

## **Effects of high dose simvastatin therapy on glucose metabolism and ectopic lipid deposition in non-obese type 2 diabetic patients**

Julia Szendroedi, MD, PhD<sup>1,2</sup>, Christian Anderwald, Mag, MD<sup>1</sup>, Martin Krssak, PhD<sup>1</sup>, Michaela Bayerle-Eder, MD<sup>1</sup>, Harald Esterbauer, MD, PhD<sup>3</sup>, Georg Pfeiler, MD<sup>1</sup>, Attila Brehm, MD<sup>1</sup>, Peter Nowotny<sup>1</sup>, Astrid Hofer<sup>1</sup>, Werner Waldhäusl, MD<sup>1</sup>, Michael Roden, MD<sup>2,4</sup>

<sup>1</sup>Department of Internal Medicine 3, Medical University of Vienna, <sup>2</sup>Karl-Landsteiner Institute of Endocrinology and Metabolism, Vienna, Austria, <sup>3</sup>Clinical Institute of Medical and Chemical Laboratory Diagnostics, Medical University of Vienna, <sup>4</sup>Institute for Clinical Diabetology, German Diabetes Center, Department of Medicine/Metabolic Diseases, Heinrich Heine University Düsseldorf, Germany

### **Corresponding Author:**

Michael Roden, MD

Email: [michael.roden@ddz.uni-duesseldorf.de](mailto:michael.roden@ddz.uni-duesseldorf.de)

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*Objectives:* Statins may exert pleiotropic effects on insulin action which are still controversial. We assessed effects of high-dose simvastatin therapy on peripheral and hepatic insulin sensitivity, as well as on ectopic lipid deposition in patients with hypercholesterolemia and type 2 diabetes.

*Research design and methods:* We performed a randomized, double-blind, placebo-controlled, single-center study. Twenty patients with T2DM received 80 mg simvastatin (BMI:  $29\pm 4$  kg.m<sup>-2</sup>, age:  $55\pm 6$  y) or placebo ( $27\pm 4$  kg.m<sup>-2</sup>,  $58\pm 8$  y) daily for 8 weeks and were compared to ten healthy humans (CON;  $27\pm 4$  kg.m<sup>-2</sup>;  $55\pm 7$  y). Euglycemic-hyperinsulinemic clamp tests combined with D-(6,6-d<sub>2</sub>) glucose infusion were employed to assess insulin sensitivity (M) and endogenous glucose production (EGP). <sup>1</sup>H magnetic resonance spectroscopy was used to quantify intramyocellular and hepatocellular lipids.

*Results:* High-dose simvastatin treatment lowered plasma total and LDL cholesterol by ~33% and ~48% ( $p < 0.005$ ), but neither affected M nor intracellular lipid deposition in soleus, tibialis anterior muscle and liver nor basal and insulin-suppressed EGP. In simvastatin-treated patients, changes of LDL-C related negatively to changes in M ( $r = -0.796$ ,  $p$  values  $< 0.01$ ). Changes of fasting free fatty acids (FFA) related negatively to changes in M ( $r = -0.840$ ,  $p$  values  $< 0.01$ ) and positively to plasma retinol-binding protein 4 (RBP4,  $r = 0.782$ ,  $p = 0.008$ ).

*Conclusion:* High-dose simvastatin treatment has no direct effects on whole-body or tissue-specific insulin action and ectopic lipid deposition. Reduction of plasma FFA likely mediates alterations in insulin sensitivity in vivo.

**ABBREVIATIONS:** Free fatty acids (FFA), lipids in skeletal muscle (IMCL) and liver (HCL), total cholesterol levels (TC), low-density and high-density lipoprotein cholesterol (LDL-C, HDL-C), nuclear magnetic resonance spectroscopy (MRS), body mass index (BMI), fasting plasma triglyceride (TG), haemoglobin A<sub>1c</sub> (HbA<sub>1c</sub>), endogenous glucose production (EGP), whole body insulin sensitivity (M), atom percent <sup>2</sup>H enrichments (APE), retinol-binding protein-4 (RBP-4), group of patients with type 2 diabetes (T2DM), placebo group (P), simvastatin treatment group (S), control group (CON), fasting plasma glucose (FPG), alanine amino transferase (ALT), aspartate amino transferase (AST), gamma glutamyl transpeptidase (GGT).

**T**ype 2 diabetes mellitus (T2DM) is commonly associated with dyslipidemia which represents a synergistic risk factor for cardiovascular disease (1). High circulating lipids (free fatty acids, FFA) induce insulin resistance due to impaired muscle glucose transport/phosphorylation and intracellular lipids in muscle (IMCL) and liver (HCL) predict insulin resistance (2).

Interventional studies emphasized that statin treatment leads to reduction of cardiovascular events with benefit for patients with T2DM (3). Statins could also contribute to diabetes prevention due to lipid lowering and so-called pleiotropic action. Statin therapy was shown to improve endothelial function, inhibit smooth muscle cell proliferation, reduce oxidative stress and inflammation (4). Retrospective analysis of the West of Scotland Coronary Prevention Study (WOSCOPS) revealed that 5-years pravastatin treatment reduces the diabetes incidence ~30%. The authors suggested that albeit lowering triglycerides (TG) could influence diabetes incidence, other mechanisms, such as anti-inflammatory action may be involved (5). However, pravastatin did not decrease the diabetes incidence in another trial including glucose intolerant humans suggesting that early inception of statins might be required for effective diabetes prevention (6). Likewise, simvastatin did not affect diabetes incidence in arteriosclerotic patients the Heart Protection Study (7). In contrast, atorvastatin marginally increased the diabetes incidence in the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT-LLA) which could be explained by statistical variation (8). Thus, the effect of statins on diabetes incidence is yet uncertain.

The direct action of statins on insulin sensitivity remains controversial, because beneficial (9), indifferent and unfavourable (10) effects were reported. Statins not only decrease LDL-C but may also interfere with

fasting and postprandial metabolism of TG-rich lipoproteins resulting in altered substrate flux to and accumulation of HCL (11; 12), which could subsequently affect muscle glucose metabolism and deposition of IMCL. Simvastatin is one of the most frequently prescribed statins due to its efficacy to reduce low-density lipoprotein cholesterol (LDL-C) levels, tolerability, and reduction of cardiovascular risk and mortality (7). Its effects on insulin action and metabolism at the maximal recommended dose of 80 mg/day are unclear. Thus, we examined the effects of 80-mg/d simvastatin therapy on (i) insulin sensitivity, (ii) IMCL and HCL, (iii) fasting and insulin-mediated suppression of plasma FFA and (iv)  $\beta$ -cell function in hypercholesterolemic normotriglyceridemic patients with T2DM employing euglycemic-hyperinsulinemic clamps combined with stable isotope dilution and nuclear magnetic resonance spectroscopy (MRS).

## **SUBJECTS AND METHODS**

**Experimental protocol**—Twenty patients with T2DM and hypercholesterolemia were included. Eligibility criteria were: (a) known duration of disease: 3-10 years; (b) age: 35-75 years; (c) body mass index (BMI)  $<32$  kg/m<sup>2</sup>; (d) LDL-C  $>4.16$  mM; (e) TG  $<2.75$  mM; (f) HbA<sub>1c</sub>  $<9\%$ ; (g) serum creatinine  $<1.8$  mg/dl; (h) liver transaminases  $<20\%$  over the upper limit with no active liver disease and creatine kinase  $<50\%$  above the upper limit; (i) no evidence of metabolic diseases other than T2DM. Patients were taking neither lipid lowering drugs nor other drugs known to interfere with metabolism of statins. The only glucose-lowering drugs allowed were metformin (S: 5, P: 7), sulfonylurea (S: 3, P: 9) and (S: 2, P: 1). Ten age-, sex- and BMI-matched healthy volunteers (controls, CON) were examined only at baseline.

The study had a double-blind, randomised, placebo-controlled and parallel

group design. The trial has been registered (clinical trials gov identifier: NCT00704314). The sample size was calculated using data from our previous studies in diabetic patients who complied with the inclusion criteria of the present study and were examined with identical experimental methods. The false positive and false negative error rates tolerated were  $Z\alpha=1.96$  for a two tailed  $\alpha$  of 0.05 and  $Z\beta=0.84$  for a  $\beta$  of 0.2. An increase or decrease of  $\sim 20\%$  of the mean values for the primary target variables, insulin-stimulated whole body glucose disposal (M-value) and insulin-suppression of EGP, was considered to be physiologically and clinically. The respective mean values were  $\sim 5 \pm 1 \text{ mg}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$  for M-values [ $3 \pm 0.3$  (13),  $8 \pm 1$  (14)] and  $\sim 0.5 \pm 0.1 \text{ mg}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$  for EGP suppression (13; 14). These considerations revealed a sample size of 8 as the minimal number of patients on simvastatin. Expecting a drop out rate of  $\sim 15\%$ , 10 participants were included for each study group.

After a run-in period of 3 weeks, the patients were randomised to treatment with 80 mg daily simvastatin (Merck Sharp & Dohme, Hoddesdon, UK) or placebo for 2 months. Glucose metabolism, IMCL, HCL were determined before and after treatment following overnight fasting for at least 12 hours. According to previous studies sulfonylurea; metformin and alpha-glucosidase inhibitors were withdrawn at one and three days before the clamps, respectively (13; 14). The study was approved by the local ethics committee and patients consented to participate.

#### Glucose metabolism

At 7.00 a.m. patients were transferred to the metabolic unit. A primed infusion of D-[6,6-d2]glucose [ $3.6 \text{ mg/kg body weight} \times (\text{fasting plasma glucose}/90)$ ] followed by a continuous infusion ( $0.036 \text{ mg}/\text{min} \times \text{kg body weight}$ ) was started to determine EGP (15). At 9.00 a.m., a primed continuous infusion of  $40 \text{ mU}\cdot\text{min}^{-1}\cdot(\text{m body surface$

$\text{area})^2$  was administered for 150 min to assess insulin sensitivity (M) and the ratio of M over the prevailing plasma insulin concentration (M/I) by hyperinsulinemic-isoglycemic (at baseline fasting plasma glucose, FPG) clamps in CON and to standardize for increased FPG a hyperinsulinemic-euglycemic ( $\sim 100 \text{ mg/dl}$ ) clamps in T2DM. In T2DM, euglycemia was achieved by identical primed continuous insulin infusion as in CON and no additional insulin infusion was required. A 20% dextrose infusion, 2-% enriched with D-[6,6-d2] glucose was periodically adjusted to maintain euglycemia (15).

**Analytical procedures**—Glucose was measured by the glucose oxidase method (Glucose analyzer II, Beckman Instr., Inc., Fullerton, CA). Atom percent  $^2\text{H}$  enrichments (APE) in glucose were determined by gas chromatography-mass spectrometry (15). FFA were assayed microfluorimetrically (Wako Chem USA Inc., Richmond, VA) in blood sample using orlistat to prevent in vitro lipolysis (15). TG were measured colorimetrically (Roche, Vienna, Austria). Insulin, C-peptide and glucagon were determined by double-antibody radio immunoassay (15). Retinol-binding protein-4 (RBP-4) were assayed nephelometrically using an antiserum to human plasma RBP (code OUVO; Dade Behring Inc., Deerfield, IL) (16).

#### $^1\text{H}$ MRS

Volunteers were lying supine inside a 1.5-T spectrometer (Magnetom, Siemens, Erlangen, Germany). HCL was quantified employing breath-hold triggered single voxel sequence without water-suppression applied on the  $27\text{-cm}^3$  cubical volume within the right lateral liver (2). IMCL were determined in  $1.73\text{-cm}^3$  cubical volumes within M.soleus and M.tibialis ant. Employing water-suppressed PRESS and the AMARES algorithm as implemented in the jMRUI software package. After  $T_2$  relaxation, IMCL were quantified from the intensity of the

(CH<sub>2</sub>)<sub>n</sub>=(1.25 ppm) resonance, which was compared with the water resonance intensity obtained from spectra without water suppression.

**Calculations and statistics**—The computer solved homeostatic model assessment (HOMA2) was used to derive surrogate parameters of basal  $\beta$ -cell function (HOMA-B) and insulin sensitivity (HOMA-IR). EGP was calculated from the difference between rates of glucose appearance (Ra) (15) and of mean glucose infusion. Statistical analyses were performed using SPSS 6.0 software (SPSS Inc., Chicago, IL, USA). Data are presented as means $\pm$ SD ( $\pm$ SE in the figures). Comparisons between groups were and drug-induced effects were assessed by ANOVA with/without repeated measurements with Tukey post hoc testing. Within-group differences were determined using two-tailed Student's t tests. Differences were considered significant at the 5% level for M, FFA and EGP, and at 1% for other parameters in order to correct for interrelated comparison. Linear correlations are Pearson product-moment correlations and were considered significant at the 5% level for M, FFA and EGP, and at 1% for all other relations.

## RESULTS

**Baseline characteristics**—Baseline characteristics of patients with T2DM after allocation to either placebo (P) simvastatin (S) therapy and CON are shown in Table 1. HbA1c, FPG and TG were increased in both diabetic groups, total cholesterol (TC) and LDL-C were slightly higher in S than in CON. In T2DM, HOMA-IR was  $\sim$ 3.4 fold higher than in CON, whereas HOMA-B was comparable. Gamma-glutamyl transpeptidase (GGT) was  $\sim$ 76% and  $\sim$ 62% higher in T2DM than in CON (p=0.020 vs. S, p=0.062 vs. P). Basal EGP was  $\sim$ 21% higher in T2DM (S: 1.7 $\pm$ 0.3; P: 1.7 $\pm$ 0.4; CON: 1.4 $\pm$ 0.4 mg.kg<sup>-1</sup>.min<sup>-1</sup>, p<0.05 vs.T2DM). IMCL in M.soleus

and in M.tibialis ant. were comparable to CON (S: 1.4 $\pm$ 0.5 and 0.2 $\pm$ 0.2%; P: 1.3 $\pm$ 0.6 and 0.3 $\pm$ 0.2%; CON: 1.5 $\pm$ 0.9 and 0.4 $\pm$ 0.4%). By contrast, HCL were  $\sim$ 3.6 fold higher in T2DM (S: 14.2 $\pm$ 8.6; P: 14.1 $\pm$ 5.8; CON: 4 $\pm$ 4%, p<0.001 vs.T2DM, Fig. 1B). Across the whole study population HCL tended to relate positively to FPG (r=0.544, p<0.005), HbA1c (r=0.409, p<0.05) and GGT (r=0.442, p<0.05) without reaching predefined statistical significance (p<0.01), but related negatively to M (r=-0.386, p<0.05). IMCLs did not correlate with any other metabolic parameters.

**Whole body metabolism during the clamps**—Within 60 min of the clamps, plasma glucose levels reached steady state conditions before and after treatment (5.7 $\pm$ 0.3 and 5.7 $\pm$ 0.3 mmol/l in S, 5.9 $\pm$ 0.6 and 5.7 $\pm$ 0.2 mmol/l in P, 4.9 $\pm$ 0.4 mmol/l in CON) and did not differ within or among the intervention groups. During the last 60 min of the clamps, plasma glucose levels before and after treatment were 5.4 $\pm$ 0.3 vs. 5.4 $\pm$ 0.3 mmol/l in S, 5.5 $\pm$ 0.3 vs. 5.4 $\pm$ 0.3 mmol/l in P and 4.9 $\pm$ 0.3 mmol/l in CON and did not differ within or among the intervention groups but was lower in CON vs. T2DM (p<0.005). Plasma insulin concentrations were 580 $\pm$ 102 vs. 609 $\pm$ 109 pmol/l in S and 537 $\pm$ 80 vs. 551 $\pm$ 94 pmol/l in P and 515 $\pm$ 58 pmol/l in CON and did not differ within or among the intervention groups. M-values were  $\sim$ 42% lower in T2DM and did not differ between the intervention groups (CON: 7.4 $\pm$ 2.4, S: 4.1 $\pm$ 1.9, P: 4.5 $\pm$ 2.7 mg.kg<sup>-1</sup>.min<sup>-1</sup>; P<0.005 T2DM vs. CON, Fig. 1A). Similarly, M/I was lower in T2DM (CON: 0.01 $\pm$ 0.005 (mg.kg<sup>-1</sup>.min<sup>-1</sup>).(pmol.l<sup>-1</sup>)<sup>-1</sup>, p<0.01) but not different between intervention groups (Table 2). Insulin-mediated suppression of EGP (Table 2) and FFA (CON: 94 $\pm$ 5, S: 87 $\pm$ 10, P: 92 $\pm$ 2%) was comparable in all groups. Plasma TG related positively to HOMA-IR (r=0.683, p=0.00003) and negatively to M (r=-0.555,

$p=0.001$ ), HbA1c ( $r=-0.539$ ,  $p=0.002$ ) and FPG ( $r=-0.497$ ,  $p=0.005$ ).

**Effects of simvastatin on lipid and glucose metabolism**—Intervention-related changes of plasma lipids and glucose metabolism are shown in Table 2. At 2 months, plasma total and LDL-C decreased by ~33% and ~48% in S, but remained unchanged in P. There were no significant changes of TG, HDL-C and fasting FFA after simvastatin therapy compared to baseline. Nevertheless, S had ~29% and ~35% lower TG and FFA than P. In S, the decreases in LDL-C and FFA were positively associated ( $r=0.774$ ,  $p<0.001$ ) but did not relate to changes in TG. Despite no significant changes of M after simvastatin treatment, changes of FFA were negatively correlated with the change of M in S ( $r=-0.840$ ,  $p=0.002$ ) which was weakened by the exclusion of one subject with excessive changes in M and FFA ( $r=-0.641$ ,  $p=0.063$ ). The relationship between changes of M and LDL-C ( $r=-0.796$ ,  $p=0.006$ ) was completely lost by omission of this subject ( $r=0.242$ ,  $p=0.531$ ) (Fig. 2 A). Adjustment for FFA disrupted the relationship between the changes of LDL-C and M ( $r=0.424$ ,  $p=0.256$ ), whereas the association between changes of FFA and M remained robust after adjustment for LDL-C ( $r=0.584$ ,  $p=0.099$ ). Changes of M/I after simvastatin treatment also related positively to changes of the plasma FFA ( $r=0.674$ ,  $p=0.033$ ). Plasma RBP-4 did not differ between the groups (S:  $5.4\pm 0.4$ , P:  $5.0\pm 0.5$  mg/dl) but tended to relate positively to HOMA-IR ( $r=0.479$ ,  $p=0.032$ ). After simvastatin treatment, plasma RBP-4 correlated to the change in FFA ( $r=0.782$ ,  $p=0.008$ ) (Fig. 2B). IMCLs and HCL remained unchanged (S:  $1.4\pm 0.6$ ;  $0.3\pm 0.3$  and  $11.0\pm 6.5\%$ , P:  $1.7\pm 1.0$ ;  $0.4\pm 0.5$  and  $11.5\pm 8.0\%$ ) (Fig. 1). Changes of insulin sensitivity did not relate to muscle and liver lipids. Also, basal EGP and EGP suppression were not affected by treatment (S:  $1.7\pm 0.2$

$\text{mg}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ ,  $72\pm 14\%$ ; P:  $1.5\pm 0.4$   $\text{mg}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ ,  $74\pm 12\%$ ).

## DISCUSSION

**Effects on serum lipids**—High-dose simvastatin treatment reduced LDL-C by ~48% in agreement with the maximum achievable LDL-C reduction. Increases in HDL-C and decreases of fasting TG and FFA were not observed in our only slightly hypertriglyceridemic patients. Simvastatin might therefore exert larger effects on HDL-C and TG in more severe hypertriglyceridemia.

**Effects on insulin sensitivity**—Simvastatin treatment slightly reduces insulin sensitivity using the quantitative insulin sensitivity check index (17) in line with findings in T2DM (10). Others reported that simvastatin does not change (18) or increases insulin sensitivity (HOMA-IR) in severely hypertriglyceridemic, hypercholesterolemic patients with T2DM (9). Only few studies demonstrated changes in whole-body insulin sensitivity employing clamps (10; 19). At a dose of 80 mg/day, we found no effect of simvastatin on whole-body insulin sensitivity in non-obese metabolically well-controlled patients with T2DM. This does not exclude a specific simvastatin effect on hepatic insulin sensitivity. Our patients with T2DM exhibited marked hepatic insulin resistance indicated by only ~70% EGP suppression. However, simvastatin did not ameliorate EGP suppression in our patients with T2DM which is in line with the only previous study on pravastatin treatment in familial hypercholesterolemia (20). Statins not only decrease LDL-C but may also interfere with fasting and postprandial triglyceride-rich lipoprotein metabolism resulting in altered substrate flux and accumulation of HCL (11; 12; 21). Our patients exhibited a tight correlation between excessive HCL storage and M-value similar to previous reports (2). Simvastatin did not affect either HCL nor IMCL in two differently composed muscles.

Also no relationship between changes of insulin sensitivity and ectopic lipids was found.

**Effects on parameters influencing insulin sensitivity**—According to current paradigms, mechanisms determining insulin sensitivity comprise of (i) circulating FFA arising from adipocyte lipolysis, lipoprotein secretion or dietary fat intake, (ii) cytokines from adipose tissue or liver and (iii) low grade inflammation. Recently simvastatin was found to improve FFA composition, fasting lipid fractions, and postprandial plasma TG even in normotriglyceridemic patients (21). In the present study, reduction of plasma FFA during the clamp reflecting insulin-mediated suppression of lipolysis remained unchanged after therapy. Statins could affect insulin resistance via declining plasma TG in T2DM. TG levels were negatively related to M at baseline and changes in fasting FFA were found to induce considerable effects on insulin sensitivity. Accordingly, evidence is accumulating that rather than IMCL, intracellular long-chain fatty acyl coenzyme A and diacylglycerol inhibit muscular insulin action by stimulating serine phosphorylation of insulin receptor substrate-1 (22).

Statins may further affect inflammatory markers (4) which could relate to changed adipocytokines. Circulating RBP4, mainly produced by adipocytes, is related to whole-body insulin sensitivity and elevated in insulin resistant states (23), but its role remains controversial (16). Here we show that serum RBP4 relates to a surrogate of fasting insulin sensitivity and to changes in plasma FFA upon simvastatin therapy. Nevertheless, serum RBP4 did not relate to whole-body insulin sensitivity as assessed from the euglycemic clamp and simvastatin did not affect RBP4.

**Effects on fasting  $\beta$ -cell function**—High-dose lipophilic statins may induce unfavourable pleiotropic effects including impairment of insulin secretion (24; 25). The

proposed mechanism suggests that these statins inhibit the glucose-induced elevation of free  $[Ca^{2+}]$  in cytoplasm, thereby diminishing insulin secretion. However, other studies reported increased or unchanged fasting insulin (9; 10). We found neither changes in fasting insulin nor in HOMA-B during simvastatin therapy.

Of note, some limitations of this study need to be considered. First, the number of participants per treatment group is low, but was based on a sample size calculation considering that increases of whole-body and hepatic insulin sensitivity by ~20% represent a clinically relevant treatment effect. Second, only patients with untreated hypercholesterinemia in need of cholesterol lowering drug treatment according to current guidelines. Thus, this trial comprised of a typical but preselected population which does not allow extrapolation of the results to normolipidemic T2DM or nondiabetic populations. Third, the extensive metabolic characterization revealed a high number of parameters assessed so that the level of significance was adjusted to correct for interrelated comparison. Nevertheless, despite the extensive metabolic characterization by gold standard techniques, a number of anti-inflammatory and anti-oxidant mechanisms that potentially affect insulin action were not explored in the present study. As a result, the issue whether a possible dissociation exists among different pleiotropic effects of statins cannot be completely resolved. Finally, different glucose lowering drugs were used in both groups and withdrawn before the clamp. However, antidiabetic medication did not have any impact on whole body and hepatic insulin sensitivity and patients on thiazolidinediones or insulin were not included in this study.

Thus, this study shows that even high-dose simvastatin treatment which effectively reduces LDL-C neither directly improves whole-body or hepatic insulin sensitivity nor

intracellular lipid deposition in near normotriglyceridemic patients with T2DM.

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#### **FIGURE LEGENDS**

**Fig. 1.** Whole-body insulin sensitivity (M-value) (A), ectopic lipid deposition in liver (B) m.soleus (C) and m.tibialis (D) in patients with type 2 diabetes before and after treatment with 80 mg simvastatin per day (S, n=10, filled bars) or placebo (P, n=10, striped bars) and healthy humans (CON, n=10, empty bars,  $p < 0.005$  vs. S and P).

**Fig. 2.** Correlation of changes in fasting FFA with the changes in whole-body insulin sensitivity (M-value) (A) and serum retinol-binding protein-4 (RBP4) (B) in patients with type 2 diabetes before and after treatment with 80 mg simvastatin per day (S, n=10).

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**Table 1:** Baseline characteristics of type 2 diabetic patients (S, P) and matched non-diabetic volunteers (CON).

	Simvastatin 80 mg/d (S)	Placebo (P)	Controls (CON)
N (f/m)	10 (3/7)	10 (5/5)	10 (5/5)
BMI (kg/m <sup>2</sup> )	28.9±3.5	27.3±3.7	27.4±4
age (a)	55±6	58±8	55±7
HbA1c (%)	6.7±0.6	6.7±0.7	5.6±0.2 ‡
FPG (mM)	8.7±1.3	8.5±1.3	4.9±0.4 §
HOMA-B	64±23	69±27	81±17
HOMA-IR	2.7±0.9	2.7±0.8	0.8±0.2
Fasting EGP (mg.kg <sup>-1</sup> .min <sup>-1</sup> )	1.7±0.3	1.7±0.4	1.4±0.4**
TG (mM)	1.7±0.5	1.9±0.6	1.1±0.4 *, †
FFA (µM)	503±229	618±206	613±206
TC (mM)	7.6±2.5	6.6±0.8	5.6±0.9 *
TG/HDL-C	2.9±1.0	3.3±1.2	1.8±0.8 ¶
HDL-C (mM)	1.4±0.3	1.4±0.2	1.5±0.2
LDL-C (mM)	5.4±2.3	4.3±0.6	3.6±0.8 *
ALT (U/l)	37±13	34±11	26±9
AST (U/l)	25±7	21±4	26±7
GGT (U/l)	37±13	34±11	21±12 *

Anthropometric and laboratory characteristics (means ± SD) of type 2 diabetic patients after allocation to either placebo or simvastatin therapy and healthy controls. Body mass index (BMI), fasting plasma glucose (FPG), surrogate parameters of basal β-cell function (HOMA-B) and basal insulin sensitivity (HOMA-IR), total triglycerides (TG), free fatty acid (FFA), total cholesterol levels (TC), high density and calculated low density lipoproteins (HDL-C, LDL-C), alanine amino transferase (ALT), aspartate amino transferase (AST), gamma glutamyl transpeptidase (GGT) were determined.

\*, P<0.05 CON vs. S; \*\* P<0.05 CON vs. S and P, †, P<0.005 CON vs. P; ‡, P<0.0005 S and P vs. CON; §, P<0.00001 S and P vs. CON; ||, P<0.00005 S and P vs. CON; ¶, P<0.01 P vs. CON.

**Table 2:** Effects of simvastatin on lipid profiles and glucose metabolism

	Simvastatin 80 mg/d (S)	Placebo (P)
HbA1c (%)	6.7±0.6 (-0.01±0.3)	6.7±0.6 (-0.01±0.4)
HOMA-B	71±31 (+6.8±16.6)	67±29 (-1.3±/1)
HOMA-IR	2.7±0.6 (-0.03±0.6 *)	3.3±1.2 † (+0.6±0.5)
M (mg.kg <sup>-1</sup> .min <sup>-1</sup> )	4.7±3.3 (+0.6±2.1)	3.8±1.6 (-0.3±2.0)
M/I (mg.kg <sup>-1</sup> .min <sup>-1</sup> ).(pmol.l <sup>-1</sup> ) <sup>-1</sup>	0.008±0.005 (0.002±0.01)	0.006±0.003 (-0.001±0.008)
Rd (mg.kg <sup>-1</sup> .min <sup>-1</sup> )	5.3±3.1 (0.0±2.9)	4.0±1.3 (-1.2±1.2)
EGP during clamp (mg.kg <sup>-1</sup> .min <sup>-1</sup> )	0.48±0.32 (0.29±0.95)	0.39±0.33 (-0.01±0.60)
EGP suppression (%)	72±14% (-3±13%)	74±12% (4±16)
TG (mM)	1.5±0.4 * (-0.2±0.5 *)	2.1±0.8 (+0.3±0.4)
FFA (µM)	392±130 * (-111±205)	600±234 (-18±211)
TC (mM)	5.1±1.0 †, ‡ (-2.5±1.8 ‡)	6.6±0.8 (0.0±0.6)
TG/HDL-C	2.7±1.2 (-0.1±/1.2)	3.7±1.7 (+0.4±0.7)
HDL-C (mM)	1.4±0.3 (+2.9±5.9)	1.4±0.3 (-1.8±7.1)
LDL-C (mM)	2.8±0.9 †, ‡ (-2.6±1.6 §)	4.2±0.5 (-0.2±0.4)
ALT (U/l)	40±20 (+6±16)	29±12 (+2±5)
AST (U/l)	31±15 (+6±14)	22±6 (+1±5)
GGT (U/l)	39±23 (+2±15)	36±8 (+2±6)
RBP4 (mg/dl)	5.0±1.1 (-0.4±0.8)	5.8±1.7 (0.7±0.6)

Laboratory characteristics (means ± SD) of type 2 diabetic patients after treatment with 80 mg/d simvastatin for 8 weeks or application of placebo, changes compared to baseline are given in brackets. Surrogate parameters of basal β-cell function (HOMA-B) and basal insulin sensitivity (HOMA-IR), total triglycerides (TG), whole body glucose

disposal (M), free fatty acid (FFA), total cholesterol levels (TC), high density and calculated low density lipoproteins (HDL-C, LDL-C), alanine amino transferase (ALT), aspartate amino transferase (AST), gamma glutamyl transpeptidase (GGT) were determined. \*,  $P < 0.05$  S vs. P; †,  $P < 0.005$  vs. baseline; ‡,  $P < 0.005$  S vs. P; §,  $P < 0.0005$  S vs. P.

Fig. 1

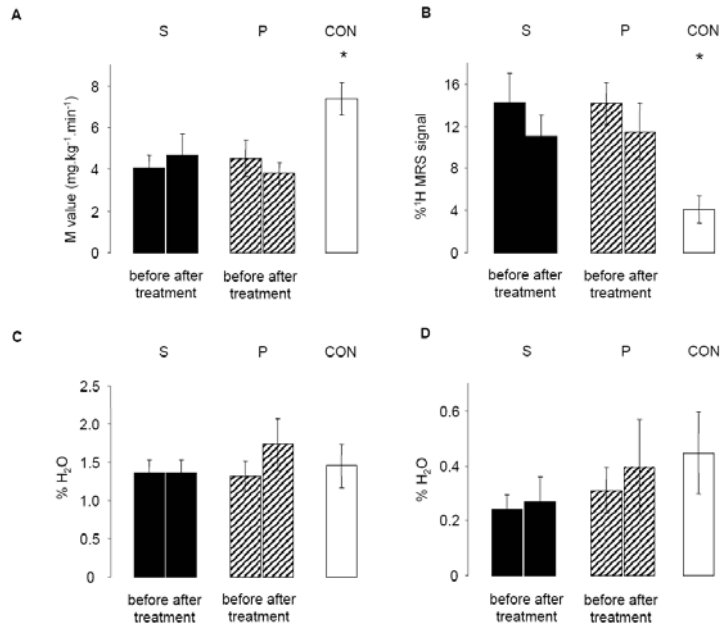


Figure 2

