Research Article

Diabetic Cardiovascular Autonomic Neuropathy: Insulin Resistance, Lipids and Simvastatin

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**A R T I C L E  I N F O**

Article history:
Received: 22 August, 2020
Accepted: 7 September, 2020
Published: 18 September, 2020

Keywords:
Type 2 diabetes mellitus
cardiac autonomic neuropathy
insulin resistance
blood lipid profile
simvastatin

**A B S T R A C T**

Background: Treatment of diabetic cardiac autonomic neuropathy (CAN) is a complex process, that includes: lifestyle modification; reducing of insulin resistance (IR); optimal glycemic control; management of diabetic dyslipidemia; antioxidants; vitamins; treatment of myocardial metabolic abnormalities; thrombosis and others. The aim of study was to investigate the effects of simvastatin on insulin resistance and blood lipid profile parameters in patients with type 2 diabetes mellitus (DM) and the definite stage of cardiac autonomic neuropathy.

Methods: The study involved 107 patients with type 2 DM among them 16 patients without CAN, 19 with subclinical stage of CAN and 72 with definite CAN. Median age of patients was 53.6±0.41 years, disease duration - 4.1±2.4 years and median glycated hemoglobin (HbA1c) - 7.01±0.09%. The control group included 14 almost healthy people without DM. Patients with definite CAN were allocated into two treatment groups: 1st group - 22 patients received standard hypoglycemic therapy and simvastatin 20 mg/day; 2nd group - control (n = 15). The duration of the study was 3 mos. The concentrations of glucose, HbA1c, immunoreactive insulin (IRI) in the blood were determined. Lipid metabolism was assessed by the concentration of total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglycerides (TG) measurements. The IR index (HOMA-IR), atherogenic coefficient (AC), TG/HDL-C parameters, and TG-glucose (TyG) index were calculated.

Result: It was established that in patients with type 2 DM with subclinical stage of CAN there was statistically significant increase in the parameters of HbA1c, IRI, TC, TG and HOMA-IR, AC, TyG indices and decrease of TG/HDL-C and HDL-C compared to control; increase of IRI, TG, TG/HDL-C and TyG indices compared to patients with type 2 DM without CAN. The definitive stage of CAN is characterized by an increase of HbA1c, IRI, TC, LDL-C levels and HOMA-IR, AC indices and a significant decrease in the concentration of HDL-C (compared to patients with subclinical CAN). As a result of our study, we found out that prescription of simvastatin to patients with definite stage of CAN was accompanied by a statistically significant decrease in the concentration of TC, LDL-C, TG and an increase in the content of HDL-C (compared to 2nd, control group).

Conclusion: Obtained results justify the appropriateness of statins prescription to patients with type 2 DM and the definite stage of CAN.

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Introduction

It was estimated that there were 415 million people with diabetes mellitus (DM) aged 20-79 years in 2015, and the number was predicted to rise to 642 million by 2040 [1]. The development of cardiovascular autonomic neuropathy (CAN) is associated with the lesion of the autonomic nervous system, and maybe accompanied by coronary vessels ischaemia, arrhythmias, ‘silent’ myocardial infarction, severe orthostatic hypotension (OH) and sudden death syndrome [2-4]. Cardiovascular autonomic neuropathy treatment is a complex process, that includes:
lifestyle modification; reducing of insulin resistance (IR); optimal
glycemic control; management of diabetic dyslipidemia (DLP);
antioxidants; vitamins; treatment of myocardial metabolic
abnormalities; thrombosis; management of OH; symptomatic treatment
of concomitant diseases and others [5, 6].

The aim of this study was to investigate the effects of simvastatin on
blood lipid profile, triglyceride-glucose index and insulin resistance
parameters in patients with type 2 diabetes mellitus and the definite stage
of the cardiovascular autonomic neuropathy.

Materials and Methods

I Study Population

The study involved 107 patients with type 2 DM among them 16 patients
without CAN, 19 with subclinical stage of CAN and 72 with definite
CAN. Median age of patients was 53±0.41 years, disease duration -
4.12±0.24 years and median glycated hemoglobin (HbA1c) -
7.01%±0.09%. The control group contained 14 almost healthy people
without DM, that could be compared with the treatment group by
demographic characteristics. CAN was diagnosed according to
previously proposed criteria [2]. The work was done according to the
principles of the Helsinki Declaration II and was approved by the
Medical Ethics Committee of Danylo Haltsky Lviv National Medical
University. All participants signed informed consent prior to their
inclusion into the study. Patients with definite CAN were allocated into
two treatment groups: 1st group - 22 patients received standard
hypoglycemic therapy and simvastatin 20 mg/day; 2nd group - control
(n = 15). The duration of the study was 3 months.

II Biochemical Methods

The concentration of glucose in the blood was determined by the glucose
oxidase method while HbA1c level was assessed by using a highly
sensitive method of ion-exchange liquid chromatography with D-10
analyzer and BIO-RAD reagents (United States). Determination of
immunoreactive insulin (IRI) was performed using commercial kits from
Immunotech insulin immunoradiometric assay reagents (Czech
Republic). Lipid metabolism was assessed by the concentration of total
cholesterol (TC), triglyceride (TG), low-density lipoprotein cholesterol
(LDL-C), high-density lipoprotein cholesterol (HDL-C); atherogenic
coefficient (AC) and TG/HDL-C parameters. The TG-glucose (TyG)
index was calculated using the Ln [fasting triglyceride (mg/dL) x fasting
glucose (mg/dL)] [7]. The lipid fractions were determined by using
HUMAN reagents (Germany) for the analyser HUMANLAYZER 2000.
Homeostasis model assessment (HOMA) IR index (HOMA-IR) was
calculated according to the formula: fasting IRI (mcIU/mL) x fasting
glucose (mmol/L)/22.5 [8].

III ECG Recordings

Resting 12-lead surface electrocardiography (ECG) with a paper speed
of 25 mm/s and a signal size of 10 mm/mV was recorded in the morning
period. We performed resting ECG analysis included measurement of
the following parameters: heart rhythm, heart rate, conduction intervals,
and Holter-ECG [(ECG ‘EC-3H’ (‘Labtech’, Hungary)] analysis
included measurement of 24 hours ECG, circadian indexes and heart rate
variability parameters.

IV Statistical Analysis

Statistical analysis was based on the variational method using a
statistical parametric t-test, nonparametric Wilcoxon t-test, and Fisher’s
Pearson correlation coefficient. Data are presented as mean ± standard
error of the mean (SEM). All tests were performed using the ANOVA
(Microcal Origin v. 8.0) software. Statistical significance was set at p <
0.05.

Results

As can be seen from the results, in patients with type 2 DM with
subclinical stage of CAN, compared with the results obtained in the
group of patients with type 2 DM without verified CAN, there was
statistically significant increase in the content of IRI (+24.44%) in the
absence of statistically significant changes in other parameters (Table 1).

Table 1: The IRI and HOMA-IR parameters in patients with type 2 DM and CAN (M±S).

| Parameters                  | Patients with type 2 DM (n = 107) |
|-----------------------------|-----------------------------------|
|                             | Without CAN [group 1 (n = 16)] | Subclinical CAN [group 2 (n = 19)] | Definite CAN [group 3 (n = 72)] | Group 4 [control group (n = 14)] |
| HbA1c, %                    | 6.58±0.16*                     | 6.74±0.19†                      | 7.18±0.11§††                   | 5.44±0.17                       |
| IRI, mcIU/L                 | 16.12±1.15*                    | 20.06±1.31§                    | 27.31±1.11§*§§                 | 11.57±0.62                      |
| HOMA-IR, mIU/l              | 4.36±0.47†                     | 5.73±0.61†                     | 8.35±0.49§††                   | 2.45±0.14                       |

Table: IRI, Immunoreactive insulin; HOMA-IR: Homeostasis Model Assessment Insulin Resistance; DM: Diabetes Mellitus; CAN: Cardiovascular Autonomic Neuropathy; HbA1c: glycated HbA1c.

The results are presented as mean ± standard error of the mean (SEM).
Statistical significance was set at p < 0.05. * - significance of differences
between type 2 DM without CAN and control; † - subclinical CAN and
control; § - definite stage of CAN and control; ‡ - type 2 DM without
CAN and subclinical CAN; ** - type 2 DM without CAN and definite
stage of CAN; †† - type 2 DM with subclinical and definite stage of
CAN.

The definite stage of CAN in patients with type 2 DM is characterized
by an increase of IRI concentration (+136.04%) compared to control (p
< 0.001); +69.42% compared to patients without CAN (p < 0.001);
+36.14% compared to patients with subclinical CAN (p < 0.001), and
HOMA-IR (+240.82% compared to control, p < 0.001); (+91.51% compared
to patients without CAN, p < 0.01); +45.72% compared to patients
with subclinical CAN. Therefore, the most statistically
significant hyperinsulinemia (determined according to the IRI
concentration) as well as IR (HOMA-IR) were verified in patients with
type 2 DM and definite stage of CAN. The results of lipids
concentrations, as well as atherogenic indices are presented in (Table 2).
As a result of our study, we found out that the use of simvastatin was not statistically significant influenced by the treatment group p > 0.05). As a result of our study, we found out that the use of simvastatin was not statistically significant influenced by the treatment group p > 0.05). The results are presented as Δ%, mean ± standard error of the mean (SEM). Statistical significance was set at p < 0.05. * - difference of differences between type 2 DM without CAN and control; † - subclinical CAN and control; § - definite stage of CAN and control; †† - type 2 DM without CAN and subclinical CAN; §§ - type 2 DM without CAN and definite stage of CAN; ††† - type 2 DM with subclinical and definite stage of CAN.

As can be seen from the obtained results in patients with type 2 DM and subclinical CAN was a statistically significant increase of TG level (+110.32% compared to control group, p < 0.01); +58.68% compared to patients without CAN (p < 0.05); decrease in the concentration of HDL-C (-27.78%; compared to control group, p < 0.001) against the background of the absence of statistically significant changes in other parameters (Table 2). The definite stage of CAN is characterized by a further increase in the content of TC (+46.49% compared to the control group, p < 0.001); (+30.08% - to patients with type 2 DM without verified CAN, p < 0.01); (+20.34% to subclinical stage, p < 0.001); TG (approximately 2.03 times, p < 0.001); (+53.29% - for patients with type 2 DM without CAN, p < 0.001); LDL-C (+82.7% - to control, p < 0.001); (+44.82% - to patients with type 2 DM without CAN, p < 0.01); (+40.58% - to subclinical stage, p < 0.001), and a significant decrease in the concentration of HDL-C (-37.3% - to the control group, p < 0.001); (-25.47% - to patients with type 2 DM without CAN, p < 0.001), and (-13.19 % to subclinical stage, p < 0.01).

Changes in the values of some metabolism indicators in patients with type 2 DM with definite CAN after 3 months treatment with simvastatin are presented in the (Table 3).

### Discussion

TyG index, the product of fasting glucose and TG in the blood, has been proposed as a simple method for determining IR in healthy subjects [9, 10]. The use of the HOMA-IR homeostasis model, the insulin suppression test, and the hyperinsulinemic -euglycemic clamp suggested that the TyG index correlates with IR [9, 11-13]. TyG indexes are reported to be elevated in type 2 DM patients compared to parameters in patients with prediabetes [13-16]. Despite its clinical convenience, the accuracy of the TyG index may be limited. For example, although TG has been suggested to be an independent risk factor for DM, the TG level is strongly influenced by a high carbohydrate diet, alcohol consumption, and lifestyles such as exercise. However, due to its convenience and
relatively low cost, TG measurements are widely conducted in clinical practice [13].

The 3-hydroxy-3-methylglutaryl-coenzyme (HMG-CoA) reductase inhibitors (lovastatin, pravastatin, fluvastatin, simvastatin, atorvastatin, rosuvastatin, pitavastatin). By inhibiting HMG-CoA reductase, statins block the pathway for synthesizing cholesterol in the liver. The reduction in cholesterol level induces an increased expression of the low-density lipoprotein receptor, which results in decreased concentration of LDL-C and other apolipoprotein B-containing lipoproteins [17]. Secondary prevention statin studies such as MRC/BHF Heart Protection Study (HPS) showed significant risk reduction among individuals with diabetes mellitus. Based on this, the primary prevention of cardiovascular diseases (CVD) with atorvastatin in type 2 DM in the Collaborative Atorvastatin Diabetes Study (CARDs) was designed to assess the effects of aggressive lipid-lowering on the primary prevention of atherosclerotic CVD in individuals with type 2 DM. In individuals with average or mildly elevated LDL-C at baseline (mean 117 mg/dL), an LDL-C reduction to a mean of 82 mg/dL was accompanied by a 37% reduction in major cardiovascular events compared with placebo. CARDs, which originally planned a mean follow-up of 4 years, was terminated 2 years early because of the significant benefit achieved in the statin group [18].

In summary, statins: decrease LDL-C ≈ 21-55% by competitively inhibiting rate-limiting step of cholesterol synthesis in the liver, leading to upregulation of hepatic LDL receptors (primarily), decrease TG ≈ 6-30% and increase HDL-C ≈ 2-10% [18].

Thus, hyperinsulinemia/IR, lipid metabolism disorders are accompanied by an increase the concentration of TG, TC and LDL-C, decrease HDL-C in patients with type 2 DM, in particular, with CAN [6, 19]. Therefore, the appointment of statins is necessary in the treatment of DLP in patients with type 2 DM with definite stage of cardiovascular autonomic neuropathy.

Conclusion

Development of hyperinsulinemia and insulin resistance among patients with type 2 DM and CAN are accompanied by atherogenic changes in lipid profile namely by an increase in TC, TG, LDL-C, AC, TyG index and decrease in HDL-C. The most pronounced atherogenic changes observed among patients with definite stage of cardiovascular autonomic neuropathy.

Obtained results could witness about the essential importance of hyperinsulinemia, IR and DLP in the pathogenesis of the cardiovascular autonomic neuropathy. Prescription of simvastatin to patients with definite stage of CAN contributed to a statistically significant decrease in the concentration of TC, LDL-C, TG, and an increase in the content of HDL-C (compared to the control group). Obtained results justify the appropriateness of statins prescription to patients with type 2 DM and definite stage of cardiovascular autonomic neuropathy.

Acknowledgments

Not applicable.

Funding

The work was performed within the frame of the State task of the Danylo Halitsky National Medical University, Lviv, Ukraine.

Conflicts of Interest

None.

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