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Statin treatment is associated with insulin sensitivity decrease in type 1 diabetes mellitus: a prospective, observational 56 month follow-up study

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Abstract:

Objective: Statins are effective in the primary and secondary prevention of cardiovascular events in individuals with and without diabetes mellitus. Emerging evidence, however, suggest that statins might reduce insulin sensitivity and secretion in healthy population as well as in type 2 diabetes. We wanted to investigate the effect of statin therapy introduction on insulin sensitivity in type 1 diabetes mellitus (T1DM) patients.

Methods: This prospective observational 56 months long study included 832 randomly selected T1DM patients aged 25-61 years. Uncontrolled dyslipidemia and clinician perceived need for treatment, rather than randomization, was basis for individuals being started on either atorvastatin or simvastatin (10-40 mg); N=345, 41.47%. Patients on statin treatment were compared to those unexposed to statin. Insulin sensitivity was accessed using equation derived from euglycemic-hyperinsulinemic clamp studies estimated glucose disposal rate (eGDR).

Results: Patients who started statin therapy (59.42% atorvastatin and 40.58% simvastatin) experienced a greater decrease in insulin sensitivity (19.27 % *vs* 12.82 % $p<0.001$) as well as metabolic control deterioration compared to statin free group. The risk of decrease in insulin sensitivity attributable to statin use was 36.7% (HR 1.36 (95% CI 1.31, 1.43) after adjustment for age, gender, disease duration, smoking status and the concomitant antihypertensive therapy.

Conclusion: Although there is still a lack of a clear molecular explanation on the adverse effects of statin therapy on insulin sensitivity, we showed that it deteriorates insulin sensitivity and metabolic control in type 1 DM. The cardiovascular benefits of statin treatment might outweigh the risk of developing insulin resistance, but the possible metabolic control worsening merits to be considered.

Key words: type 1 diabetes mellitus, inuslin sensitivity, statins

1. Introduction

Statins represent a class of medications widely used in hypercholesterolaemia treatment (1). They act by inhibiting 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, an intracellular enzyme which plays a central role in cholesterol production (2). Most statins are similar in structure to the enzyme's substrate, HMG-CoA, and act as competitive inhibitors. Inhibition of this enzyme by statins translates into lowering low density lipoprotein (LDL)-cholesterol via enhanced LDL receptor expression (3, 4). As high LDL levels are causally associated with increased cardiovascular disease (CVD), statin treatment is effective in the primary and secondary prevention of CVD that is generally safe and well tolerated (5-8). Emerging evidence, however, suggest that long-term statin treatment is associated with type 2 diabetes mellitus (T2DM) occurrence (9-12). Although mechanisms underlying the association of statin therapy with diabetes remain unclear (13), recent data suggest that that statin treatment may increase the risk of T2DM due to decreases in both insulin sensitivity and insulin secretion (12).

Although insulin resistance (IR) typically characterises T2DM, while the insulin deficiency is a primary defect in patients with type 1 diabetes mellitus (T1DM), there are suggestions that there is a certain degree of IR in T1DM (14, 15). The mechanisms of IR in T1DM is likely due to a combination of supraphysiologic levels of exogenous insulin and obesity. In the past, it was thought that IR in T1D was primarily related to hyperglycemia (16), however, it was recently proposed that adults with T1DM have both impaired glucose utilization and impaired insulin-induced non-esterified fatty acid suppression, independent of glycemic control (17). Skeletal muscle IR is a known feature of T1DM and is due to decreased glucose transport into myocytes from impaired insulin-stimulated upregulation of GLUT4 mRNA (18).

The data linking statins with increase in IR are especially concerning since this class of drugs are used by millions of diabetic patients worldwide (19). Thus, it would be of special clinical interest to investigate the effect of statins on glycaemic control in T1DM patients without endogenous insulin

secretion. Here we analysed the effect of statin therapy introduction on metabolic control and insulin sensitivity in T1DM patients during 56 months of prospective, observational follow-up.

2. Methods

Participants and clinical measurement at the baseline study

The study was performed in 2010–2015 at the In-Patient Department of Diabetology of the Vuk Vrhovac University Hospital, Medical School University of Zagreb, Croatia and included 832 (345, 41.47% starting statin treatment) randomly selected T1DM patients aged 25-61 years. Histories and complete physical examination and laboratory tests were performed in all subjects in order to exclude diseases other than T1DM or medications that might affect insulin sensitivity. Type 1 diabetes was defined by undetectable meal stimulated C-peptide concentrations (C-peptide <0.2 ng/mL) and positive islet cell and glutamic acid autoantibodies (at least from the previous medical record if the measurement was performed in our Clinic laboratory, respectively).

The study was conducted according to the guidelines laid down in the Declaration of Helsinki and cleared by Merkur University Hospital Ethics Review Board for human studies. Written informed consent was obtained from and signed by all patients.

Treatment and follow up

The administration of each medicine, atorvastatin or simvastatin was determined by our In Patient clinic doctors to the patients with uncontrollable dyslipidaemia (total serum cholesterol and/or LDL cholesterol exceeding the reference range). The total serum cholesterol and LDL-cholesterol upper limits for the reference range in the consideration of statin therapy were 6 mmol/L and 3.0 mmol/L i.e. 5.5 mmol/L and 2.5 mmol/L in the presence of other cardiovascular risk factors such as smoking, visceral obesity (waist circumference >80 cm for females and >102 cm for males) and hypertension. The begining of the follow up was defined as the administration date of each medicine, and the end of

follow up was November 30, 2015. The study protocol consisted of every 14 months full check-up and measurements were identical to those of the baseline study.

Anthropometric measurements and laboratory analysis

Basic anthropometric measurements were performed as follows: waist circumference was measured on bare skin as the narrowest circumference between the 10th rib and the iliac crest while hip circumference was measured at the widest point of the gluteal muscles using a tailor measure and expressed in centimetres in order to calculate WHR. Weight was measured using a balanced beam scale with light clothing without shoes and expressed in kilograms (kg) and height was measured using a wallmounted stadiometer and expressed in centimeters (cm) in order to calculate BMI. Blood pressure was measured twice in the sitting position with a mercury sphygmomanometer after a resting period of 10 min (mmHg, reference interval 130/80). Fasting venous blood samples were collected for the determination of lipid profile status [total cholesterol (mmol/l, reference interval 5.0), HDL cholesterol (mmol/l, reference interval [1.0 for men, [1.3 for women), LDL cholesterol (mmol/l, reference interval\3.0), VLDL cholesterol (mmol/l), and triglycerides (mmol/l, reference interval\1.7)], HbA1c (%, reference interval 3.5–5.7). HbA1c was measured spectrophotometrically by turbidimetric immuno-inhibition (Olympus AU600;p Beckman-Coulter, USA). Total serum cholesterol, HDL cholesterol and triglycerides in serum were measured by an HDL-C were estimated by homogenous enzymatic colorimetric method (20-22). LDL cholesterol was estimated using Friedewald formula: LDL-C = TC 2 HDL-C 2 TG/2.2 (mmol/L). In this formula, TG stands for triglycerides, and TG/2.2 (or TG/5) serves as a proxy for VLDL cholesterol. the ratio of the mass of triglyceride to that of cholesterol in VLDL is assumed to be relatively constant (23).

Calculations

Insulin sensitivity was calculated using the equation derived from euglycemic-hyperinsulinemic clamp studies-estimated glucose disposal rate (eGDR): 24.31–12.2X(WHR)–3.29X(AHT)–0.57X(HbA1c), where the units are $mgkg^{-1}min^{-1}$, WHR indicates the waist to hip ratio, AHT indicates blood pressure, and is expressed as: 0-no, 1-yes. Those on blood pressure medications or with blood pressure >140/90 mmHg were considered to have hypertension, the equation was derived from a substudy of 24 EDC (Epidemiology of Diabetes Complications) participants who underwent euglycemic-hyperinsulinemic clamp studies (24). Lower eGDR levels indicate greater IR.

Statistical analysis

Statistical analyses were conducted using the SPSS version 17 (SPSS, Chicago, IL, USA). BMI, waist circumference, total cholesterol, LDL-cholesterol, HDL-cholesterol, triglycerides, glucose and HbA1c levels and eGDR were log-transformed to correct for their skewed distribution. Baseline characteristics of the groups were compared using t test or $\chi 2$ test. The change in the numerical variables was accessed by ANOVA test followed by Bonferroni's correction. HRs for the risk of eGDR decrease were calculated with Cox regression. Risk of eGDR decrease according to the type of statin (simvastatin, atorvastatin, vs no statin) study were calculated with Cox regression (Fig. 1.). Adjustments were made for age, BMI, waist circumference, current smoking, use of beta-blockers and use of diuretics. A p value less than 0.05 was considered as statistically significant.

3. Results

Patients who started statin therapy (N= 345, 41.47%; 59.42% atorvastatin and 40.58% simvastatin) were older, had lower insulin sensitivity while higher rate of hypertension, i.e. they revealed higher rate of cardiovascular risk factors (Table 1.). They experienced a greater decrease in insulin sensitivity (19.27 % *vs* 12.82 % $p<0.001$) as well as metabolic control deterioration accounting for increase in body weight, HbA1c, total daily insulin requirement as well as blood pressure compared with statin

free group despite the lipid profile amelioration (Table 2). There were no medication changes during the study period. The risk of decrease in insulin sensitivity attributable to statin use was 36.7% (HR 1.36 (95% CI 1.31, 1.43) after adjustment for age, gender, disease duration, smoking status and the concomitant antihypertensive therapy (66% patients were using trandolapril, 26.5% bisoprolol and 13.5% thiazide diuretics with no significant in-between group difference) (Figure 1a.). The risk was significantly attributable to both atorvastatin (HR 1.34 (95% CI 1.27, 1.41) and simvastatin (HR 1.42 (95% CI 1.34, 1.51), i.e. no significant difference in the risk of eGDR reduction was observed between two statins (Fig. 1.b.).

4. Discussion

We investigated the association of statin treatment with the risk of insulin sensitivity decrease as well as its effect on metabolic control in a cohort of T1DM patients during 56 months follow up. Our study reports several findings: 1) statin therapy introduction was associated with a 36% increased risk of reduced insulin sensitivity after adjustment for confounding factors; 2) no significant difference was found between atorvastatin and simvastatin on the risk of insulin resistance and 3) statin treatment was associated with an increase in HbA1C.

Statins have a long track record of improving clinical outcomes in patients with high LDL cholesterol. Treatment of elevated LDL cholesterol levels with statins leads to a dramatic drop in the risk of heart attack, stroke, and death from CVD causes in individuals with and without diabetes mellitus (7). Over 4 years, for every 1.03-mmol/L drop in the LDL cholesterol level, there is a 13% reduction in the risk of death from any cause in patients without diabetes mellitus and a 9% reduction in patients with diabetes mellitus (7). These beneficial effects of statins have been suggested in various stages of CVD process: statins have been implicated in plaque regression (25), plaque stabilization (26), reduction of inflammation (as noted by a reduction in C-reactive protein CRP levels) (27), reversal of endothelial dysfunction (28), and decreased thrombogenicity (29). They are thought to result from a reduction in

proinflammatory nonsteroidal isoprenoid compounds synthesis through the inhibition of mevalonic acid processing by HMG-CoA reductase.

Careful review of findings from many trials, however, shows that statins can raise plasma glucose concentration levels, and more patients who are on statin therapy are diagnosed with DM compared with those not on statins. Based on registry or prescription-based data, previous studies have reported that statin treatment was associated with higher risk of type 2 DM onset ranging from 10-46% (12, 30, 31). In a collaborative meta-analysis of 13 randomised statin trials including in total nearly 90000 participants, statin therapy was associated with a 9% increased risk for type 2 diabetes, based on fasting plasma glucose concentration values or physician reported diagnosis of diabetes (32). The decrease in insulin sensitivity reflected by elevated levels of 2h plasma glucose is one of the proposed mechanisms explaining this co-incidence (12). Although pancreatic β-cell destruction is a prominent feature of autoimmune diabetes, there is a growing number of patients with T1DM and IR who appear to be at increased risk of CVD mortality and development of diabetes related complications, a greater need for higher insulin doses, and multifactorial intervention, thus, more aggressive treatment (14, 15). To the best of our knowledge, the effect of statin therapy on insulin sensitivity in T1DM has not been evaluated so far. We clearly demonstrated that statin treatment in T1DM was associated with an increase in worsening glycemic control, an increase in blood pressure and reduction in insulin sensitivity during follow-up. More importantly, statin treated group had a reduction in LDL-C in the first 14 months but then had a progressive increase back to baseline by the 56 month. LDL-cholesterol levels in statin-treated patients were off target at the end of the study whitch was and similar to the control group. It would appear that the most likely cause of this observation was lack of adherence to treatment.

There are several cell-based studies using both adipocytes and muscle cells performed in order to understand the mechanism of statin induced insulin sensitivity decrease. Nakata et al. (2006) (33) suggested that statins inhibit isoprenoid biosynthesis which might lower insulin signaling proteins expression in adipocytes and thereby reduce glucose transporter expression or translocation (29). More recent, the potential causes of statin induced IR using a muscle cell based model system was

performed (34). Based on their study research, simvastatin might cause IR through a novel fatty acid based mechanism independent of its cholesterol lowering effects. They hypothesized that by blocking HMG CoA reductase, simvastatin leads to accumulation of acetyl CoA, a precursor of fatty acid synthesis. Fatty acids are synthesized from acetyl-CoA and malonyl-CoA precursors, ant thus a potential consequence of treatment of cells with this drug is that it could lead to intracellular buildup of fatty acids. Free fatty acid accumulation is a known modulator of protein kinase-C (PKC) pathway because it interferes with insulin receptor substrate- 1 protein cascade and thus inhibits glucose uptake by Glut-4 transporter translocation. It is important to point out here that the statin's effect on IR has been reported in patients with distinct statins suggesting that the effect is tied to their mechanism of action, i.e HMG CoA reductase inhibition and is not an off target effect.

The present study has a number of potential limitations. First, it was observational, which limited our ability of full patient randomisation and thus infers a full causal relation between statin tratment and the decrease in insulin sensitivity in T1DM patients. The groups (statin and no statin group) were not matched and although these differences were taken into account during the statistical analysis, the statin group was "metabolically unhealthier" than the no statin group. Both groups demonstrated deterioration in insulin sensitivity, but individuals that have a degree of uncontrolled dyslipidemia, with perceived need for treatment, were more prone to progressive IR than those who do not. That is to say, inadvertently some bias was introduced into these 2 group comparisons. The observed differences in the two groups might predict more progressive IR in the statin-treated group. However, this does not detract from our observation, but rather supports concept that statin-induced deterioration of insulin sensitivity is more likely to occur in individuals with IR. Second, we measured insulin sensitivity using clinical parameters with eGDR and did not have access to direct, detailed measures of insulin resistance using euglycemic-hyperinsulinemic clamp test. Third, although there were no medication changes during the study period, illness, lifestyle changes, treatment adherence could have affected the obtained results.

However, we showed that statins may increase the deterioration in insulin sensitivity and metabolic control in T1DM. The cardiovascular benefits of statin treatment might outweigh the risk of worsening IR, however the risk and benefit must be considered..

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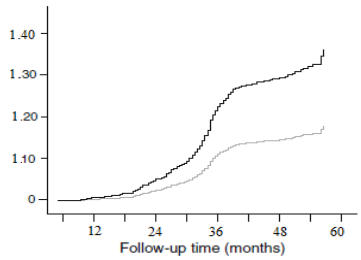
6. Author contributions: Lea Duvnjak designed and intelectually supervised the study, while both Lea Duvnjak and Kristina Blaslov did the data acquisition, interpreted the data and wrote the manuscript.

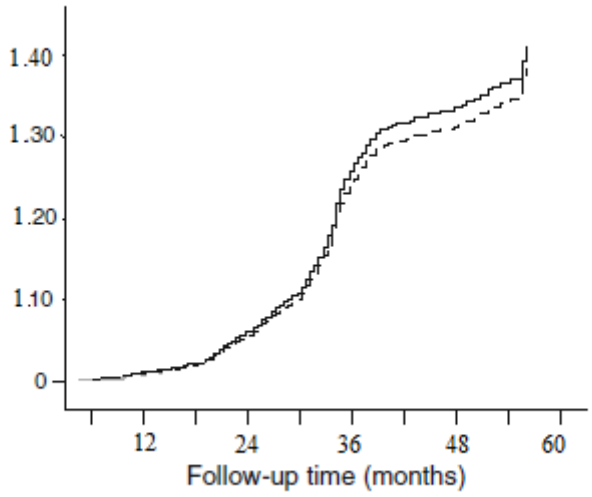
7. Conflict of interest: No competing financial interests exists.

Figure 1.a) Risk of insulin sensitivity decrease by statin treatment during 56 months follow up



Legend: vertical line indicates hazard ratio (HR); black line-statin treated group (N=345); grey line-statin free group (N=487)

Figure 1.b) Risk of insulin sensitivity decrease by atorvastatin and simvastatin treatment group during 56 months follow up



Legend: vertical line indicates hazard ratio (HR); black continuous line-atorvastatin (N=205), black dotted line simvastatin (N=140).

Table 1. Baseline comparisons of statin-free group versus statin-treated group

Characteristics	**No statin (N=487)**	**Statin (N=345)**	**p**
Age (years)	38±11	41±6	<0.001
Disease duration (years)	15.35±10.64	18.53±7.12	<0.001
Current smoker (%)	15.81	26.37	<0.001
Waist (cm)	83.09±10.5	85.99±12.41	0.001
BMI (kg/m^2)	24.42±3.62	25.12±3.07	0.002
HbA1c (%)	7.38±1.07	7.24±1.42	0.105
eGDR ($mg\ kg^{-1}\ min^{-1}$)	9.75±2.03	9.36±2.88	0.023
Total daily insulin dose (IU/kg)	0.601±0.020	0.651±0.031	<0.001
Total cholesterol (mmol/L)	5.04±0.95	5.01±0.75	0.625
LDL-cholesterol (mmol/L)	2.82±0.77	2.89±0.82	0.209
HDL cholesterol (mmol/L)	1.68±0.43	1.66±0.39	0.493
Triglycerides (mmol/L)	1.07±0.64	1.08±0.06	0.772
Statin dose (N, patients):			
atorvastatin 10 mg	-	24	
atorvastatin 20 mg	-	180	
atorvastatin 40 mg	-	2	---
simvastatin 10 mg	-	6	
simvastatin 20 mg	-	131	
simvastatin 40 mg	-	2	

Systolic blood pressure (mmHg)	127.76±12.33	131.13±14.5	0.001
Diastolic blood pressure (mmHg)	81.16±8.6	82.45±6.10	0.017

Legend:*between group comparison; two sided t-test

Table 2. Comparison of clinical and biochemical risk factors between type 1 diabetes mellitus individuals by starting statin treatment during the study period

Characteristics	**No statin (N=487)**					**Statin (N=345)**					**p**
	Baseline	**14th month**	**28th month**	**42nd month**	**End of follow up**	**Baseline**	**14th month**	**28th month**	**42nd month**	**End of follow up**	
Waist (cm)	83.09±10.5	83.23±11.5	83.91±9.4	83.9±10.0	84.13±11.0	85.77±10.75	85.99±12.41	86.56±11.62	87.83±10.51	88.29±12.68	**0.133 ***0.036
BMI (kg/m^2)	24.42±3.62	24.81±2.55	24.93±4.12	24.97±3.61	25.04±3.65	25.12±3.07	25.58±2.01	25.82±3.01	26.01±2.03	26.74±1.06	**0.007 ***<0.001
HbA1c (%)	7.38±1.07	7.35±1.81	7.32±1.46	7.30±0.91	7.28±1.02	7.24±1.42	7.44±1.53	7.32±1.37	7.41±1.12	7.56±1.74	**0.136 ***0.005
eGDR (mg kg^{-1} min^{-1})	9.75±2.03	9.41±1.97	9.37±1.49	8.89±2.01	8.5±2.22	9.36±2.88	8.56±1.79	8.19±1.03	8.03±0.91	8.04±2.29	**0.24 ***0.004
Total daily insulin dose (IU/kg)	0.601±0.020	0.608±0.051	0.603±0.033	0.604±0.055	0.604±0.031	0.651±0.031	0.675±0.033	0.692±0.011	0.705±0.021	0.722±0.012	**0.073 ***0.001
Total cholesterol (mmol/L)	4.92±0.82	4.94±0.94	4.97±0.83	5.04±0.95	5.14±0.67	5.01±0.75	4.46±1.1	4.69±0.89	4.96±0.81	4.96±0.93	**0.06 ***0.005
LDL-cholesterol (mmol/L)	2.78±0.81	2.82±0.77	2.77±0.79	2.79±0.69	2.86±0.69	2.89±0.82	2.13±0.79	2.57±0.87	2.61±0.69	2.87±0.74	**0.39 ***0.73
HDL cholesterol (mmol/L)	1.68±0.43	1.65±0.42	1.68±0.55	1.78±0.39	1.69±0.39	1.66±0.39	1.55±0.42	1.48±0.39	1.55±0.86	1.57±0.91	**0.71 ***0.07
Triglycerides (mmol/L)	1.07±0.64	1.14±0.72	1.01±0.64	0.98±0.49	1.06±0.55	1.08±0.06	1.23±0.71	1.15±0.20	1.11±0.61	1.17±0.72	**0.79 ***0.02
Systolic blood	127.76±12.33	124.24±15.76	124.48±15.97	127.83±13.69	128.28±19.88	131.13±14.5	132.42±17.62	131.68±15.61	135.85±11.91	133.43±10.73	**0.565 ***0.02

pressure (mmHg)											1
Diastolic blood pressure (mmHg)	78.45±8.42	78.08±8.64	81.16±8.	77.5±8.37	81.93±5.19	82.45±6.10	84.42±9.47	87.75±9.45	88.57±8.61	86.56±7.16	**0.091 ***0.001

Legend:*between group comparison; **ANOVA test for the group of patients without statins followed by Bonferroni's correction; *** ANOVA test for the group of patients on statins followed by Bonferroni's correction

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