Evidence for metabolic aberrations in asymptomatic persons with type 2 diabetes after initiation of simvastatin therapy

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Hydroxymethylglutaryl coenzyme A reductase inhibitors (statins) prevent vascular events and are widely prescribed, particularly in persons with type 2 diabetes. However, intolerability because of myopathic symptoms often limits their use. We investigated the effects of simvastatin on parameters of mitochondrial function and muscle gene expression in 11 subjects with type 2 diabetes, none of whom had statin intolerance. After withdrawal of statins for 2 months, we obtained blood samples, performed vastus lateralis muscle biopsies, and assessed whole body resting energy expenditure (REE). We then reinitiated therapy using simvastatin, 20 mg/d, for 1 month before repeating these studies. As expected, simvastatin lowered low-density lipoprotein, but did not induce myalgias or significant increases in serum creatine kinase. However, we found subtle but significant reductions in muscle citrate synthase activity and REE. In addition, quantitative polymerase chain reaction and gene set enrichment analysis of muscle samples revealed significantly repressed gene sets involved in mitochondrial function and induced gene sets involved in remodeling of the extracellular matrix. Furthermore, the effects of simvastatin on muscle gene sets showed some similarities to previously described changes that occur in Duchenne muscular dystrophy, polymyositis, and dermatomyositis. Although statins inhibit an early step in coenzyme Q (CoQ) biosynthesis, we observed no differences in CoQ content within skeletal muscle mitochondria, muscle tissue, or circulating platelets. In summary, we report subtle changes in whole body energetics, mitochondrial citrate synthase activity, and microarray data consistent with subclinical myopathy. Although the benefits of statin therapy are clear, further understanding of muscular perturbations should help guide safety and tolerability. (Translational Research 2015;166:176–187)

Abbreviations: CoQ = coenzyme Q; DMD = Duchenne muscular dystrophy; ECM = extracellular matrix; GEO = gene expression omnibus; GSEA = gene set enrichment analysis; HbA1c = hemoglobin A1c; HDL = high-density lipoprotein; HMG-CoA = hydroxymethylglutaryl coenzyme A; HPLC = high-performance liquid chromatography; LDL = low-density lipoprotein; qPCR = quantitative polymerase chain reaction; REE = resting energy expenditure; RQ = respiratory quotient; SV1 = study visit 1; SV2 = study visit 2

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AT A GLANCE COMMENTARY

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Background

Hydroxymethylglutaryl coenzyme A reductase inhibitors (statins) are widely prescribed to prevent vascular events. However, intolerability because of myopathic symptoms often limits their use.

Translational Significance

We studied subjects with type 2 diabetes, all of whom tolerated statin therapy with no myopathic symptoms. Statin therapy was withdrawn for 2 months, after which simvastatin, 20 mg/d, was administered for 1 month. Metabolic and messenger RNA microarray studies performed before and after this treatment period revealed evidence for subclinical myopathy. Understanding the effects of statins on muscle tissue should contribute to their tolerability and safe use.

INTRODUCTION

Hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) have proven effective in preventing vascular events and are currently recommended for most persons, aged more than 40, with diabetes.[1] However, their use is often limited because of intolerance, most of which is because of muscle pain.

Some reports have suggested that statin-induced myopathy may be because of mitochondrial dysfunction,[2,3] which would lead to impaired oxidative phosphorylation. One possible reason might be reduced ubiquinone (coenzyme Q or CoQ) content. This is based on knowledge that HMG-CoA reductase is the first step in both cholesterol and CoQ biosynthesis.[4] However, whether statin therapy reduces CoQ levels in humans is controversial,[5-9] and CoQ may be reduced in diabetes as well.[10,11] On the contrary, there is very little information regarding CoQ levels in diabetic patients taking statins.

There is evidence that statins slightly increase incident diabetes,[12-14] whereas effects on insulin sensitivity are debated.[15] Insulin resistance is associated with mitochondrial dysfunction,[16] so it is possible that statin-induced hyperglycemia and diabetes risk may be mediated at the mitochondrial level.

On the basis of the previous considerations, we hypothesized that statin treatment of subjects with type 2 diabetes might reduce CoQ content within skeletal muscle, impair markers of mitochondrial function, reduce resting whole body energy expenditure, and increase circulating glucose.

Here, we measured skeletal muscle mitochondrial CoQ and platelet CoQ content in 11 subjects with type 2 diabetes before and after 1 month of simvastatin treatment. These subjects did not have myalgia and reported no symptoms temporally related to statin therapy. We also assessed phenotypic characteristics including resting indirect calorimetry, measured skeletal muscle citrate synthase activity, measured plasma glycated albumin (GA) as a short-term marker of glucose metabolism, and carried out prestatin and poststatin messenger RNA (mRNA) microarray analysis and confirmatory quantitative polymerase chain reaction (qPCR) on muscle biopsy samples.

METHODS

Human subjects and study protocol. The research was carried out according to the principles of the Declaration of Helsinki and reviewed and approved by our institutional Human Subjects Committee. All subjects signed informed consent. We enrolled 12 subjects, aged 56–67 years with type 2 diabetes. We report data for 11 subjects as 1 subject was withdrawn after he experienced a non-ST elevation myocardial infarct before returning for the final study visit. The protocol is graphically depicted in Fig 1.

Inclusion criteria consisted of type 2 diabetes diagnosed by an endocrinologist, absence of a history of ketoacidosis, and supported by C-peptide >0.8 ng/mL; age 30–70 years; hemoglobin A1c (HbA1c) 6.5%–10.0% inclusive; calculated fasting low-density lipoprotein (LDL) cholesterol <130 inclusive before therapy with a statin; and meeting guideline indications for statin therapy in diabetes as defined by the American Diabetes Association in 2009.[17]

Exclusion criteria included any neurologic, muscular, genetic, or other condition known to affect muscle function or exercise tolerance; electrolyte abnormalities; untreated hypothyroidism; abnormalities in calcium, phosphate, or magnesium concentrations, or any other metabolic disturbance affecting muscle function; cigarette smoking in the past year; cardiac, pulmonary, or any other disorder affecting exercise tolerance or interfering with blood or tissue oxygenation; inconsistent or variable physical activity; pregnancy or planned pregnancy during the study; use of any medications known to inhibit statin metabolism by cytochrome P450 34A; any other medical or psychological condition judged to limit compliance with the protocol or interpretation of results; existing vascular disease; history of rhabdomyolysis or severe muscle symptoms when on statins or creatine kinase >10 × normal. We chose the