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Simvastatin (40mg/day), Adiponectin Levels, and Insulin Sensitivity in Subjects with the Metabolic Syndrome

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Abstract

The metabolic syndrome (MS) is characterized by low grade inflammation, and confers an increased risk for diabetes mellitus and cardiovascular disease. Statins reduce cardiovascular events in MS patients and have pleiotropic effects in addition to low density lipoprotein cholesterol (LDL) lowering. Since there is a paucity of data examining the effect of statins on adiponectin levels and insulin sensitivity in the MS, we tested the effect of simvastatin (40mg/day) compared to placebo on circulating adiponectin levels and homeostasis model assessment of insulin resistance (HOMA) in MS subjects in a randomized, double-blind, placebo-controlled study. Simvastatin therapy failed to affect circulating adiponectin levels or insulin sensitivity compared to placebo over 8-weeks. In conclusion, although simvastatin is anti-inflammatory, it failed to affect adiponectin levels or improve insulin sensitivity in subjects with MS.

Keywords

statin; insulin resistance; adiponectin; pleiotropism

Introduction

One in 4 individuals in the US population has the metabolic syndrome (1). Subjects with the metabolic syndrome (MS) have a 5-fold increased risk of diabetes and 2-fold increased risk of cardiovascular disease (2). We have previously shown that simvastatin therapy in subjects with MS compared to placebo results in significantly reduced high sensitivity C-reactive protein (CRP) levels, significantly decreased monocyte interleukin-6 (IL-6) and tumor necrosis factor (TNF) alpha levels, 2 cytokines which play a major role in insulin resistance (3). We also showed that simvastatin therapy significantly decreased monocytic nuclear factor kappa B (NFκB) and increased Akt and phosphatidyl inositol 3-kinase activity in MS subjects compared to placebo (4,5). Monocyte-macrophages have been shown to directly influence adipocyte biology and systemic insulin resistance in mice (4,5). Also, the percentage of macrophage infiltration in adipose tissue correlates with obesity and insulin resistance (6). Adiponectin is an important adipocytokine that is thought to couple regulation of insulin sensitivity with energy metabolism and serve to link obesity with insulin resistance (7,8). Plasma levels of adiponectin are decreased in obesity, in subjects with MS and in Type 2 diabetes mellitus and may play a key role in development of both insulin resistance and atherosclerosis (7,8). Also,

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lifestyle modification, thiazolidenediones, fenofibrate and the CB1 antagonist, rimonabant have been shown to significantly increase plasma adiponectin and insulin sensitivity (7–9). However, there is conflicting data with regards to the effect of statin monotherapy on plasma adiponectin levels and insulin sensitivity (10–15). Since we have shown that simvastatin therapy decreases monocyte IL-6 and TNF and upregulates phosphatidyl inositol 3-kinase, a pivotal signaling pathway in insulin action and glucose transport, we tested the effect of simvastatin (40 mg/day) on adiponectin levels and homeostasis model assessment of insulin resistance (HOMA), an index of insulin sensitivity in subjects with the metabolic syndrome, a population at high risk for diabetes, in whom the effect of statin monotherapy on adiponectin or HOMA has not been reported.

Methods

This study was approved by the Institutional Review Board at University of California Davis Medical Center and all subjects gave informed consent. This was a randomized, double blind, placebo-controlled study. For this study, subjects with the Metabolic Syndrome (n=50) as defined using the criteria of the National Cholesterol Education Panel-Adult Treatment Panel III were studied and other selection criteria have been reported previously (3).

At the baseline visit, subjects were randomized to receive either placebo or simvastatin (40 mg/day) for a period of 8 weeks. Fasting blood was obtained at baseline and at the end of an 8-week period in each group (placebo and 40 mg/d of simvastatin). Baseline chemistries were measured using standard laboratory techniques. Insulin and adiponectin levels were measured in plasma at baseline and following 8 weeks of simvastatin or placebo using immunoassay reagents from Linco, both of which had intra- and inter-assay coefficient of variation of <12%. HOMA was calculated as [fasting glucose in mg/dL*0.0555) * Immunoreactive Insulin (uIU/ml)]/22.5(13).

Data are expressed as mean +/− S.D for parametric data and as median (25^{th}, 75^{th} percentile) for non-parametric data. Statistical analysis was performed by the GCRC biostatistician using SAS software. Following repeated measures analysis of variance, baseline and post-treatment differences between groups was assessed using Mann Whitney (Monte Carlo 2-tailed estimate) tests. Percent change and delta differences between groups were compared using Wilcoxon signed rank tests. Spearman rank correlation coefficients were computed to assess associations between variables of interest.

Results

The male/female ratio, age and body mass index of the group was 14/36, 51 ± 12 years and 39 ± 7 kg/sqm respectively. As reported previously and in Table 1 (3), simvastatin therapy, resulted in a significant reduction in LDL cholesterol, hs-CRP and monocyte IL-6 and TNF compared to both baseline and placebo. \

As shown in Table 1, compared to placebo, simvastatin therapy failed to significantly alter glucose and insulin levels, leading to a null effect with regards to HOMA, an index of insulin sensitivity. In addition, there was no significant affect of simvastatin therapy on plasma adiponectin levels in subjects with MS compared to placebo (Table 1).

Discussion

The statin drugs effectively lower cholesterol levels in patients with and without coronary artery disease and are associated with a reduction in cardiovascular events in patients with and without MS. We recently demonstrated that simvastatin therapy significantly reduced hsCRP levels and monocyte biomediators (IL-6, TNF) and also showed significant downregulation of

NFKb and upregulation of AKT and phosphatidyl inositol 3-kinase following simvastatin therapy in MS subjects (3). Owing to the central role played by phosphatidyl inositol 3 kinase in insulin action, we decided to examine the effects of simvastatin therapy on HOMA, an indicator of insulin sensitivity and circulating adiponectin levels in this placebo-controlled study in patients with MS since this has not been reported before. Since this was not a pre-specified outcome, we did not measure insulin sensitivity by the gold standard, euglycemic clamp technique, but used HOMA, an accepted index of insulin sensitivity.

So far, despite the multiple pleiotropic effects of statin therapy, there is little consensus about the effects of statin on insulin sensitivity and adiponectin levels. Previously, fluvastatin therapy failed to have any additional effect compared to therapeutic lifestyle changes on adiponectin levels and HOMA in patients with dyslipidemia (13). Koh et al also failed to show any significant effects of atorvastatin monotherapy on plasma adiponectin levels or insulin sensitivity in patients with combined hyperlipidemia, and in subsequent studies, with simvastatin (20 mg/day) in diabetics or hypertensive subjects(11,12,14). Atorvastatin therapy in 2 independent studies, also has not resulted in improvement in insulin sensitivity or adiponectin levels in subjects with impaired fasting glucose and diabetics (16,17). Sakamoto et al reported that pravastatin therapy increased adiponectin levels compared to baseline in Japanese patients with coronary artery disease, however this was not a placebo-controlled study (15). Furthermore, no studies have examined the effect of statin therapy in patients with MS, a high risk population for diabetes; this is the novel aspect of the present study.

Simvastatin therapy in MS subjects, fails to significantly affect insulin sensitivity or plasma adiponectin levels in this 8-week study. Future studies will test if long term statin therapy alone or in combination with other agents could improve insulin sensitivity or adiponectin levels. There is no question that statin therapy represents a quantum leap with regards to therapeutic intervention of patients at risk of cardiovascular disease (18,19). However, in the Heart Protection Study, simvastatin therapy did not affect rate of new onset diabetes. These results emphasize the importance of combination therapy for patients at risk of diabetes or diabetics such as addition of thiazolidenediones, metformin or cannabinoid receptor 1 blocker, in addition to therapeutic lifestyle changes, the primary choice of therapy in MS subjects, to improve insulin resistance and endothelial function as well as reduce inflammation and upregulate adiponectin levels, thus improving the overall cardiometabolic profile. However, much further research is needed with the peroxisome proliferator-activated receptor (PPAR) gamma agonist or selective cannabinoid receptor 1 blocker, such as rimonabant.

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Table 1

Effect of Simvastatin Therapy on Homeostasis model assessment of insulin resistance and Adiponectin in Subjects with the Metabolic Syndrome

Variable	Placebo		Simvastatin	
	Baseline	Week 8	Baseline	Week 8
Insulin (uU/mL)	16.9 ± 8.9	17.2 ± 7.4	16.1 ± 8.7	17.1 ± 9.1
Glucose (mg/dL)	109 ± 35	100 ± 33	114 ± 55	104 ± 47
HOMA-IR	4.5 ± 0.8	4.4 ± 0.7	4.5 ± 1.1	4.2 ± 0.9
Adiponectin (ug/mL)	7.3±1.9	7.2 ± 1.4	7.7 ± 2.1	8.2 ± 1.8
Hs-CRP (mg/L)	5.3 (2.4,6.6)	5.2 (2.4,9.1)	3.6 (3,6.1)	2.3 (1.2,3.6)*

Data are mean ± S.D. for all variables except hs-CRP which is median (25^{th} percentile, 75^{th} percentile);

* $p<0.005$ compared to baseline and placebo