ORIGINAL ARTICLE

Metformin added to intensive insulin therapy reduces plasma levels of glycated but not oxidized low-density lipoprotein in young patients with type 1 diabetes and obesity in comparison with insulin alone: a pilot study

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KEY WORDS

lipid metabolism, metformin, type 1 diabetes

ABSTRACT

INTRODUCTION There are scarce data about the effect of metformin on lipid profile in patients with type 1 diabetes.

OBJECTIVES The present study is the first prospective clinical trial evaluating the effect of combined therapy of metformin and insulin on the pool of oxidized and glycated low-density lipoproteins (LDL) in young patients with type 1 diabetes and concomitant obesity.

PATIENTS AND METHODS A total of 33 obese patients with type 1 diabetes treated with intensive insulin therapy were randomized into a group where metformin was added. The remaining 19 patients continued to receive intensive insulin therapy (control group). In all patients, lipid profile and glycemia were assessed using routine laboratory tests. Oxidized and glycated LDL were measured using commercially available kits. Laboratory tests were performed at baseline and at a control visit after 6 months of treatment.

RESULTS A significant decrease in the levels of glycated hemoglobin, fasting plasma glucose, postprandial glucose, average glucose, triglycerides, glycated LDL, and body mass index was observed in the group receiving combined therapy. A similar decrease was not observed in the control group. The remaining lipid parameters were not changed during follow-up in any of the groups.

CONCLUSIONS Addition of metformin to intensive insulin therapy in young obese patients with type 1 diabetes results in a significant reduction of glycated LDL levels. This can be possibly explained by better glucose control, which improved insulin sensitivity of the peripheral tissues and reduced body mass in this patient group.

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INTRODUCTION In diabetes, regardless of its pathophysiology, long-term impairment of metabolic pathways is accompanied by dysregulation of the transcription factors, resulting in altered metabolism of lipoproteins including lipoprotein lipase, cholesterol ester transport protein, microsomal transfer protein, or hepatic lipase.[1,2] Phenotypically, lipid profiles in diabetic patients are characterized by increased levels of triglycerides and small dense low-density lipoprotein (LDL) as well as decreased plasma levels of high-density lipoprotein (HDL).[1] Moreover, increased glycosylation of LDL accelerates atherosclerosis and affects vascular homeostasis.[3] Therefore, the European Society of Cardiology recommends that patients with overt and

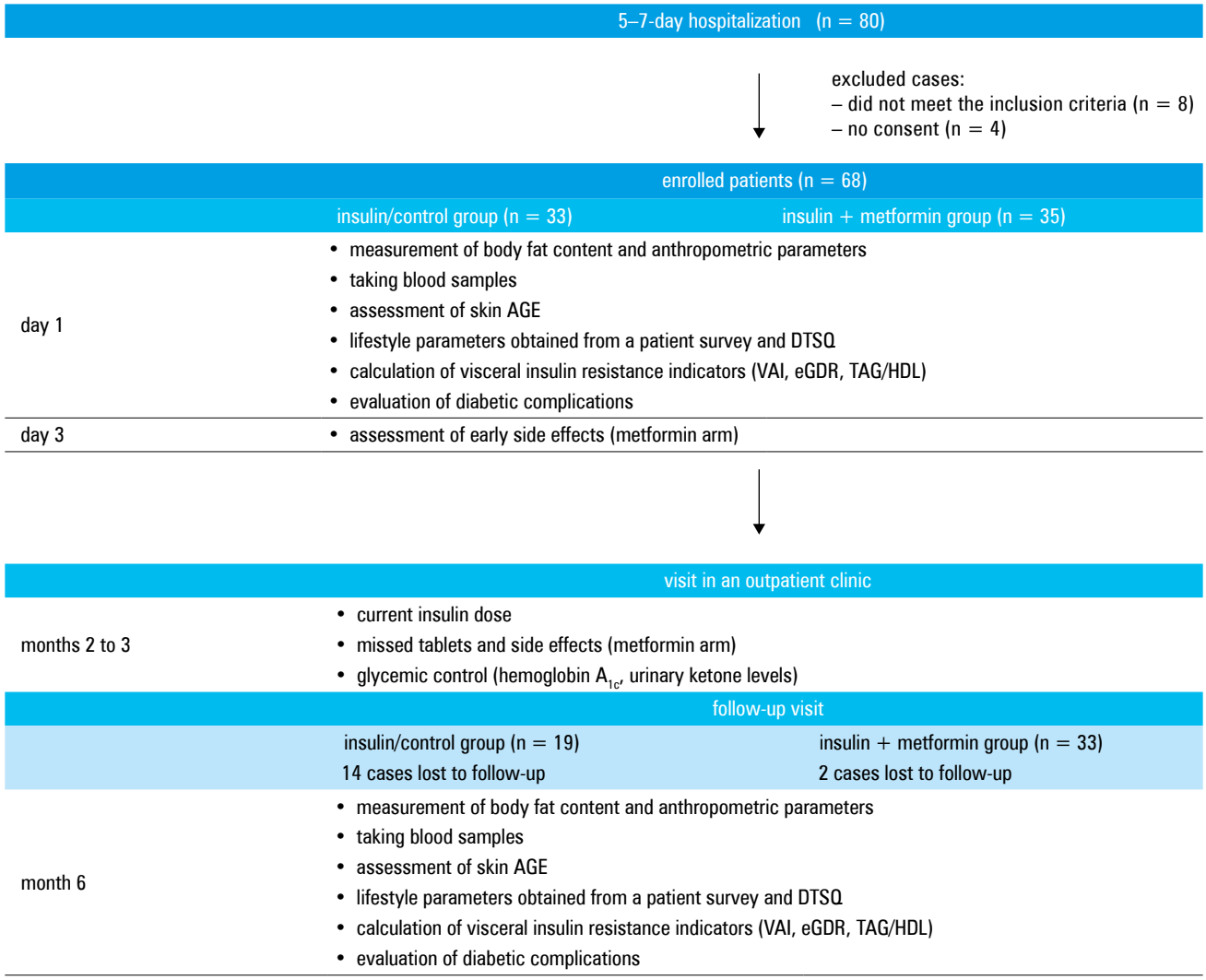

FIGURE 1 Study algorithm
Abbreviations: AGE – advanced glycation end product, DTSQ – Diabetes Treatment Satisfaction Questionnnaire, eGDR – estimated glucose disposal rate, TAG/HDL – ratio of triglicerides to high-density lipoprotein, VAI – visceral adiposity index

impaired glucose metabolism (prediabetes) have their glycemic parameters strictly controlled as a major way to improve their lipid profile.[4] A different approach is recommended based on the underlying pathophysiology. In insulin deficiencies (type 1 diabetes), supplementation of insulin is the therapy of choice. In diabetes with impaired insulin sensitivity, the initial treatment includes agents that increase tissue sensitivity to insulin, such as biguanides (metformin).[5] In addition, metformin inhibits the absorption of carbohydrates from the digestive tract and hormone-sensitive lipase in the adipose tissue, endogenous synthesis of triglycerides in the liver, and has a desired effect on the serum lipid profile.[1] Although there are no doubts about the benefits of this treatment in patients with type 2 diabetes,[6-8] little is known about the effects of metformin on lipid profile in patients with type 1 diabetes.[9] The aim of our study was to assess the effect of combination therapy with metformin/insulin vs. insulin alone on the lipid profile (total cholesterol, LDL and HDL cholesterol, triglycerides) and the pool of atherogenic oxidized and glycated LDL among young patients with type 1 diabetes and concomitant obesity.

PATIENTS AND METHODS

This prospective randomized study was conducted in a group of 68 patients with type 1 diabetes, of whom 52 completed the study (27 women and 25 men; mean age, 33.6 ±11.1 years). Patients were treated in the years 2010 and 2011 at the Department of Diabetology, Poznan University of Medical Sciences, Poznań, Poland. All patients had type 1 diabetes diagnosed by autoimmune antibodies and were treated with intensive insulin therapy. Thirty-three patients received metformin and insulin therapy (metformin group), while the remaining 19 patients were treated with insulin alone (control group).

The inclusion criteria were as follows: age between 18 and 60 years, duration of diabetes more than 5 years, lack of metabolic control (hemoglobin A_{1c} [HbA_{1c}] over 7.5% despite participation in the World Health Organization education program) and intensive insulin therapy.

The exclusion criteria were as follows: metabolically decompensate diabetes with acetonuria, suspected lack of compliance as well as glucose and ketone self-monitoring, hypoglycemic unawareness or recurrent severe hypoglycemia (defined as more than 2 episodes of hypoglycemia with

TABLE 1 Characteristics of the studied groups at the beginning of the study

Metabolic parameters at baseline	Combined therapy (metformin and insulin) n = 33	Control group (insulin only) n = 19	*P* value
age, y	35.3 ±11.2	30.5 ±10.6	0.3
BMI, kg/m^2	29.5 ±3.2	27.1 ±2.4	0.006
duration of diabetes, y	15.9 ±7.8	15.89 ±7.7	0.3
hypertension, %	45.5	47.3	0.9
hypothyroidism, %	12,1	21	0.4
smoking habits, %	12.1	21	0.4
neuropathy, %	12.1	15.8	0.8
retinopathy (proliferative and nonproliferative), %	39.4	41	0.9
statins, %	24.2	26.3	0.9
ACEIs, %	54.5	57.8	0.8
ALT, U/l	17 ±1.4	22.5 ±4.9	0.2
AST U/l	18 ±1.4	20 ±1.4	0.4
creatinine, mg/dl	1.0 ±0.1	0.9 ±0.1	0.8
ADPG, mg/dl	166.6 ±43.1	155.3 ±35.8	0.5
FPG, mg/dl	182.2 ±76.0	170.8 ±64.2	0.9
PPG, mg/dl	200.9 ±66.7	201.0 ±53.8	0.9
HbA_{1c}, %	9.0 ±1.9	8.3 ±1.0	0.2
HbA_{1c}, mmol/mol	75 ± (–3)	67 ± (–13)	0.2
total cholesterol, mg/dl	200 ±32.5	193.2 ±45.2	0.6
triglycerides, mg/dl	133.0 ±77.2	120.9 ±55.0	0.6
HDL cholesterol, mg/dl	57.2 ±15.8	61.4 ±11.9	0.2
LDL cholesterol, mg/dl	120.7 ±29.3	115.4 ±39.0	0.4
oxidized LDL, U/l	57.1 ±37.1	51.1 ±40.6	0.3
glycated LDL, mg/dl	1.6 ±1.6	1.2 ±0.6	0.5

Conversion factors to SI units are as follows: for glucose – 0.05551, cholesterol – 0.02586, and triglycerides – 0.0114

Abbreviations: ACEIs – angiotensin-converting-enzyme inhibitors, ADPG – average daily plasma glucose, ALT – alanine transaminase, AST – aspartate transaminase, BMI – body mass index, FPG – fasting plasma glucose, HbA_{1c} – hemoglobin A_{1c}, HDL – high-density lipoprotein, LDL – low-density lipoprotein, PPG – postprandial plasma glucose

glucose levels below 60 mg/dl accompanied by loss of consciousness requiring emergency treatment) in the past 3 months, recurrent diabetic ketoacidosis (more than 2 episodes in the past year), pregnancy or sexual activity in women who simultaneously refused to take birth control. Patients with renal impairment (based on the value of estimated glomerular filtration rate of less than 60 ml/min according to the Modification of Diet in Renal Disease formula) and liver disease (aminotransferases levels higher than twice the upper normal limit) were also excluded from the study.

Study design and protocol All patients were hospitalized for 1 week to optimize insulin therapy, conduct screening for complications, provide re-education, and assess patients' ability to comply with the study protocol. Then, therapy was introduced. An outcome visit was scheduled no earlier than after 6 months of treatment (FIGURE 1).

Ambulatory control visits were scheduled every 8 weeks of treatment. During control visits, patients returned pill containers and were asked about their current insulin dose, missed tablets, and side effects. Poor compliance was defined as the number of missed doses (above 15% of the total number of doses during the study) or more than 7 consecutive days without treatment.

It was an open-label study. The study protocol was not registered at clinicaltrials.gov and was not approved by the Institutional Review Board, but it was conducted according to the guidelines stated in the Declaration of Helsinki and was approved by the local bioethics commission. All subjects were informed about the aim of the study and gave their written consent.

Measurements of anthropometric and biochemical parameters were performed before starting metformin and at the end of the study, after 6 months of treatment. Metformin (at a mean dose of 1124.1 ±523.1 mg/d) was taken with meals to minimize gastrointestinal side effects. Individual doses were adjusted to body fat content. Overweight patients followed the regime of 500 to 1500 mg/d, and those with obesity took the dose of 1000 to 2550 mg/d according to drug tolerance. Patients were treated with the original metformin formulation.

Lifestyle parameters, including eating habits (daily intake of carbohydrate exchangers,

TABLE 2 Characteristics of the study groups at the end of the study

Metabolic parameters at the end of the study	Combined therapy (metformin and insulin) n = 33	Control group (insulin only) n = 19	*P* value
BMI, kg/m^2	28.9 ±3.2	27.3 ±2.9	0.08
ADPG, mg/dl	137.5 ±22.4	185.6 ±45.8	0.001
FPG, mg/dl	126.4 ±42.1	207.3 ±8.1	<0.001
PPG, mg/dl	136.3 ±41.6	170.6 ±73.9	0.23
HbA_{1c}, %	7.7 ±1.2	8.1 ±1.4	0.4
HbA_{1c}, mmol/mol	61 ±(–10)	65 ±(–8)	0.4
total cholesterol, mg/dl	192.9 ±34.6	185.8 ±34.7	0.41
triglycerides, mg/dl	112.0 ±67.9	80.4 ±32.2	0.04
HDL cholesterol, mg/dl	62.4 ±15.1	63.4 ±10.2	0.47
LDL cholesterol, mg/dl	112.1 ±32.2	111.3 ±32.9	0.84
oxidized LDL, U/l	51.2 ±40.5	46.0 ±39.9	0.52
reduction in oxidized LDL, U/l (oxidized LDL2 – oxidized LDL1)	–5.8 ±46.4	–5.1 ±25.2	0.79
glycated LDL, mg/dl	1.0 ±0.5	2.2 ±4.9	0.27
reduction in glycated LDL, mg/dl (glycated LDL2 – glycated LDL1)	–0.6 ±1.6	1.0 ±4.8	0.03

For conversion factors, see **TABLE 1**

Abbreviations: LDL1 – low-density lipoprotein at baseline, LDL2 – low-density lipoprotein at the end of the study, others – see **TABLE 1**

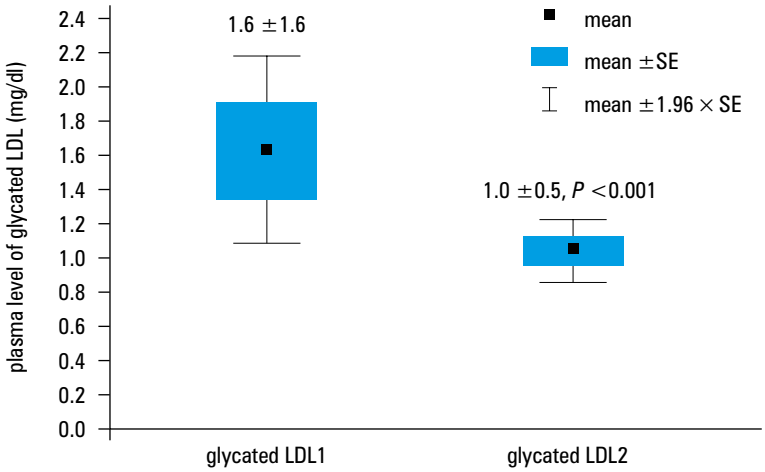

FIGURE 2 Plasma levels of glycated low-density lipoprotein in the group treated with combined therapy
Abbreviations: SE – standard error, others – see **TABLES 1** and **2**

frequency of meals) and exercise (type of exercise and weekly physical activity) were obtained using a patient survey. The systolic and diastolic blood pressures were recorded twice by the Korotkoff method in a sitting position after 5-minute rest.

The laboratory analyses were as follows: the fasting and postprandial (2 h) venous plasma glucose levels were assessed with routine laboratory tests; HbA_{1c} was measured using high-performance liquid chromatography. Quantitative assessment of alanine aminotransferase (ALT), aspartate aminotransferase (AST), triglycerides, total and HDL cholesterol was performed by the enzymatic colorimetric method using the Cobas 6000 system (Roche Diagnostics, Germany). LDL cholesterol levels were measured indirectly using the Freidewald formula (with its exceptions). Plasma samples were collected from patients after an overnight fast. Oxidized LDL was measured using the Mercodia kit (Sweden). The Glicacor kit (Exocell, United States) was used to determine glycated LDL levels. All laboratory tests were done at baseline and at 6 months. The average daily glucose levels were calculated with a 7-point glucose daily profile on the day before admission as well as at the control visit, measured by sensory technique using a patient's glucometer.

Statistical anlysis Normality was tested using the Shapiro–Wilk *W* test. For normal distribution of variables, the *t* test was used (for 2 independent and dependent variables). The Mann–Whitney *U* test (for 2 independent variables) and the Sign test as well as Wilcoxon matched pairs test (for 2 dependent variables) were used for nonnormal distribution of the variables. The results are presented as mean ± standard deviation (SD). To optimize the statistical analysis, we provided an additional parameter illustrating the reduction of glycated LDL, namely the ratio of glycated LDL2 to glycated LDL1, which in a multiple regression model were associated with the levels of fasting plasma glucose (FPG), postprandial plasma glucose (PPG), and average daily plasma glucose (ADPG) at baseline as well as with the differences in the above parameters during follow-up. A multivariate analysis was performed using logistic regression. The statistical significance was established when *P* value was less than 0.05. The statistical analysis was performed using the STATISTICA 8.0 software.

RESULTS Randomization was 1:1, but 2 patients in the metformin group and 14 in the control group were lost to follow-up (68 patients were recruited; 52 patients completed the study).

TABLE 3 Metabolic parameters during follow-up in the group with combined therapy

Study group (n = 33)	At baseline (n = 33)	At 6 months (n = 33)	*P* value
BMI, kg/m^2	29.5 ±3.2	28.9 ±3.2	0.005
ADPG, mg/dl	166.6 ±43.1	137.5 ±22.4	0.002
FPG, mg/dl	182.2 ±76.0	126.4 ±42.1	0.001
PPG, mg/dl	200.9 ±66.7	136.3 ±41.6	<0.001
HbA_{1c}, %	9.0 ±1.9	7.7 ±1.2	0.008
$HbA_{1c,}$ mmol/mol	75 ±(–3)	61 ±(–10)	0.008
total cholesterol, mg/dl	200 ±32.5	192.9 ±34.6	0.2
triglycerides, mg/dl	133.0 ±77.2	112.0 ±67.9	0.04
HDL cholesterol, mg/dl	57.2 ±15.8	62.4 ±15.1	0.1
LDL cholesterol, mg/dl	120.7 ±29.3	112.1 ±32.2	0.3
oxidized LDL, U/l	57.1 ±37.1	51.2 ±40.5	0.5

For conversion factors, see **TABLE 1**

Abbreviations: see **TABLE 1**

A total of 52 subjects (27 women; 25 men) with a body mass index (BMI) of 28.6 ±3.2 kg/m^2, HbA_{1c} of 8.7% ±1.7% (72 ± [–5] mmol/mol), FPG of 178.5 ±71.9 mg/dl, PPG of 201.0 ±62.2 mg/dl, and ADPG of 162.9 ±40.8 mg/dl were randomized into insulin/metformin and insulin groups (**TABLE 1**). There were no differences between the groups in terms of eating habits and physical activity profiles. Patients randomized to the metformin group initially differed from the subjects in the control group by a higher BMI. The results after 6 months of therapy are presented in **TABLE 2**.

A decrease in HbA_{1c} levels, FPG, PPG, triglycerides, glycated LDL (**FIGURE 2**), and BMI was observed in the metformin group during follow-up (**TABLE 3**). A similar decrease was not reported in the control group with the exception of a trend toward a reduction in triglyceride levels (120.9 ±55.0 mg/dl vs. 80.4 ±32.2 mg/dl, *P* = 0.059). A reduction in glycated LDL as well as the level of glycated LDL measured at the end of the study (the final result) were correlated with a decrease in PPC (r = –0.3 and r = –0.28, P <0.05, respectively). The ratio of glycated LDL (at the end of the study) per glycated LDL (at baseline) was significantly associated with the differences (between both time points) in PPG, –0.01805 (95% confidence interval [CI], 0.031 to –0.005) and ADPG, 0.026 (95% CI, 0.001–0.05).

A multivariate analysis (including age, statin use, BMI ratio [the ratio of BMI at the end of the study to BMI at baseline], LDL ratio, HBA_{1c} ratio), performed using logistic regression, confirmed that the reduction of glycated LDL was associated with the reduction of HBA_{1c} during follow-up (0.011; standard deviation, 0.006; Wald parametric test, 4.023; P = 0.045; Exp (B), 0.061).

During follow-up, a decrease in BMI, triglycerides, glycated LDL, ADPG, FPG, PPG, and HbA_{1c} was observed in the metformin group. Additionally, at this time point, there were significant differences in BMI and triglycerides between the metformin and control groups. Surprisingly, glycated LDL decreased only in the metformin group. On the other hand, oxidized LDL was not affected either by insulin or combined therapy.

DISCUSSION

The novelty of our study is the assessment of oxidized and glycated LDL and their comparison in obese patients with type 1 diabetes treated with metformin and insulin vs. insulin alone. This issue has been poorly documented in the literature.

The profiles of transported lipids in type 1 diabetes are characterized not only by their increased levels but also by aberrant patterns.[1,10-12] Exogenous insulin treatment, especially in obese patients with type 1 diabetes, may lead to insulin resistance.[9] In patients with type 2 diabetes, treatment with biguanides sensitizing cells to insulin led to a reduction of atherogenic lipid fractions.[8,13] The effects of biguanides in type 1 diabetes were also investigated in numerous trials.[9,14] However, there are only few reports on the effect of insulin/metformin vs. insulin alone on plasma lipoprotein levels in obese patients with type 1 diabetes,[9] and the results from those studies are inconclusive. The different levels of mean blood glucose, FPG, and PPG between the compared groups were the major confounding factor. Differences in glucose levels may affect plasma lipoprotein concentrations.[1] Furthermore, the differences between the groups that received hypolipidemic pharmacotherapy should also be considered. In our study, the groups were not different in terms of lipid parameters at baseline. Subjects who required lipid-lowering treatment continued it with unchanged regimen during the 6 preceding months as well as during the study. At the end of the study, triglycerides and glycated LDL (final result) were decreased in patients treated with insulin/metformin in contrast to those who received only insulin. In addition, all subjects showed a reduction of glycated LDL, triglycerides, and BMI during follow-up as a result of combined therapy. This was due to metformin-mediated reduction of the body weight and improved glucose control (decrease

of FPG, PPG, ADPG, and HbA_{1c} in the metformin group). To explain this, we should compare patients with the same absolute reduction in FPG, PPG, ADPG, and HbA_{1c} from the metformin vs. control groups. Unfortunately, the small number of subjects undermines the reliability of such comparison. However, we provided the ratio of glycated LDL (at the end of the study) to glycated LDL (at baseline), which was significantly associated with the absolute reduction of PPG or ADPG in the entire study population. Thus, it cannot be excluded that the absolute decrease in glycated LDL in the group treated with combined therapy may depend on the absolute reduction of plasma glucose, an effect which was not observed in the group treated with insulin alone. This was confirmed in a multivariate analysis. Logistic regression indicated lower ratio of HBA_{1c} at the end of the study to HBA_{1c} at baseline (reduction of HBA_{1c} during follow-up) as an important, independent, and the only factor responsible for the reduction of glycated LDL (among other parameters described in the Results section).

Finally, it cannot be excluded that the reduction of glycated LDL levels is a direct consequence of metformin use, which results in the lowering of the pool of triglycerides transported by LDL, thus leading to an improvement in the lipid profile. This effect has been proposed previously and remains highly debatable.[15,16]

A reduction in oxidized LDL was not observed in any of the groups, also in comparison with the baseline values. This is particularly disappointing, especially in the metformin group, considering the antioxidative properties of metformin.[17]

Both glycated and oxidized LDL are highly atherogenic.[18,19] Therefore, type 1 diabetic patients treated with combined therapy who have lower levels of glycated LDL and unchanged levels of oxidized LDL compared with subjects receiving insulin monotherapy should have slower progression of atherogenesis, lower cardiac risk, and fewer cardiac events. For this reason, those patients should have the benefit of combined metformin/insulin therapy. We are aware of several study limitations, which are mainly related to the size of the study groups as well as a considerable dropout rate. There may also be errors in the measurement of plasma lipoproteins. However, this study represents a pioneering endeavor in terms of research into the synergistic effect of combined metformin/insulin therapy compared with insulin monotherapy on the plasma levels of oxidized and glycated LDL in type 1 diabetic patients with concomitant obesity.

To summarize our findings, during follow-up, we observed a decrease in triglycerides, BMI, and glycated LDL in subjects treated with insulin and metformin. We conclude that this effect was caused by better glycemic control and an increase in tissue insulin sensitivity among patients treated with metformin as concomitant medication. A significant decrease in oxidized LDL levels in both study groups was not observed. To confirm the results of this study, a large clinical trial is required.

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ARTYKUŁ ORYGINALNY

Dodanie metforminy do stosowanej intensywnej insulinoterapii u młodych otyłych pacjentów z cukrzycą typu 1 powoduje spadek stężeń glikowanych lipoprotein o małej gęstości (ale nie oksydowanych lipoprotein o małej gęstości) w porównaniu z leczeniem wyłącznie insuliną: badanie pilotowe

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SŁOWA KLUCZOWE

cukrzyca typu 1,
metformina,
metabolizm lipidów

STRESZCZENIE

WPROWADZENIE Niewiele jest danych dotyczących wpływu metforminy na profil lipidowy pacjentów chorujących na cukrzycę typu 1.

CELE Badanie jest pierwszą prospektywną próbą kliniczną oceniającą wpływ łączonej terapii metforminą wraz z insuliną na pulę oksydowanych oraz glikowanych lipoprotein o małej gęstości (*low-density lipoprotein* – LDL) u młodych pacjentów z cukrzycą typu 1 i współistniejącą otyłością.

PACJENCI I METODY 33 otyłych pacjentów z cukrzycą typu 1, leczonych intensywnie insuliną, przydzielono losowo do grupy dodatkowo otrzymującej metforminę. U pozostałych 19 pacjentów kontynuowano intensywną insulinoterapię (grupa kontrolna). U wszystkich pacjentów oznaczano profil lipidowy i badano glikemię za pomocą rutynowo stosowanych technik laboratoryjnych. Oksydowane i glikowane LDL oznaczano za pomocą zestawów komercyjnych. Oznaczeń laboratoryjnych dokonywano na początku badania oraz na wizycie kontrolnej, po 6 miesiącach leczenia.

WYNIKI W grupie leczonej insuliną i metforminą stwierdzono istotne zmniejszenie poziomów glikowanej hemoglobiny, glikemii na czczo, glikemii poposiłkowej, średniej glikemii, triglicerydów, glikowanych LDL i wskaźnika masy ciała. Nie obserwowano podobnego efektu w grupie kontrolnej. W trakcie badania pozostałe paramtery lipidowe nie ulegały zmianie w żadnej z grup.

WNIOSKI Dodanie metforminy do intensywnej insulinoterapii u młodych otyłych pacjentów z cukrzycą typu 1 powoduje istotne zmniejszenie stężeń glikowanych LDL. Prawdopodobnie efekt ten należy tłumaczyć lepszą kontrolą glikemii, przekładającą się na poprawę insulinowrażliwości tkanek obwodowych i redukcję masy ciała w tej grupie chorych.

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