol levels, but may lack power, or cause adverse effects. Lapaquistat is an investigational oral squalene synthase inhibitor. We report on the results of a multinational study that was conducted locally (TAK 475-021).

Method: Adult subjects, on the highest recommended dose of statins, with low-density lipoprotein (LDL) cholesterol > 2.59mmol/L, were eligible for this efficacy and safety study. Following a 26-week double-blind placebo controlled period, all subjects received open label Lapaquistat (100 mg daily for 34 weeks).

Results: Forty-one heFH subjects (25 male and 16 female) aged 43.3 ±13.2 years were randomised to receive either placebo or Lapaquistat (100mg daily orally). Baseline lipid levels on stable therapy, with either Atorvastatin 80 mg (n = 30), or Simvastatin 80 mg (n = 11), were LDL cholesterol 4.4 ±0.9 mmol/L, total cholesterol 6.13 ±0.9 mmol/L, high-density lipoprotein (HDL) cholesterol 1.14 ±0.3 mmol/L, and triglyceride 1.3 ±0.6 mmol/L. During the open label phase, there was a significant reduction in LDL cholesterol (17%, p-value < 0.01) and in total cholesterol (TC) (11%, p-value < 0.01), as well as a significant increase in HDL cholesterol (6%, p-value = 0.02) compared to baseline. No adverse events were related to the study drug. No laboratory safety concerns arose during the study, including elevations of transaminases and creatine kinase.

Conclusion: A significant proportion of heFH patients do not achieve target LDL cholesterol on maximal statin therapy. In this small cohort of South African subjects, Lapaquistat 100mg was a well-tolerated and safe LDL cholesterol-lowering agent when added to statin therapy to assist lipid control in heFH. However, greater LDL cholesterol lowering was still required in most subjects.
probability estimates were calculated before and after January 1990, the time at which statins and other advances in lipid therapy where introduced.

**Results:** Median survival and time to first major adverse cardiovascular event (MACE) were markedly prolonged in post-1990 treated patients, compared to pre-1990 treated HoFH patients. Mean LDL cholesterol decreased by approximately 30% post-1990 therapy.

**Conclusion:** Lipid-lowering therapy, mainly statins, introduced since 1990, has delayed cardiovascular events and significantly prolonged the survival of HoFH patients.

### Comparison of lipid profiles in human immunodeficiency virus-infected treatment-naïve patients, and patients on combination antiretroviral therapy

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**Background:** Antiretroviral therapy (ART) improves survival in human immunodeficiency virus (HIV) positive patients, but many patients develop metabolic complications such as insulin resistance, dysglycaemia, dyslipidaemia, and changes in body fat distribution. The prevalence of dyslipidaemia in HIV-positive patients on ART in sub-Saharan Africa is unknown. The objective of the study was to determine the prevalence of dyslipidaemia in HIV-positive patients on ART.

**Method:** Patients were recruited from public sector HIV clinics in Cape Town. Patients with active infections, severe diarrhoea, recent tuberculosis, pregnancy, or recent glucocorticoid use were excluded. Only patients who had taken NNRTI-based ART for a minimum of six months were included in the ART cohort. Clinical and anthropometric data were collected. Fasting lipids, oral glucose tolerance test (OGTT) were measured. LDL particle size were measured. Dysglycemia, dyslipidemia, and changes in body fat distribution were measured.

**Results:** Nine-hundred-and-one patients were recruited (ART-naïve 436; ART 465; 77% female; mean age 33 years). The ART cohort had higher body mass index (BMI) and waist circumference, but decreased calf circumference. The table below shows the median (interquartile range) of lipid values.

<table>
<thead>
<tr>
<th>Lipid Category</th>
<th>No antiretroviral therapy</th>
<th>Antiretroviral therapy</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Triglycerides</td>
<td>0.85 (0.69, 1.14)</td>
<td>1.01 (0.77, 1.36)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Total Cholesterol</td>
<td>3.62 (3.14, 4.21)</td>
<td>4.43 (3.81, 5.29)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>High-density lipoprotein cholesterol</td>
<td>0.83 (0.67, 1.04)</td>
<td>1.09 (0.88, 1.36)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Low-density lipoprotein cholesterol</td>
<td>2.34 (1.94, 2.82)</td>
<td>2.79 (2.22, 3.46)</td>
<td>&lt; 0.0001</td>
</tr>
</tbody>
</table>

Only five patients on ART (0 awaiting ART) had severe hypercholesterolaemia of > 7.5 mmol/L. No patient had triglycerides > 15 mmol/L. Triglycerides were higher, with efavirenz vs. nevirapine [1.15 (0.92, 1.57)] vs. 0.85 [0.69, 1.10]; p-value <0.0001]. Abnormal oral glucose tolerance test (OGTT) was found in 26% of patients on ART and in 21% of patients awaiting ART, and was predictive of dyslipidaemia. LDL particle size did not differ significantly between the two groups.

**Conclusion:** The observed lipid changes may at least, in part, reflect a return to a normal baseline as nutrition and immune status improves with ART. Severe dyslipidaemia was rare in this cohort.

### South African blacks being treated for hyperlipidaemia have a high prevalence of type 2 diabetes and the metabolic syndrome and are not reaching the low-density lipoprotein cholesterol target: results from the CEPHEUS SA study

**Katharine Kyriacou, John C. Schamroth, Dasa Blom, on behalf of the CEPHEUS Investigators**

**Background:** With rapid urbanisation, the prevalence of hyperlipidaemia and atherosclerotic cardiovascular disease is increasing in the African black population. The centralised pan-South African survey on the under-treatment of hypercholesterolaemia in patients using lipid lowering drugs (CEPHEUS) evaluated what proportion of patients treated with lipid-lowering drugs were achieving the low-density lipoprotein (LDL) cholesterol target.

**Results:** Of the 2 996 patients enrolled, 510 patients (17%) were urbanised black Africans. Compared to the other ethnic groups [1 385 (46%) Caucasians, 481 (16%) mixed ancestry and 621 (21%) Asians], black patients were more likely to be female (67% vs. 48%), were more obese [body mass index (BMI, 32.6 kg/m²)], and had a higher prevalence of hypertension (88 vs. 72%) and type 2 diabetes (74 vs. 47%). These are all components of the metabolic syndrome. However, they were less likely to have established vascular disease [CHD (16 vs. 35%); peripheral artery disease (PAD) (3 vs. 5%); stroke (6 vs. 5%)]. Overall, 42% of black patients were not at the European (ESC) LDL cholesterol target vs. 48% of the overall study population.

**Conclusion:** The prevalence of the metabolic syndrome and type 2 diabetes is high in urbanised blacks receiving lipid-lowering drug therapy. However, hyperlipidaemia is not being adequately addressed in this population. Therefore black patients may require a more intensive assessment and management of their cardiometabolic risk factors.

### Marine foods as a source of protein for middle and later Stone Age hunter-gatherers on the Western Cape coast

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**Background:** The nutritional value of food at the shoreline is of interest with regard to fatty acids, as well as protein. The aim of this analysis was to determine the protein content of mollusks, fish, birds
and mammals that might have provided nourishment to an emerging modern population over the past 200 000 years.

**Method:** Material was acquired by various routes, including commercial establishments, marine and coastal management, and the South African Foundation for the Conservation of Coastal Birds (SANCCOB). Tissue representing edible portions was selected for homogenisation and analysis by the Markwell modification of the Lowry reaction in 27 species, some of which comprised multiple samples. The protein content is expressed as g per 100 g of edible tissue.

**Results:** Overall, the protein content ranged from 3.17 in the black mussel (Choromytilus meridionalis) and 40.9 in Hartlaub’s gull. Molluscs varied from 3.17 to 13.8 for white mussel (Donax serra), 19.96 (Turbo sarmaticus, foot process) and 21.67 for (Scutellastera longicosta). The crustacean, Jasus lalandii, contained 10.7 in its tail. Fish ranged from 7.4-13.1. Marine birds had contents of 10.1-40.9 in their muscle, while the liver contained 18.4-39.8, and the brain, 13.5-18.25. The whales’ and dolphins’ muscle ranged from 15.3-18.42, their livers, 16.95-31.26, and brain, 12.3-15.8. Within species there was significant variation.

**Conclusion:** Coastal resources were an adequate source of protein supply, even if the staple food was mollusks, but other nutrients need to be explored, as well as seasonal effects.

**17:00:** LASSA Annual General meeting

**Monday 11 April 2011**

**8:30-10:30: Oral Presentations**

**39 Using large-scale epidemiological evidence to help evaluate biomarkers in cardiovascular disease**

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Despite the known importance of classical risk factors, such as smoking, elevated blood lipids, high blood pressure and cardiovascular disease, the incidence of cardiovascular disease in individuals who lack these traits, together with evidence that interventions which successfully target such factors do not entirely abrogate the risk of disease, has encouraged investigators to continue searching for novel biomarkers. Consequently, in recent decades, many circulating molecular biomarkers and thousands of genetic variants related to lipid, inflammatory, metabolic and haemostatic pathways have been investigated.

However, to date, these novel factors have generally been investigated in observational studies, typically involving only a few hundred cases and only few hundred controls, which, due to the inherent statistical uncertainties of small sample sizes, may be prone to chance findings, selective publication biases and potentially overstated conclusions. However, the reliable identification and detailed characterisation of any such associations with cardiovascular disease is essential if ongoing research is to help improve our understanding of cardiovascular disease aetiology, as well as better predict disease risk in individuals, and suggest new targets for interventional therapies.

In the absence of individual studies of a very large size, appropriate synthesis of the available reports of molecular biomarkers by meta-analysis, should provide a better preliminary indication of their relevance to cardiovascular disease than individual studies involving just a few hundred cases. This approach should also enable study of the separate and combined effects of genetic, biochemical and lifestyle factors that should yield new scientific insights that contribute importantly to the prediction and prevention of cardiovascular disease.

**40 Processed red and white wines do not lose their antioxidant function after alcohol reduction**

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**Background:** Low-alcohol wines have been available for several decades, and although numerous studies have suggested health benefits ranging from moderate consumption of wine with regular alcoholic levels, there have been few studies that directly compare such wines with their low-alcohol equivalents. It is also uncertain whether the alcohol, or the other components in wine, contribute towards health benefits reported in epidemiological studies. This pilot study compared the antioxidant properties of red and white wines with their processed low-alcohol counterparts.

**Method:** Two different red wines at three different alcohol concentrations [A: 13%, 6% and 2% alcohol (n = 18)] and B: 15%, 14% and 2% alcohol (n = 18) were tested. Two different alcohol concentrations [13% and 3% (n = 12)] of a white wine were tested. Vacuum extraction was carried out to lower the alcohol content. All wines were analysed for concentration of total phenols, antioxidant capacity (ORAC), and capacity to protect against copper-induced oxidation of LDL (LDLx), as well as against radical-induced lysis of red blood cells, as measured by lag times.

**Results:** Red wines A and B showed a significant increase in total phenol concentration and ORAC in the 2% sample, compared with the 13% and 15% samples respectively. In addition, Wine A showed a significant increase in LDLx lag times for the same preparations. These increases were in accordance with concentration effects. The white wine also showed a significant increase in total phenol concentration and lag times for haemolysis, but a significant decrease in ORAC, in the 3% compared with the 13% samples.

**Conclusion:** The reduction in alcohol content by vacuum extraction in both the red and white wines did not adversely affect the antioxidant properties of the wine. There was a small concentration effect on the total phenols in all the wines, as well as on the ORAC in both the red wines (and on LDLx lag times in red wine A) and on lag times for haemolysis in the white wine.
Utility of 3-alpha-hydroxy-sterol dehydrogenase assay in plasma for metabolic defects in sterol and bile acid metabolism

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**Background:** The aim was to evaluate the 3-alpha-hydroxy-sterol spectrophotometric assay in the screening for unusual sterol metabolic defects elevating plasma cholestanol, cholestasis, and metabolic defects causing hyper-cholanaemia.

**Method:** Patient records and frozen fasted samples were analysed where the diagnoses of cerebrotendinous xanthomatosis (CTX) and phytosterolaemia had been proven in cholestatic liver disease, or where bile salt metabolic errors were suspected. A standard curve used sodium cholate up to 100 micromol/L with the Bioquant Total Bile Acid Assay Kit designed for five microlitres of sample at absorbance 405 nm in a microtitre plate.

**Results:** Healthy unaffected relatives, or other such samples, served to confirm a normal range of < 10 micromol/L. Samples were available on four CTX patients, four phytosterolaemic patients, 13 with cholestatic liver enzyme derangements, and seven with other disorders. In untreated CTX subjects, the 3-alpha-hydroxysterols were elevated (15-57 micromol/L) and in two treated cases were lowered by 93% and 72%. None of the phytosterolaemic subjects had elevated concentrations. Hypercholanaemia was confirmed at 17 - 486 micromol/L in a variety of cholestatic conditions. Normal results were found in two patients with normalolipidaemic tendon xanthomatosis, and one patient had severe hypercholanaemia, suspected to be a recessive disorder of bile salt metabolism.

**Conclusion:** The assay can screen for CTX, but not for phytosterolaemia. It may be useful to detect unusual bile salt metabolic errors and to monitor cholestatic liver disease.

Emerging anabolic treatments for osteoporosis

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Anabolic treatment that remodel bone tissue and restore bone biomechanical competence is essential in the treatment of osteoporosis. In addition, long-term antiresorptive therapy may have limitations because of the reduced renewal of bone tissue. The only pure anabolic drugs available at present are intact parathyroid hormone (PTH) (1-84) (Preotact) and the truncated PTH (1-34) (Teriparatide), while strontium ranelate may possess antiresorptive, as well as anabolic properties. The marketed antiresorptive and anabolic antosteoporotic drugs have limitations in their use due to adverse effects, or to the occurrence of rare, but severe late complications. Furthermore, indications may be restricted by co-existing diseases, or treatment duration may be limited. However, new anabolic drugs are being developed that mimic the effect of PTH, or target the calcium sensing receptor (CaSR) or the Wnt/β-catenin signalling pathway. The PTH mimetics are truncated or altered PTH fragments, parathyroid hormone-related peptide (PTHrP) and calcilytics stimulating endogenous PTH secretion. Calcimimetics (e.g. strontium) and calcilytics (e.g. lithium) may also affect bone cells directly through the CaSR. The Wnt pathway that stimulates osteoblastic proliferation, differentiation and function, may be activated by neutralising antibodies to secreted inhibitors of Wnt signalling (e.g. sclerostin or dickkopf), or by small molecules (e.g. lithium) that inhibit the glycogen synthase kinase 3β mediated degradation of β-catenin. Finally, blocking of activin A by soluble receptor fusion proteins has been shown to increase bone mass by a dual anabolic-antiresorptive action. The present lecture summarises the physiological background and present evidence for these effects.

10:30: Tea/Coffee

11:00-12:30: Oral Presentations

Genetic testing in patients with hypopituitarism

Plaffe R

New insights into thyroid hormone action

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Thyroid hormone (TH) is a critical regulator of development, metabolism and other key physiologic functions in man. Circulating TH mediates its effects on target tissues, principally by regulating expression of gene expression. Recent discoveries have now elucidated that cellular levels of TH are exquisitely controlled at the local level to provide the exact amount of TH needed at a particular time. Dysfunction of these control systems, which include TH transporters, deiodinases and TH receptor signalling systems, leads to disease. Thus, a further understanding of these systems will provide significant insight into the role of TH in normal physiology, and also insight into potential new therapies for human disease.

12:30: Close