CLINICAL STUDY

Atorvastatin administration is associated with dose-related changes in IGF bioavailability

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Abstract

Objective: IGF levels, their binding proteins (IGFBPs) and high-dose statin therapy have been linked to the development of diabetes. We aimed to identify whether atorvastatin caused dose-related changes in IGF proteins.

Design and methods: We measured IGF1, IGF2, IGFBP1 and IGFBP3 concentrations at baseline, 6 and 12 months in Protection Against Nephropathy in Diabetes with Atorvastatin trial participants with type 2 diabetes randomised to 10 mg ($n=59$) vs 80 mg ($n=60$) of atorvastatin ($n=119$; mean (s.d.): age 64 (10) years; 83% male; HbA1c 61 (10) mmol/mol; blood pressure 131/73 mmHg).

Results: Atorvastatin was associated with overall reductions in circulating IGF1, IGF2 and IGFBP3 concentrations ($P<0.05$ for all changes). The adjusted mean (95% CI) between-group differences that indicate dose-related changes in IGF proteins were not significant for IGF1: -3 (-21 to 14) ng/ml; IGF2: -23 (-65 to 18) ng/ml and IGFBP3: -0.34 (-0.71 to 0.03) μ g/ml, negative values indicating numerically greater lowering with high dose. The IGFBP1 concentration did not change with atorvastatin therapy overall but the adjusted mean (95% CI) between-group difference indicating a dose-related change in log IGFBP1 was highly significant -0.41 (-0.69 to 0.13 , $P=0.004$).

Conclusion: IGF1, IGF2 and IGFBP3 concentrations decreased following atorvastatin therapy. A differential effect of low- vs high-dose atorvastatin on IGFBP1 concentrations was observed with likely implications for IGF bioavailability. The dose-related differential impact of atorvastatin treatment on concentration of IGF proteins merits investigation as a mechanism to explain the worsening of glucose tolerance with statin therapy.

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Introduction

3-hydroxy-3-methylglutaryl coenzyme A inhibitors (statins) have an established role in the prevention of cardiovascular disease (1). However, recent studies suggest that high-dose statin therapy may be associated with a small but significant increase in the risk of type 2 diabetes through unknown mechanisms (2). The ligands IGF1 and IGF2 have structural and functional homologies with insulin and their downstream signalling pathways have many commonalities with that of insulin (3). Low IGF1 concentration has been linked with increased rates of glucose intolerance and type 2 diabetes (4, 5, 6), though there are some suggestions that high IGF1 levels may also be related to an increase in diabetes incidence (7). Polymorphisms in the *IGF1*

gene have been associated with fasting insulin in genome-wide association studies (8).

IGF2 is critical in embryonic growth and development but its post-natal roles are less clear. IGF2 signalling can occur through the insulin receptors, and excessive IGF2 production in neoplasms is known to cause hypoglycaemia (9).

IGF binding protein 1 (IGFBP1) is an acute modulator of IGF1 and IGF2 bioavailability, and altered IGFBP1 levels have also been linked to diabetes rates (10, 11, 12). IGFBP3 is the principal carrier protein of IGF1 and IGF2. *In vitro* studies suggest that statins have profound effects on insulin and IGF1 signalling (13). The aim of our study was to identify dose-related changes in the circulating levels of IGFs and their major binding proteins with statin therapy in patients with type 2 diabetes.

Materials and methods

Subjects

We studied individuals in the Protection Against Nephropathy in Diabetes with Atorvastatin (PANDA) study that has been previously described (14). Briefly, participants were >40 years with type 2 diabetes and microalbuminuria recruited from four secondary care-based diabetes clinics in Manchester, UK. Exclusion criteria included pregnancy, proteinuria >2 g/day, serum creatinine >200 µmol/l, blood pressure >160/90 mmHg at randomisation, serum cholesterol >7 mmol/l, abnormal liver function, HbA1c >86 mmol/mol (10%), untreated hypothyroidism, intolerance of statin or angiotensin II receptor-blocking drugs, subjects taking atorvastatin doses >10 mg daily or the equivalent doses of other statins, use of any non-statin lipid-lowering agent or the presence of any illness that could affect the trial.

After a statin washout period of up to 2-week duration, patients were randomised to either 10 or 80 mg (2×40 mg tablets) atorvastatin including matching placebo tablets in a double-blind fashion. Placebo tablets were used so that patients in the low- and high-dose groups received the same number of identical tablets. The study was approved by the local research ethics committee, informed consent was obtained from all patients and investigations were carried out in accordance with the principles of the Declaration of Helsinki as revised in 2000.

Laboratory measurements

Analysis of fasting IGF1, IGF2, IGFBP1 and IGFBP3 was performed on blood samples drawn at baseline, 6 and

12 months. Plasma IGF1 and IGFBP3 were measured using an Immulite 1000 Immunoassay system (Siemens Healthcare Diagnostics, Inc., Tarrytown, NY, USA), utilising an enzyme-labelled chemiluminescent immunometric assay. Serum IGF2 was measured using a locally developed two-site extraction-based ELISA using antibodies that have been previously reported (15). Plasma IGFBP1 was measured using a locally developed two-site ELISA that can detect all phosphoisoforms of this protein. MABs 6301 (capture antibody) and 6303 (detection antibody) were obtained from Medix Biochemica (Kauniainen, Finland). The analytical sensitivities, inter-assay and intra-assay coefficients of variation for the assays were IGF1: 20 ng/ml, <8.4%, <4.5%; IGF2: 5 ng/ml, <9.2%, <9.2%; IGFBP1: 0.1 ng/ml, <7%, <9.4%; and IGFBP3: 0.1 µg/l, <10% and <6% respectively.

Statistical analyses

A log-transformation of the skewed IGFBP1 values meant that assumptions of normality were maintained and parametric tests were used throughout. In order to estimate for IGF1 bioavailability, molar ratios of IGF1:IGFBP1 and IGF1:IGFBP3 were included in their analysis. Unadjusted mean (95% CI) within-individual change from baseline to 12 months in IGF1, IGF2 and the binding protein levels was calculated for high- and low-dose atorvastatin groups (Fig. 1). The main endpoint of the study was the differential effects of high- vs low-dose atorvastatin on concentrations of plasma IGF1, serum IGF2, plasma IGFBP1 and plasma IGFBP3 over a 12-month period. A linear mixed-effects model was used to calculate the effect of atorvastatin dose (10 vs 80 mg) on circulating levels of the four IGF

Figure 1 Mean change in IGF1, IGF2, IGFBP1 and IGFBP3 concentrations from baseline in subjects treated with 10 and 80 mg atorvastatin.

proteins across longitudinal data collected at ~6 and 12 months. In each analysis, these levels were adjusted for the following covariates defined *a priori*: mean centred time, age, gender, baseline measurements of the IGF proteins, BMI and the use of insulin and statins before randomisation. In each case, an interaction term, mean centred time and atorvastatin dose with respect to any of the proteins measured was found to be non-significant and removed from the model. Accordingly, the analysis was configured to identify the differential impact of the 80 mg dose of atorvastatin compared with the 10 mg dose on each of the IGF proteins. All analyses were performed using Stata 11 (Statacorp., College Station, TX, USA). Two-tailed $P < 0.05$ was considered statistically significant.

Results

Clinical characteristics of the study population at randomisation are shown in Table 1. As previously described, those randomised to high- vs low-dose atorvastatin were similar with respect to age, gender, microalbuminuria, hypertension and glycaemic control at randomisation (14). A high proportion of participants in both the high- and low-dose atorvastatin study groups had a statin washout period that was up to 2 weeks in duration. We excluded one subject from analysis who had biologically implausible results.

The baseline concentrations of the IGF proteins in the high- and low-dose treatment groups are shown in Table 2 (columns 2 and 3), and the changes in each of these at 6 and 12 months are shown in Fig. 1. Atorvastatin therapy was associated with significant

Table 1 Baseline clinical characteristics at randomisation by treatment group. Data are mean (s.d.) or %, unless stated. Hypertension was defined as BP > 130/80 mmHg or anti-hypertensive therapy.

Baseline characteristic	Atorvastatin 10 mg	Atorvastatin 80 mg
<i>n</i>	59	60
Age (years)	65 (10)	63.5 (9.5)
Male (%)	81	85
Hypertension (%)	98	96
Diabetes duration (years)	12.6 (8.7)	11.1 (7.8)
BMI (kg/m ²)	32 (29–35)	34 (28–38)
Diabetes therapy		
Oral hypoglycaemic agents (%)	48	40
Insulin only (%)	14	10
Insulin and OHA (%)	32	43
MDRD eGFR (ml/min per 1.73 m ²)	61 (44–76)	72 (54–85)
Total cholesterol (mmol/l)	5.1 (1.0)	5.2 (1.1)
HbA1c (%)	7.8 (1.2)	7.6 (1.4)
HbA1c (mmol/mol)	62 (10)	60 (8)
Statin washout period of up to 2 weeks (%)	90	97

MDRD eGFR, modification of diet in renal disease-estimated glomerular filtration rate; OHA, oral hypoglycaemic agents.

reductions in circulating levels of IGF1, IGF2 and IGFBP3 when groups taking low- and high-dose atorvastatin were combined. The unadjusted mean (95% CI) change in IGF proteins for combined low- and high-dose atorvastatin groups were IGF1: –22 (–35 to –10) ng/ml; IGF2: –46 (–75 to –16) ng/ml and IGFBP3: –1.0 (–1.3 to –0.7) mg/l ($P < 0.05$ for all changes; Table 2). The corresponding data for IGFBP1 were 5 (–19 to 29) ng/ml, $P = \text{NS}$. The concentration of IGFBP1 was reduced in subjects receiving high-dose atorvastatin but was increased from baseline with low-dose therapy (Fig. 1). However, we did not assess the statistical significance of within-group changes because the results may have been misleading due to the absence of a placebo-only-treated group.

Table 2 (columns 5 and 6) shows the results of the mixed-effects longitudinal model in which between-group differences over 12 months were adjusted for baseline levels of each biomarker, age, sex, BMI and the use of statin washout period and use of insulin therapy at baseline. The adjusted mean (95% CI) between-group difference in log-IGFBP1 was highly significant (–0.41 (–0.69 to –0.13), $P = 0.004$). In these analyses, negative values indicate numerically higher lowering of IGF values with 80 mg dose compared with the 10 mg dose. The corresponding data for IGFBP1 without log-transformation was also statistically significant (adjusted mean (95% CI) between-group difference in IGFBP1: –37 (–68 to –6), $P = 0.02$). These data are presented in Table 2 for comparison with other unadjusted data (i.e. not adjusted for baseline levels of each biomarker, age, sex, BMI and the use of a statin washout period and use of insulin therapy at baseline). There was a corresponding significant increase in IGF1/IGFBP1 ratio: mean (95% CI) 7 (1 to 12), $P = 0.02$. Here, a positive value indicates that subjects on 80 mg atorvastatin had higher mean IGF1/IGFBP1 ratio values during follow-up compared with subjects on the 10 mg dose of atorvastatin. The adjusted mean (95% CI) between-group difference in IGF proteins between the high- and low-dose atorvastatin treatment groups was not significant for IGF1 (–3 (–20 to 14)), IGF2 (–23 (–65 to 18)) and IGFBP3 (–0.34 (–0.71 to 0.03)). There was no correlation between change in HbA1c and IGFBP1 (or any of the other measured IGF proteins) over the 12-month period of this study.

Discussion

Here, we present the first study demonstrating the effects of different statin doses on longitudinal trends in IGFs and their binding proteins. The observed changes are important because changes in IGF bioavailability have known associations with diabetes incidence, and higher rates of incident diabetes have been observed with high-dose statin therapy (2).

Table 2 IGF endpoints: baseline data, unadjusted 12-month change for combined groups and adjusted mean (95% CI) differences between high- and low-dose atorvastatin groups over the 12-month follow-up period. Baseline data are mean (s.d.) or median (IQR). Change and difference data are mean (95% CI) values. Data are adjusted for baseline level of IGF molecule, age, sex, BMI, use of insulin therapy and use of a washout period. A negative value for adjusted mean difference indicates that patients receiving atorvastatin 80 mg daily had lower average values during follow-up than those receiving 10 mg daily. For example, IGF1 levels were 3 mmol/l lower ($P=0.72$) during follow-up in patients taking atorvastatin 80 mg daily compared with those taking 10 mg daily. A positive value for adjusted mean difference indicates that patients receiving atorvastatin 80 mg daily had higher average values during follow-up than those receiving 10 mg daily. The number of patient samples available for each analysis: 10 mg daily dose: 50–52 patients; 80 mg daily dose 50–51 patients. Mean (inter-quartile range) follow-up was 12.0 (11.7–12.4) months.

Biomarker	Baseline value in atorvastatin 10 mg daily group ($n=59$)	Baseline value in atorvastatin 80 mg daily group ($n=60$)	Unadjusted mean (95% CI) change between final visit and baseline for all patients (10 mg and 80 mg/day groups combined)	Adjusted mean (95% CI) difference between high- and low-dose groups over 12 months of follow-up	P value for adjusted mean difference between groups during follow-up, adjusted for baseline differences
IGF1 (ng/ml)	154 (61)	152 (62)	−22 (−35 to −10)*	−3 (−20 to 14)	0.72
IGF2 (ng/ml)	461 (156)	504 (165)	−46 (−75 to −16)*	−23 (−65 to 18)	0.27
IGFBP1 (ng/ml)	74 (29 to 142)	54 (32 to 113)	5 (−19 to 29)	−37 (−68 to −6)	0.02
IGFBP3 (mg/l)	4.5 (1.4)	4.9 (1.7)	−1.0 (−1.3 to −0.7)*	−0.34 (−0.71 to 0.03)	0.07
IGF1/IGFBP1	14 (16)	17 (31)	0 (−5 to 4)	7 (1 to 12)	0.02
IGF1/IGFBP3	0.2 (0.06)	0.2 (0.06)	0.01 (−0.00 to 0.02)	0.01 (−0.01 to 0.02)	0.48

* $P<0.05$.

Main findings

We showed that atorvastatin therapy overall (low- and high-dose atorvastatin combined) was associated with a decrease in IGF1, IGF2 and IGFBP3 levels. We have also demonstrated a dose-dependent effect of atorvastatin on plasma IGFBP1 concentration. Low-dose atorvastatin therapy increased IGFBP1 levels, while high-dose treatment resulted in a decrease.

IGFBP1 system in health and disease

IGF1 and IGF2 are potent anabolic factors that are fundamental to growth, development and metabolism (3). Both peptides have significant structural homology with insulin and share similar downstream signalling pathways, suggesting a role in glucose homeostasis (16, 17).

The biological actions of IGF1 and IGF2 are determined by their interactions with six binding proteins, described as IGFBP1 to IGFBP6. IGFBP1 is the principal acute regulator of IGF1 biological actions. IGFBP1 is potently and dynamically inhibited by insulin (18), and levels are affected by the diet and prandial state as well as other factors like age and BMI (19). IGFBP1 is a marker of insulin sensitivity (20). In clinical and population studies, low circulating IGFBP1 concentration has been associated with insulin resistance (11, 21) and an increased risk for incident gestational diabetes, glucose intolerance and type 2 diabetes (4, 10, 11, 22).

Differential effects of statin dose on IGFBP1 and implications for diabetes risk

Recent meta-analyses have suggested that, when compared with placebo, statin therapy was associated

with a 9% higher risk for incident diabetes (23) and, when compared with low-dose statin therapy, high-dose statin therapy was associated with a further 12% elevation in risk (2). There is also evidence that statin therapy is associated with worsening glycaemic control in individuals who already have type 2 diabetes (24). On a cellular level, we have previously shown that statins can directly reduce insulin signalling by depleting cells of dolichol, a derivative of mevalonate, which in turn affects insulin receptor processing with the eventual result of fewer, mature, insulin receptors at the cell surface (13). In this study, which involved individuals with type 2 diabetes, an exploratory analysis did show that high-dose atorvastatin was associated with worse glycaemic control at the 2-year follow-up (HbA1c was 2.4 mmol/l (0.3%) higher ($P=0.017$)) after 2 years of high-dose therapy (14), but these differences were not significant at 1 year (not shown).

We showed that compared with the low-dose therapy, high-dose atorvastatin was associated with lowering of IGFBP1 levels, which has been associated with an increased risk for gestational diabetes, glucose tolerance and type 2 diabetes (4, 10, 11, 22). The cause of the dose-dependent effect of atorvastatin on IGFBP1 concentration is unclear. However, as a dose-dependent effect of atorvastatin on insulin resistance has been described (25), it is tempting to speculate that changes in insulin concentration and insulin resistance may be implicated. If high-dose atorvastatin caused greater insulin resistance and hyperinsulinaemia compared with low-dose atorvastatin, then this could suppress hepatic IGFBP1 production and decrease circulating IGFBP1 concentration. As we did not measure insulin levels, we are unable to test this hypothesis.

Effect on other IGF proteins and implications for diabetes risk

The majority of our patients had a 2-week statin washout period that was up to 2 weeks in duration. This may have been long enough to allow IGF proteins to return towards normal pre-treatment levels. In our within-group analysis, we showed longitudinal reductions in IGF1, IGF2 and IGFBP3 with both low- and high-dose atorvastatin therapy. The design of our trial means that these data are less robust than our comparison of the low- and high-dose atorvastatin groups. However, these data are in keeping with the results of a study involving 156 patients with hypercholesterolaemia who experienced lowering of IGF1 levels with low-dose simvastatin therapy (26). Although we showed that the effect on these protein concentrations was not dose dependent, the overall fall in insulin-like activity resulting from lower IGF1 and IGF2 concentration could potentially contribute to increased glucose concentrations, perhaps partly mediated by a compensatory elevation in GH. The changes in IGF proteins might go some way to explain the increased risk of incident diabetes in patients receiving statin therapy compared with placebo (23).

Effect on other IGF proteins and implications for cardiovascular and malignancy risk

Altered concentrations of IGF proteins have been associated not only with subsequent worsening of glucose tolerance but also increased macrovascular risk (4, 12, 27, 28). However, statin therapy unambiguously decreases cardiovascular risk, suggesting that associations of low IGF bioavailability with an adverse cardiovascular profile are not sustained in the presence of statin therapy. Arguably, the cardiovascular benefits of atorvastatin therapy would be even greater without the increased incidence of diabetes.

Strengths and weaknesses

This is the first study to demonstrate dose-dependent effects of a statin on IGFs and two binding proteins that influence IGF bioavailability. These data are particularly valuable because the patients were well characterised and were involved in a randomised double-blind placebo-controlled clinical trial comparing the clinical effects of different statin doses. The study does have some weaknesses. First, it was a relatively small study with a short duration of follow-up, but nevertheless, we were able to show dose-dependent effects of atorvastatin on the IGF system. However, the limited sample size may explain the lack of significant correlation between changes in IGFBP1 and HbA1c. Secondly, although the study was designed prospectively, this was a *post hoc* analysis of a trial designed for another purpose – i.e. to assess the effects of statin dose on renal function.

Thirdly, this was a study of patients with type 2 diabetes and albuminuria and therefore the results may have limited generalisability. Fourthly, we did not measure glucose tolerance or insulin resistance that would have helped clarify the underlying pathophysiological mechanisms. Lastly, we performed the study in patients with type 2 diabetes, and therefore, we were not able to relate changes in IGF proteins to incident diabetes.

Clinical implications and future work

There are no immediate clinical implications of this work, but this is an important area for future research because of the increasing and widespread use of statin medication. Although statins have major health benefits, there is a need to understand the mechanisms behind potential adverse effects so that we might develop ways to mitigate these effects. Our study needs to be replicated in larger and more diverse populations in the first instance.

We report an overall decrease in the concentration of the IGFs with atorvastatin therapy and a dose-dependent change in IGFBP1 concentration following atorvastatin administration in patients with type 2 diabetes. The effects of atorvastatin on IGF1, IGF2, IGFBP1 and IGFBP3 concentration could suggest a possible mechanism linking high-dose 3 hydroxy 3-methylglutaryl coenzyme A reductase inhibitor treatment with higher rates of incident type 2 diabetes.

The online version of this manuscript contains an additional table (Supplementary Table 1, see section on supplementary data given at the end of this article) that represents the mean circulating concentrations of IGF1, IGF2, IGFBP1 and IGFBP3 at study baseline, 6 months and at study completion (12 months) for study subjects administered 10 mg atorvastatin, 80 mg atorvastatin and for the study population as a whole.

Supplementary data

This is linked to the online version of the paper at <http://dx.doi.org/10.1530/EJE-12-0844>.

Declaration of interest

J M Gibson and M K Rutter have received travel grants and honoraria for speaking at meetings sponsored by Pfizer. M Gittins's salary has previously been partly funded by research grants from Pfizer. The University and Hospital trusts employing M K Rutter and J M Gibson have received research grants from Pfizer UK. The authors report no other conflicts of interest.

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