SAMPLE DOCUMENT

Biomedical Science – UK English

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Introduction

~~It is well established that the~~The metabolic syndrome is known to be associated with an increased risk of cardiovascular disease (CVD ~~(~~; 1-3~~),~~); however, the pathophysiological mechanisms have yet to be ~~fully~~ elucidated. Central obesity and insulin resistance are key components of the metabolic syndrome and it has been suggested that central obesity causes hypertension and hypertriglyceridemia independently as well as through the induction of insulin resistance (4).

In obesity, expansion of the fat mass results in adiposopathy which is associated with a pro-inflammatory state evidenced by the chronic, low-grade elevation of inflammatory markers such as C-reactive protein (CRP) and ~~tumor~~tumour necrosis factor α (TNF-α). In this pro-inflammatory state, peripheral monocytes may become activated enabling them to infiltrate the adipose tissue potentiating inflammation and contributing to adipose dysfunction (5), as well as being ~~brought~~ recruited to sites of endothelial dysfunction and ~~starting~~ initiating atherosclerostic plaque development (6). CC chemokines, such as monocyte chemotactic protein-1 (MCP-1), macrophage inhibitory protein-1β (MIP-1β) and eotaxin-1, along with their respective receptors are critically involved in monocyte activation and tissue infiltration. Since the role of inflammation in the pathogenesis of atherosclerosis is well ~~established~~known, it has been suggested that a combination of established inflammatory markers, such as CRP, and novel biomarkers, the CC chemokines, may ~~offer~~provide additional prognostic information ~~and therefore~~to help improve CVD risk stratification and management (7).

HMG-CoA reductase inhibitors, statins, initially prescribed ~~for their lipid lowering properties~~to lower lipids have proven successful in reducing cardiovascular mortality and morbidity (8-10). While reductions in LDL and other atherogenic lipid particles are likely to explain most statin benefit, pleiotropic actions including the reduction of serum levels of CRP and MCP-1 (11-14) ~~and~~as well as oxidative stress (15) may contribute to cardiovascular event reduction. With regard to the metabolic syndrome, atorvastatin ~~has been reported to~~ dose-dependently ~~reduce~~reduces total, LDL and oxidized LDL cholesterol with pleiotropic effects~~,~~ as evidenced by reduced hs-CRP and matrix

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metalloproteinase-9~~,~~ only ~~observed~~ in the high dose (~~80mg~~80 mg/day, 12 weeks) treatment group (15). More recently~~,~~ the improvement in lipid profile by atorvastatin (40 mg/day, 90 days) has been shown to be accompanied by decreased monocyte cytokine release and reduced levels of hs-CRP, factor VII and PAI-1 (16). ~~In~~A randomised placebo controlled clinical study was conducted in order to investigate the expression of novel inflammatory markers, CC chemokines, in the metabolic syndrome and their modulation by low dose atorvastatin ~~a randomised placebo controlled clinical study was conducted~~.

Patients and Methods

The study ~~protocol~~ was approved by the Office for Research Ethics Committees Northern Ireland (reference number 06/NIR03/79) and allocated ~~the~~an International Standard Randomised Controlled Trial Number ISRCTN71301517. Clinical trial details were logged in the EudraCT database (reference number 2006-000873-32) and a Clinical Trial Authorisation was obtained from the Medicines and Healthcare Products Regulatory Agency.

Exclusion criteria for the control ~~subjects~~participants were any of the five features of the metabolic syndrome described above~~,~~: age < 35 or > 65, use of lipid-lowering therapy or hormone replacement therapy, transaminases greater than twice the upper limit of normal, eGFR < 50 ~~mLs~~mls/min.

All clinical trial ~~patients~~participants attended the Diabetes Centre at the Royal Victoria Hospital for assessment. At the initial visit, ~~we measured~~ height, weight, blood pressure, waist and hip circumference~~.~~ were measured. Fasting venous blood (20 ~~mls~~ml) blood was collected as follows~~,~~: K-EDTA samples for HbA1c, serum separator gel tubes for lipid profile, liver function tests and CRP, and fluoride-oxalate samples for plasma glucose. Serum was isolated (centrifugation at ~~1500g~~1500 g for 10 minutes) within an hour of venepuncture and aliquoted ~~prior to~~for storage at -70°C. All metabolic syndrome ~~patients~~participants underwent a 75 g oral glucose tolerance test with a further plasma glucose measurement after 2 hours. Metabolic syndrome subjects were ~~randomized~~randomised to either atorvastatin 10 mg daily or placebo for 6 weeks.~~-~~ At visits 2 and 3, weeks 1 and 6 respectively, weight and blood pressure were recorded. A single fasting blood sample was taken for the same tests as above with the exception of HbA1c, which was not measured at visit 2. ~~For safety purposes, liver~~Liver function tests were also performed ~~at these visits~~for safety purposes. At the third visit, compliance was assessed by tablet count. The lean control group attended one study visit and the same ~~initial measurements were made~~factors as ~~for~~ the metabolic syndrome group ~~except for~~were measured but not the glucose tolerance test.

~~At each visit, the fasting~~Fasting glucose and insulin ~~measurements~~ were ~~used~~measured in order to calculate the Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) index (19). HbA1c was assayed by ion~~-~~ exchange high~~-~~ performance liquid chromatography (HPLC) on an Adams™ HA-8160 automated analyser (Menarini Diagnostics, Wokingham, Berkshire) and reported on a scale aligned to that of the method used in the Diabetes Control and Complications Trial (20). Lipids, glucose, liver function tests, creatinine and creatine kinase were ~~measured~~analysed by standard chemical/spectrophotometric methods on a Roche Modular analyser. LDL cholesterol was calculated from measurement of total cholesterol, HDL and ~~triglycrides~~triglycerides (21). Estimated glomerular filtration rate was ~~calculated~~determined using the MDRD formula (17). CRP was ~~measured~~quantified by immunoturbidimetry on the Modular, and insulin was measured by immunoassay on an IMx analyser (Abbott Diagnostics, Maidenhead, Berkshire).

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