SAMPLE DOCUMENT

Biomedical Science – UK English

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Introduction

The metabolic syndrome is known to be associated with an increased risk of cardiovascular disease (CVD; ~~.~~ ~~(~~1-3); however, ~~. There is little information about~~ the pathophysiological mechanisms have yet to be elucidated. Central obesity and insulin resistance are key components of the metabolic syndrome and it has been suggested that central obesity ~~may~~ causes hypertension and hypertriglyceridemia ~~on their own~~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 ~~such as~~evidenced by the ~~prolonged~~chronic, low-grade elevation of inflammatory markers such as C-reactive protein (CRP) and tumour necrosis factor α (TNF-α). In this pro-inflammatory state, peripheral monocytes ~~in circulation~~ may become activated ~~causing~~ enabling them to ~~move into~~infiltrate the adipose tissue ~~causing~~ potentiating inflammation and contributing to adipose dysfunction (5), as well as being ~~going~~ recruited to sites of endothelial dysfunction and 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 ~~have a main role~~are critically involved in monocyte activation ~~of monocyte~~ and tissue infiltration~~vasion of tissue~~. Since the role of inflammation in the pathogenesis of atherosclerosis is well known, it has been suggested that a combination of established inflammatory markers, such as CRP, and novel biomarkers, the CC chemokines, may provide additional prognostic information to ~~for prognosis and~~ help improve CVD risk ~~to~~ stratification~~y~~ and management ~~CVD risk~~ (7).

~~Statins are~~ HMG-CoA reductase inhibitors, statins, ~~-~~initially prescribed to lower lipids have proven successful in reducing cardiovascular mortality and morbidity ~~and also achieve a decrease in mortality and morbidity from heart disease~~(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) as well as~~nd~~ oxidative stress (15) may contribute to

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~~decreased~~ cardiovascular event reductions~~.~~ With regard to the metabolic syndrome, ~~There are reports of~~ atorvastatin dose-dependently reduces total, LDL and oxidized LDL cholesterol with pleiotropic effects~~ in people with the metabolic syndrome,~~ as ~~shown~~ evidenced by reduced ~~decreases in~~ hs-CRP and matrix metalloproteinase-9 ~~,~~ only ~~observed~~ in the high dose (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 ~~occur along with less monocyte cytokine release~~ and reduced levels of hs-CRP, factor VII and PAI-1 (16). A randomised placebo controlled clinical study was conducted ~~i~~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 done~~.

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Patients and Methods

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The study was approved by the Office for Research Ethics Committees Northern Ireland (reference number 06/NIR03/79) and allocated an ~~gave approval for the study. The study's~~ International Standard Randomised Controlled Trial Number ~~is~~ ISRCTN71301517. ~~-~~Clinical trial details were logged in the EudraCT database (reference number 2006-000873-32) and ~~,~~ a Clinical Trial Authorisation was obtained from ~~T~~the Medicines and Healthcare Products Regulatory Agency ~~gave a Clinical Trial Authorisation~~.

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All volunteers were recruited from the general population and gave ~~. W~~written informed consent~~. was obtained from them.~~ The presence of the metabolic syndrome was based on ~~in line with~~ the International Diabetes Federation (IDF) definition, namely abdominal obesity (defined as waist circumference ≥ 94 cm for Europid men or ≥ 80 cm for Europid women) with two or more of the following criteria: blood pressure ≥ 130/85 mmHg, fasting plasma glucose ≥ 5.6 mmol/l, or previously diagnosed type 2 diabetes, fasting triglycerides ≥ 1.7 mmol/l or HDL < 1.03 mmol/l (men) or < 1.29 mmol/l (women). Subjects ~~who had~~with hypertension, hypertriglyceridaemia or low HDL cholesterol were ~~taken~~ considered to have fulfilled the inclusion criterion. Exclusion criteria were as follows: age < 35 or > 65 years, potential pregnancy, use of lipid-lowering therapy or hormone replacement therapy, intolerance of lipid-lowering agents, history of diabetes or muscle disease, plasma total cholesterol < 4 mmol/L, transaminases greater than twice the ~~2 times the~~ upper normal ~~threshold~~limit, estimated glomerular filtration rate (eGFR) < 50 m~~l~~ls/min (17), creatine kinase > 700 U/L, or any chronic illness likely to affect markers of inflammation. Subjects ~~who were~~ not ~~already on~~currently on lipid-lowering medication but who were judged to require such treatment based on the Joint British Societies' Guidelines on the Prevention of Cardiovascular Disease in Clinical Practice (18) were also excluded, with appropriate follow-up arranged through their general practitioners. Volunteers were also given verbal advice ~~told~~ about healthy lifestyle measures, such as weight reduction and smoking cessation.~~and to lose weight and to stop smoking.~~

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Exclusion criteria for the control ~~people~~ 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~~2 times~~ the upper ~~threshold~~ limit of normal, eGFR < 50 m~~l~~ls/min.

All clinical trial ~~patients~~ participants attended~~went to~~ the Diabetes Centre at the Royal Victoria Hospital for ~~the study~~assessment. At ~~On t~~the initial ~~first~~ visit, ~~we measured the patients'~~ height, weight, blood pressure, waist and hip circumference were measured. Fasting v~~We collected v~~enous blood (20 m~~l~~s) blood ~~after an overnight fast~~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 1500 g for 10 minutes) within an hour of ~~taking blood~~venepuncture and aliquoted ~~and~~ for storage~~d~~ at -70°C. All metabolic syndrome

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~~patients~~ participants underwent~~had~~ a 75 g oral glucose tolerance test with a further plasma glucose measurement after 2 hours. Metabolic syndrome subjects were randomis~~z~~ed to either atorvastatin 10 mg daily or placebo for 6 weeks. ~~-~~At visits 2 and 3, ~~on~~ weeks 1 and 6 respectively, ~~we recorded~~ weight and blood pressure were recorded~~again~~. A single ~~One~~ fasting blood sample was taken ~~after an overnight fast~~ for the same tests as above with the exception of HbA1c, which was not measured at visit 2. L~~Also we did l~~iver function tests were also performed for safety purposes. At the third visit, compliance was~~On visit 3, we~~ assessed ~~whether the patients were taking the treatment~~ by ~~counting their~~ tablet counts~~s~~. ~~-~~The lean control group attended ~~visited~~ one study visit~~time~~ and ~~we measured~~ the same factors as the metabolic syndrome group were measured but not the glucose tolerance test.

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F~~We measured f~~asting glucose and insulin were 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 analysed~~measured~~ by standard chemical/spectrophotometric methods on a Roche Modular analyser. LDL cholesterol was calculated from measurement of total cholesterol, HDL and triglycerides (21). Estimated glomerular filtration rate was determined~~calculated~~ using the MDRD formula (17). CRP was quantified~~measured~~ by immunoturbidimetry on the Modular, and insulin was measured by immunoassay on an IMx analyser (Abbott Diagnostics, Maidenhead, Berkshire).

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