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High-dose atorvastatin is associated with lower IGF-1 levels in patients with type 1 diabetes

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ABSTRACT

Introduction: Insulin-like growth factor 1 (IGF-1) and insulin-like growth factor binding protein 1 (IGFBP-1) play an important role in vascular health. Many patients with type 1 diabetes are medicated with HMG-CoA reductase inhibitors, statins, in order to prevent vascular complications. Yet little is known about the effect of statins on the IGF-1/IGFBP-1 axis in these patients.
Objectives: The aim of this study was to evaluate the effect of atorvastatin treatment on IGF-1 and IGFBP-1 with regards to microvascular function.
Design: Twenty patients with type 1 diabetes received either placebo or 80 mg atorvastatin for two months in a double-blinded cross-over study. IGF-1 and IGFBP-1 levels were assessed before and after each treatment period. Skin microcirculation was studied using Doppler perfusion imaging during iontophoresis of acetylcholine and sodium nitroprusside to assess endothelium-dependent and endothelium-independent microvascular reactivity, respectively.
Results: Treatment with high-dose atorvastatin was associated with a significant decrease in IGF-1 levels compared to placebo ($p < 0.05$, ANOVA repeated measures), whereas no effect was seen on IGFBP-1 or the IGF-1/IGFBP-1 ratio. These variables did not correlate with measurements of skin microvascular reactivity.
Conclusions: The study found that treatment with high-dose atorvastatin was associated with reduced IGF-1 levels, which may indicate a potential negative effect on microvascular function and long-term risk of microangiopathy development.

1. Introduction

Insulin-like growth factor-1 (IGF-1) is a polypeptide hormone structurally homologous to insulin that plays an important role in energy metabolism through multiple actions. IGF-1 increases insulin sensitivity, antagonizes the effect of growth hormone and can directly stimulate glucose uptake in skeletal muscle [1]. Growing evidence has also shown that IGF-1 is an important promoter of vascular health, with a range of antiatherogenic effects [2–4]. IGF-1 increases constitutive nitric oxide synthase (NOS) activity, while at the same time inhibiting inducible NO, which in excess can promote apoptosis and inhibit myocardial function [5].

Serum IGF-1 bio-availability is controlled by six different high-affinity IGF binding proteins (IGFBP-1 through 6), of which IGFBP-1 is the most important dynamic regulator of free IGF-1 [1]. In order to try to look more specifically at bioavailable IGF-1, one can analyze the IGF-1/IGFBP-1 ratio.

Reduced IGF-1 levels have been associated with endothelial dysfunction, development of unstable arterial plaques and traditional risk factors of cardiovascular disease, including diabetes mellitus and circulating oxidized low density lipoprotein (LDL) [3]. A study of 100 patients with untreated hypertension found that low IGF-1 levels were associated with reduced endothelium-dependent vasodilation but had no association with endothelium-independent vasodilation, as measured by forearm blood flow [6].

Low IGFBP-1 has also been shown to be associated with cardiovascular disease and insulin resistance, and studies in mice have shown that moderately high IGFBP-1 induces NO production, reduces blood pressure and improves insulin sensitivity, independently of IGF-1 [7].

A large number of patients with type 1 diabetes mellitus are treated with HMG-CoA reductase inhibitors, statins, in order to decrease their risk of cardiovascular complications. Given evidence showing that IGF-1 and IGFBP-1 play an important role both for metabolism and vascular health, it is of interest to elucidate the effect of statins on this hormonal axis in patients with type 1 diabetes.[1]

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[1] NOS, nitric oxide synthase; RIA, radioimmunoassay; ACh, Acetylcholine; SNP, sodium nitroprusside

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2. Materials and methods

2.1. Study-design

In this double-blind, cross-over study 20 patients with type 1 diabetes were randomized to receive either a daily dose of 80 mg atorvastatin or placebo for two months, followed by a wash-out period of two months between treatments (Fig. 1). Investigations were undertaken before and after each treatment period.

2.2. Patients

Ten female and ten male patients were recruited from the out-patient clinic at the Department of Endocrinology and Diabetology at Danderyd Hospital, Stockholm, Sweden. Eligibility criteria were type 1 diabetes, age between 30 and 70 years, elevated levels of LDL (>2.5 mmol/L) and/or total cholesterol (>4.5 mmol/L) and no ongoing treatment with lipid-lowering drugs. Exclusion criteria included a history of macrovascular events.

2.3. Study protocol

Patients arrived at the clinic between the hours of 8 and 9 am, following a 10-h fast. After a 20 min resting period, venous blood samples were drawn and systolic arm and toe blood pressures were measured. Peripheral neuropathy in the feet was investigated through tests of vibration using a vibration fork (128 Hz) and tests of superficial sensation using a monofilament (Semmes-Weinstein 5.07). Albuminuria was measured with urinary dipstick tests (Clinitek©, Bayer HealthCare LLC, Elkhart, IN, USA) and retinopathy was assessed based on fundoscopic findings from patient records.

2.4. Biochemical analyses

Glycated hemoglobin A (HbA_{1c}) levels were assessed with high-performance liquid chromatography (Variant II; Bio-Rad Laboratories, Hercules, CA, USA) and presented in International Federation of Clinical Chemistry (IFCC) units. Lipoproteins were analyzed enzymatically with reagents from Synchron LX System(s) (Beckman Coulter, Lismeehan, Co Clare, Ireland). High-sensitivity C-reactive protein (hsCRP) was analyzed with a particle-enhanced immunoturbidimetric method (Beckman Inc., Brea, CA, USA). Serum IGF-I levels were assessed by an in-house radioimmunoassay (RIA) after separation of IGFs from IGFBPs by acid ethanol extraction and cryoprecipitation. To minimize interference of remaining IGFBPs, des (1-3) IGF-I was used as a radioligand [8]. The intra- and inter-assay coefficients of variation (CV) for IGF-1 were 4% and 11%, respectively. IGFBP-1 concentrations in serum were determined by an in-house RIA according to the method by Póvoa et al. [9]. The sensitivity of the RIA was 3 μg/L and the intra- and inter-assays CV for IGFBP-1 were 3% and 10%, respectively.

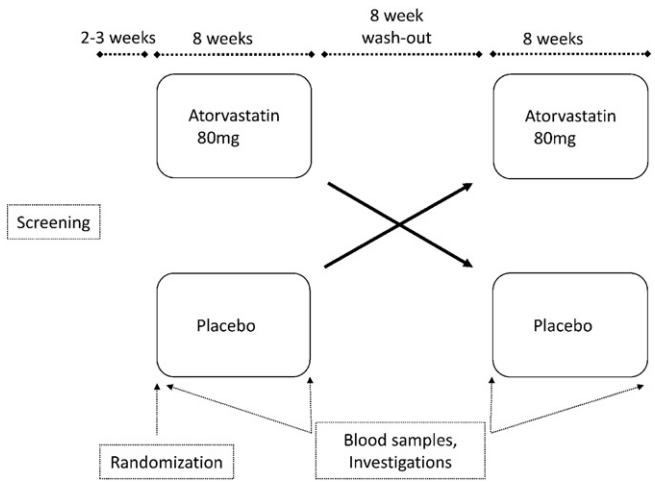

Fig. 1. Figure demonstrating the cross-over design of the study.

2.5. Skin microcirculation

Skin microcirculation was studied using iontophoresis, a non-invasive method for applying drugs transcutaneously using a small electric current. Acetylcholine (ACh, Sigma-Aldrich AB, Stockholm, Sweden) was used to investigate endothelium-dependent microvascular reactivity, whereas sodium nitroprusside (SNP, Hospira, Inc., Lake Forest, IL, USA) was used to study endothelium-independent microvascular reactivity. Electrode chambers (LI611 Drug Delivery Electrode Imaging; Perimed, Järfälla, Sweden) were attached to the volar side of the left forearm and filled with a small volume of either ACh (2%) or SNP (2%). A direct current (0.1 mA) was applied for 60 s using a battery-powered iontophoresis controller (Perilont 382b; Perimed). An anodal charge was used to deliver ACh and a cathodal charge to deliver SNP. Laser Doppler perfusion imaging (PeriScan PIM II; Perimed) was used to determine the skin microvascular flux before, during and after iontophoresis, expressed in arbitrary units (AU). Each image exposure lasted for 36 s and consisted of 150 measuring points within a skin area of 11 mm diameter. Four images were used initially to provide an average baseline flux. Microvascular flux was recorded continuously for 10 min after iontophoresis with ACh, and 14 min with SNP. Peak microvascular flux was measured. Mean CV were 11% for ACh and 20% for SNP.

2.6. Statistical analyses

The size of the study was originally determined based on power analyses to show changes in skin microcirculation in response to ACh iontophoresis following atorvastatin treatment [10]. The Shapiro–Wilks W test was used to assess conformity with a normal distribution. Variables with a non-normal distribution were log-transformed before further analysis. Repeated-measures analyses of variances (ANOVA) were used to analyze differences between and within the atorvastatin and placebo treatments. Correlations between variables were assessed using linear regression analyses. Data are presented as numbers, mean values ± SD or median with lower–upper quartile values. All results were analyzed using Statistica (StatSoft version 12).

Table 1
Baseline characteristics of patients.

Number of patients (n, men / women)	20 (10/10)
Age (years)	44 (39–61)
Duration of diabetes (years)	23 ± 15
Smokers (n, %)	1 (5)
Body mass index (kg/m^2)	25 ± 3
Systolic blood pressure (mmHg)	130 ± 15
Systolic toe/arm blood pressure index	0.96 ± 0.16
Proliferative retinopathy (n, %)	5 (25)
Peripheral neuropathy (n, %)	1 (5)
Previous or current microalbuminuria (n, %)	3 (15)
HbA_{1C} (mmol/mol)	68 ± 9
eGFR	118 (108–133)
Total cholesterol (mmol/L)	4.8 ± 0.5
LDL cholesterol (mmol/L)	3.1 ± 0.5
HDL cholesterol (mmol/L)	1.2 (1.2–1.4)
Triglycerides (mmol/L)	0.7 ± 0.3
hsCRP (mg/L)	0.61 (0.47–0.83)

Data are presented as mean ± SD, median (lower–upper quartiles) or number of patients (n). HbA_{1C} glycated hemoglobin; eGFR; estimated glomerular filtration rate; hsCRP, high-sensitivity C-reactive protein; LDL, low-density lipoprotein; HDL, high-density lipoprotein.