

EFFECT OF BARIATRIC SURGERY ON HDL QUANTITY AND QUALITY

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Background: High-density lipoprotein (HDL) particles have an important role in atheroprotection, with properties including antioxidation, anti-glycation and promotion of cholesterol efflux. Obese patients have increased systemic inflammation and thus higher risk of vascular disease. Little is known of the changes in HDL particles and HDL functionality associated with obesity. We aimed to assess the effects of obesity itself and bariatric surgery-induced weight loss on both HDL quantity and quality.

Methods: We measured HDL-C, oxidised HDL (Ox-HDL), apolipoprotein AI (ApoAI), apolipoprotein AII (ApoAII), apolipoprotein M (ApoM), Myeloperoxidase (MPO) mass, HDL-apolipoprotein E (apoE), serum paraoxonase-1 (PON1) activity and capacity of HDL to promote cholesterol efflux *in vitro* for 37 obese patients at baseline and at 6 and 12 months following bariatric surgery. We compared HDL functionality in obese patients with age and sex matched controls.

Results: At baseline, HDL-C, ApoAI and cholesterol efflux capacity were significantly lower among obese patients than healthy controls. Six months after bariatric surgery, although ApoAII and HDL-ApoE were significantly decreased (both $p < 0.05$), HDL-C, ApoA1, MPO mass, PON1 activity and cholesterol efflux were unchanged compared to baseline. At 12 months after bariatric surgery HDL quantity and quality were considerably improved. HDL-C and cholesterol efflux capacity were significantly increased compared with their baseline (both $p < 0.001$), as were PON1 activity and HDL-apoE concentration (both $p < 0.01$). MPO mass decreased and a further reduction in ApoAII was observed (both $p < 0.01$). ApoAI, ApoM and ox-HDL were unchanged. We used biological systems analysis to identify factors influencing HDL functionality.

Conclusions: Bariatric surgery significantly increases circulating HDL cholesterol levels and improves HDL quality, but effects are not apparent until 12 months after treatment.

IDENTIFICATION OF TWO RARE APOE MUTATIONS ASSOCIATED WITH FAMILIAL HYPERCHOLESTEROLAEMIA IN THE NORTH OF ENGLAND

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Mutations in three different genes (*LDLR*, *APOB* and *PCSK9*) affecting the LDL-receptor pathway are known to cause Familial hypercholesterolaemia (FH). However in approximately 20% of probands with a definite clinical diagnosis of FH no mutations are detected suggesting that there are FH causing mutations located in other genes. We report the finding of pathogenic *APOE* mutations in two probands from the North East of England with the FH phenotype.

Methods: DNA samples from probands were analysed by next generation sequencing (NGS) of the *LDLR*, *PCSK9* and *APOE* genes and a selected region of the *APOB* gene. Variants were confirmed by Sanger sequencing.

Results: Proband A was a 37 year old female with a family history of hypercholesterolaemia and elevated levels of total and LDL-cholesterol (11.7 and 8.8 mmol/L respectively) with normal levels of HDL-cholesterol and triglycerides (2.4 and 1.2 mmol/L respectively). NGS results showed

that she was heterozygous for a mutation in exon 4 of the *APOE* gene (c.500_502delTCC; p.Leu167del) previously reported in French and Italian FH families. She was also heterozygous for the *LDLR* variant c148G > T (p.Ala50Ser) previously described as both pathogenic and benign. Proband B was a 6 year old boy with a family history of premature myocardial infarction and elevated levels of total and LDL-cholesterol (8.5 and 6.4 mmol/L respectively) with normal levels of HDL-cholesterol and triglycerides (1.3 and 1.9 mmol/L respectively). NGS results showed that he was heterozygous for a previously unreported mutation in exon 4 of the *APOE* gene (c.492_493delinsCT; p.Lys164_Arg165delinsAsnTrp). Family studies are ongoing but the *APOE* mutations appear to co-segregate with hyperlipidaemia in both families, while the *LDLR* variant did not.

Conclusions: Screening of the *APOE* gene, in addition to the *LDLR*, *APOB* and *PCSK9* genes, is warranted in the setting of molecular diagnosis of FH in the UK.

WEB BASED TOOLS TO ASSESS ELIGIBILITY FOR GENETIC TESTING FOR FAMILIAL HYPERCHOLESTEROLAEMIA (FH)

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Selection of patients who are appropriate for genetic testing for FH is a balance between diagnostic yield and cost. The Wales FH service has implemented a clinical scoring system to guide the selection of patients based on lipid levels, personal and family history of cardiovascular disease plus physical signs. In an evaluation of 623 patients referred to lipid clinics, the proportion of patients with a mutation ranged from 4% in those scoring 5 or less to 85% in those scoring >15.

We have developed two web tools to increase the utility of these FH scoring criteria.

The **Pre-treatment LDL-C Estimator** uses current LDL-C concentrations and current lipid lowering treatment to estimate pre-treatment cholesterol levels. It can also be used in reverse i.e. to estimate the level of LDL-C lowering that can be expected from prescribing a specific lipid lowering treatment. Treatments include dosages of all common single and combination lipid treatments (eg statin plus ezetimibe).

The **FH Genetic Testing Assistant (The Welsh Scoring Criteria)** is a five question, multiple choice tool that incorporates clinical signs, personal and family history plus lipid levels (based on the pre-treatment LDL-C estimator) to provide a genotyping score and indication of whether or not to proceed with a genotyping referral.

Qualitative evaluation of the tools has been used to refine these for use in the clinical setting. Both tools have been shown to be easy to use and interpret. The tools also have potential for further development to include more complex calculators such as age and gender adjusted LDL-C. It is anticipated that they will help general practitioners and secondary care clinicians to decide on which patients to refer for FH genotyping.

DEVELOPMENT OF AN E-LEARNING PROGRAM ON FAMILIAL HYPERCHOLESTEROLAEMIA (FH) FOR PRIMARY CARE

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Raised cholesterol is common in healthcare settings, with over 8 million patients currently being treated with lipid lowering medications in the United Kingdom alone. It is important that individuals with Familial