Severe hypertriglyceridaemia (Triglycerides (TG) > 15 mmol/L) is an important metabolic abnormality as it can trigger potentially fatal attacks of acute pancreatitis. Genetic abnormalities of lipid metabolism, metabolic disorders, drugs, toxins and lifestyle factors may all contribute to the development of severe hypertriglyceridaemia. We reviewed our experience of severe hypertriglyceridaemia at the GSH lipid clinic.

Patients with severe hypertriglyceridaemia or pancreatitis attributed to hypertriglyceridaemia were identified by searching the GSH lipid clinic database covering 20 years of experience. Data was extracted retrospectively from the standardised admission notes and entered into a database. Statistical analysis was performed with GraphPad Prism. Results are presented as geometric mean (interquartile range; minimum-maximum) unless otherwise stated.

There were 321 patients (115 ♀, 206 ♂) with a total of 137 patient-years of follow-up. Age at presentation was 36.1 years (15.8 years; 0.02-76.3 years). Maximal recorded TG was 37.1 mmol/L (34.05 mmol/L; 6.7-265 mmol/L). In 205 patients with 6 or more months of follow-up the lowest achieved TG was 2.89 mmol/L (3.0 mmol/L; 0.3-28.6 mmol/L). There were 134 patients (42%) that experienced acute pancreatitis; 78 patients had multiple episodes. Five deaths were attributed to pancreatitis and pancreatic pseudocysts developed in 4 patients. Diabetes (65%), obesity (BMI> 30 kg/m2) (38%) and alcohol abuse (16%) were the commonest secondary causes of hypertriglyceridaemia. In 54 (17%) patients the documentation of hypertriglyceridaemia led to a new diagnosis of diabetes. Genetic causes were found in 36 (11%) of patients. Type I hyperlipidaemia was seen in 23 (7%) patients, dysbetalipoproteinaemia in 11 (3%) and 2 (0.6%) had genetic lipodystrophy.

Untreated severe hypertriglyceridaemia is associated with considerable morbidity and mortality. Most patients respond well to diet and appropriate medication. Diabetes is the most common secondary cause and should be actively sought in all patients.

Screening for dysbetalipoproteinaemia by APOB100/TC ratio

Apolipoprotein B-100 (ApoB) is the structural protein of atherogenic lipoproteins, including VLDL, IDL and LDL. Each lipoprotein contains one apo-B molecule and the plasma apo-B levels reflect the total number of circulating atherogenic lipoproteins. Dysbetalipoproteinaemia (DB) manifests as severe mixed hyperlipidaemia secondary to remnant accumulation. It may be difficult to distinguish from other mixed hyperlipidaemias and specialised testing is not widely available. We investigated whether apoB could serve as a screening test.

We retrospectively examined patients who had been investigated (apoE genotyping + VLDL compositional analysis) for DB. Patients homozygous for apoE2 and with cholesterol-enriched VLDL (VLDL-C/VLDL-TG > 0.96 or VLDL-C/Plasma-TG > 0.69 molar ratios) were classified as DB, those with other apoE genotypes and VLDL-C/VLDL-TG <0.80 + VLDL-TG/Plasma-TG<0.57 were labelled mixed hyperlipidaemia (MH). Other patients had indeterminate (I) diagnosis.

There were 54 patients with DB, 254 with MH and I was 22. Total cholesterol (mean ± SD) was 11.75±4.4, 7.94±1.7 and 8.61±1.7 mmol/L (P<0.001) respectively. Triglycerides (geometric mean ± (95%CI)) were 5.86 (4.89-7.0), 4.32 (4.41-4.45), 4.19 (3.59-4.88) mmol/L (P<0.0001). ApoB (mean ± SD) was 1.15±0.48, 1.61±0.37 and 1.68±0.52 g/L (P<0.0001). The ratio apob/TC was 0.10±0.04, 0.20±0.03 and 0.19±0.04 (P<0.001). An apob/TC ratio cutoff of <0.15 identified DB with a sensitivity of 89% and specificity was 97%.

ApoB/TC ratio is a useful screening test for DB. Remnant lipoproteins are large, cholesterol-rich lipoproteins, explaining the low ratio. The ratio is particularly helpful in identifying patients in whom further specialised testing for DB is not required.
Familial hypercholesterolaemia (FH) as a phenotype comprises severe LDL hypercholesterolaemia with a high occurrence of tendon xanthomata and premature coronary artery disease, caused by mutations in the LDL receptor, apoB and PCSK9 genes. The study of the mutations causing FH is reported.

After a full clinical assessment that excluded secondary causes, the DNA of consenting patients diagnosed with FH was analysed for founder mutations in the LDL receptor as well as other PCR-amplified exons that were analysed by heteroduplex formation and single strand conformational polymorphism. High resolution melting was introduced for the study of apoB mutations. Restriction enzyme analysis was done and sequencing was performed where necessary.

Of 7574 new patients on the database, 1627 (22%) had the FH phenotype. Mutational analysis is incomplete but emphasised common LDL receptor mutations where after apoB mutations were sought. There were 933 (57%) with a genotypic diagnosis, amongst which a few LDLR founder mutations accounted for the majority, in descending order of frequency D206E, V408M, D154N, D200G, Del197, G361V, C356Y, C329X. There were 37 subjects (0.5%) with familial binding defective apoB mutations. One kindred was reported with the PCSK9 S127R mutation in a collaborative study.

Although there are founder effects within population groups and regions that expedite mutation detection, FH is a heterogeneous condition that should be diagnosed clinically.

**Genetic causes of heterozygous familial hyper-cholesterolaemia at Groote Schuur Hospital lipid clinic**

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Familial binding defective apolipoprotein B100 (FDB) is one of the causes of the familial hypercholesterolaemia (FH) phenotype. This study investigated the occurrence of known mutations for FDB in a regional lipid clinic.

A full clinical assessment of referred patients excluded secondary causes. DNA was analysed for founder effects in LDL receptors before analysing by PCR, for FDB mutations; initially by gel electrophoresis but later by high resolution melting of amplicons of exons 26 and 29. Restriction analysis or sequencing was undertaken where appropriate. Clinical and biochemical data were compared with the commonest LDL receptor defect (D206E) after matching for age, gender, BMI and triglyceride concentrations known to modulate LDL particle size.

Of 37 subjects with FDB, there were 13 kindreds with R3500Q and one each with R3500W, R3531C and H3543Y. The clinical manifestations were similar between the groups but coronary disease onset was later in FDB (55 ± 10 vs 46 ± 12 years, p = 0.04) ApoB concentrations were identical at 1.5g/L but LDLC was insignificantly increased in the LDLR mutation, but with a significant difference in LDLC/apoB (4.1 ± 0.9 vs. 4.6 ± 1.2 mmol/g, p = 0.04). LDL size, assessed by electrophoresis, was smaller in FDB ($\chi^2 = 0.006$).

FDB due to various mutations should be considered as a cause of FH in South Africa. Subtle differences exist in the phenotype compared with LDL receptor mutations.
Homozygous familial hypercholesterolaemia (Ho FH) is a rare genetic disorder characterised by marked elevation of plasma low density lipoprotein (LDL), severe premature coronary atherosclerosis and early death. Between 1972 and 1979, 34 patients with Ho FH were seen at the Johannesburg Hospital Lipid Clinic and their characteristics were published in 1980. Due to a founder effect the prevalence in Transvaal Afrikaners was calculated to be 1 in 30 000. This is much higher than the estimated prevalence of 1 in 1 000 000 in other populations.

Now, in 2009, the total number of Ho FH patients seen at the Clinic exceeds 90. LDL-receptor screening has become available and has confirmed diagnosis of true homozygous and/or compound heterozygous FH. The epidemiological, genetic, clinical and biochemical characteristics of the Ho FH patients have been updated.

Previously treatment of Ho FH at the Clinic - in addition to a low cholesterol diet - included fibrates, bile acid sequestrants, nicotinic acid, partial ileal bypass operation, portacaval shunt operation and/or probucol. Since the late 1980’s, subsequent to the introduction of statins, treatment has been high dose statin therapy, with the more recent addition of the cholesterol absorption inhibitor ezetimibe. Although LDL-cholesterol reduction remains suboptimal - with few, if any, patients attaining LDL-cholesterol goal - survival appears to have improved, and the need for surgical intervention (coronary artery bypass surgery, aortic valve replacement) delayed.

Carotid intima-media thickness (CIMT) correlates with coronary artery disease risk. Both familial hypercholesterolaemia (FH) and Type III hyperlipidaemia are associated with an increased risk of coronary artery disease.

A review was done of Lipid Clinic patients who have undergone carotid ultrasound by standardised protocol. Images were captured in DICOM format and analysed offline using computer software. CIMT results were available for 198 patients with FH and 28 patients with Type III by genotypic or phenotypic criteria.

Patients with FH were younger than those with Type III (48.41 ± 13.6y vs. 57.4 ± 11.1y, p<0.01). Triglyceride was higher in patients with Type III (1.62 ± 1.11 vs. 6.78 ± 5.6 mmol/L, p<0.01). There were no differences in total cholesterol (8.74 ± 1.82 vs. 9.29 ± 4.14 mmol/L, p=0.24) or HDL-C levels (1.24 ± 0.42 mmol/L vs. 1.3 ± 0.45 mmol/L, p=0.53). Mean CIMT measurements were in the high normal range and were similar in the two groups (0.7602 ± 0.1703 vs. 0.7926 ± 0.1374, p=0.34) Mean CIMT measurements were different between the two groups in female patients (0.738 ± 0.1675 vs. 0.8405 ± 0.1551, p=0.04), but not in male patients (0.7846 ± 0.1877 vs. 0.7511 ± 0.1086, p=0.5).

Although lipid levels are abnormal from birth in patients with FH, compared to becoming abnormal later in life in patients with Type III, CIMT was not different between the two groups. This finding is confounded by age. Secondly, although both these conditions are known to be highly atherogenic, CIMT measurements were in the high normal range. This finding likely relates to the high number of patients on lipid lowering treatment.
Abstracts: Scientific programme 9th Congress of the LASSA

7 Carotid intima-media thickness is a predictor of coronary artery disease in South African black patients

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Background: Several studies have shown that increased carotid intima media thickness (CIMT) confers risk of future coronary artery disease (CAD) as well as stroke. The present study aimed at investigating whether CIMT is a predictor of CAD in South African black patients.

Methods and results: This was a prospective study of 53 patients (41M, 12 F; age 30–70 yrs). Twenty nine of the 38 (76 %) subjects with established CAD had increased CIMT, with an average mean CIMT of 1.13mm. On angiography single vessel CAD was present in 12 people, double-vessel disease in 11 people and triple-vessel disease in 12 people. The median percentile scores show a progressive increase as the number of vessel involvement increased. There was also a significant positive linear trend between CIMT and the number of involved coronary vessels (p < 0.0001, r = 0.44).

Conclusions: CIMT could be useful as a screening tool, for the presence and extent of CAD in the South African Black population.

8 Postprandial hyperglycaemia in urbanised South African blacks with and without coronary artery disease

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Background: Coronary artery disease (CAD) prevalence is increasing in black urbanised South Africans. Postprandial hyperglycaemia is a CAD risk factor.

Aims: To assess postprandial hyperglycaemia in blacks with and without CAD; to measure fasting and postprandial glucometabolic profiles and to compare abnormal glucose tolerance and insulin resistance prevalences.

Methods: Anthropometric data and glucometabolic variables were measured in 40 patients and 20 controls. Postprandial hyperglycaemia was assessed by OGTT and area under the curve (AUC). Insulin resistance was evaluated by hyperinsulinaemic euglycaemic clamp (M-value).

Results: Glucose AUC was higher in patients than controls (P < 0.0001). Patients had higher fasting and postprandial glucose responses (P < 0.05). Abnormal glucose tolerance was more prevalent in patients (50%) than controls (35%). M-values were lower in patients (P < 0.0001) and decreased between categories in patients, significantly in those with diabetes mellitus (P = 0.01).

Conclusions: Postprandial hyperglycaemia was common in CAD patients, 120 min glucose followed by 0 min glucose were the strongest determinants. As glucose tolerance declined, glycaemic control deteriorated and insulin resistance worsened. Abnormal glucose tolerance and insulin resistance were more prevalent in patients with CAD.
Plasma lipid peroxidation status in metabolic syndrome subjects differs from that of healthy subjects

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Plasma triglyceride and glucose concentrations were significantly increased in the MetS group compared with the healthy control group ($P = 0.0002$ and $P = 0.004$ respectively). The TBARS in nmol/mL (median, 95% CI) were significantly increased in the MetS group (2.6, 1.6 - 4.7) compared with the control group (1.9, 1.0–2.2), $P = 0.008$. Plasma oxLDL and ORAC values were not significantly different between the 2 groups. The MetS group showed a significant correlation between HDLC and oxLDL concentrations, $r = -0.919$, $P = 0.007$.

The results suggest that lipid peroxidation may be increased in subjects with MetS, increasing their risk for diabetes and cardiovascular disease. Further studies with larger numbers of subjects are required to better characterise oxidative stress and evaluate its role in the pathophysiology of the MetS.

Evaluation of safety and efficacy of colesevelam HCL in the treatment of adolescents with heterozygous familial hypercholesterolaemia: The Cape Town experience

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Patients with the familial hypercholesterolaemia (FH) phenotype are at increased risk of coronary artery disease. Treatment with statins is effective in lowering cholesterol levels, but may lack power or cause adverse effects. Colesevelam HCl is a non-absorbed hydrogel which acts as a bile salt sequestrant and is administered in tablet form. We report the local experience of a multinational study.

FH subjects aged 10–17 years by genotypic or phenotypic criteria and LDL-C > 4.14 mmol/L on stable diet were eligible for this randomised, double blind, placebo-controlled efficacy and safety study. Subjects were randomised to placebo, low-dose Colesevelam HCL (1.875 g/day) or high-dose Colesevelam HCl (3.75 g/day) for a 8 week period; thereafter all subjects were on open-label high-dose Colesevelam HCl for 18 weeks.

20 Subjects (16 male and 4 female) aged 14.08 ± 2.16 years were randomised to placebo: low-dose: high-dose = 7:7:6. The baseline lipid levels were LDL-C 5.71 ± 1.19 mmol/L, total cholesterol 7.29 ± 1.19 mmol/L, HDL-C 1.10 ± 0.26 mmol/L and triglyceride 1.05 ± 0.30 mmol/L. There were no differences between baseline and 8 week levels in the placebo and low-dose groups. In the high dose group there was a significant reduction in LDL-C (18%, $P = 0.02$) and in TC (10%, $P = 0.02$). During the open label phase there was a significant reduction in LDL-C (19%, $P < 0.01$) and TC (13%, $P < 0.01$) and a significant increase in HDL-C (10%, $P = 0.02$) compared to baseline, but the 10% rise in TG was not significant.

Despite the large size 6 tablets were easily swallowed daily. No adverse events were related to the study drug. No laboratory safety concerns arose during the study, including transaminases and creatine kinase.

Colesevelam HCl is a well-tolerated safe LDL cholesterol-lowering agent that may assist lipid control in FH.