ORIGINAL ARTICLE

Association between adjunctive metformin therapy in young type 1 diabetes patients with excess body fat and reduction of carotid intima–media thickness

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KEY WORDS

cholesteryl ester lipase, lipoprotein associated phospholipase A_2, metformin in type 1 diabetes

ABSTRACT

INTRODUCTION Lipoprotein-associated phospholipase A_2 (Lp-PLA_2) and cholesteryl ester lipase (CEL) may oxidize low-density lipoproteins (oxLDL).

OBJECTIVES The aim of the study was to determine the influence of metformin on the metabolism of atherogenic lipid fractions in relation to Lp-PLA_2 and CEL levels, as well as assess consequent improvement in the intima–media thickness (IMT) of the common carotid artery in young type 1 diabetes patients with excess body fat.

PATIENTS AND METHODS It was an open-label randomized clinical trial that lasted 6 months. It included a total of 84 people with metabolic decompensation (glycated hemoglobin >7.5%, >58.5 mmol/mol) of diabetes. Adjunctive metformin therapy (in addition to insulin) was administered in 42 patients, and the remaining 42 patients received insulin alone. Glycated low-density lipoproteins (LDLs), oxLDL, Lp-PLA_2, and CEL were assessed by commercially available enzyme-linked immunosorbent assay kits. Cartoid IMT was measured using the Carotid Analyser for Research tool. Biochemical analyses were performed using routine laboratory techniques.

RESULTS The reduction of mean carotid IMT was observed in young type 1 diabetic adults treated additionally with metformin (0.6 ±0.1 cm vs 0.53 ±0.1 cm; $P = 0.002$). This effect was probably due to weight reduction (90 ±16 kg vs 87 ±15 kg, $P = 0.054$) and the decrease in atherogenic glycated LDL levels (1.5 ±0.5 mg/dl vs 1.6 ±1.046 mg/dl, $P = 0.006$). No such correlations were observed in patients treated with insulin alone. Additionally, in patients receiving metformin, glycated LDL levels were inversely correlated with Lp-PLA_2 levels ($r = –0.31$, $P < 0.05$).

CONCLUSIONS Additional use of metformin in young type 1 diabetic patients with excess body fat leads to a significant reduction of mean IMT in the common carotid artery. Concentrations of CEL and Lp-PLA_2 were significantly increased in both study arms despite improved glucose metabolism.

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Received: May 12, 2016.
Revision accepted: June 23, 2016.
Published online: August 25, 2016.
Conflict of interest: none declared.
Pol Arch Med Wewn. 2016;
126 (7-8): 514-520
doi:10.20452/pamw.3527

INTRODUCTION Our previous article[1] was one of the first to describe the benefits of metformin use in young type 1 diabetes patients with excess body fat. After a 6-month follow-up, we observed an improvement in lipid metabolism as well as a reduction in hemoglobin A_{1c} (HbA_{1c})

concentrations and daily insulin use. These findings appear to be validated by the results obtained in large-population studies, as described by other authors.[2-4] However, a number of questions still remain, since it is also suggested that such therapy is insufficient for proper, long-term glucose control.[5]

Lipoprotein phospholipase A_2 (Lp-PLA_2) is carried by various plasma lipoproteins, namely, low-density lipoproteins (LDLs), and has the capacity to hydrolyze phospholipids in sn-2 position into long acyl chains and proatherogenic phosphatidylcholine.[6-9] Once oxidized and combined with phosphatidylcholine, the acyl chains constitute proinflammatory triggers.[6-9] Due to the outlined properties, Lp-PLA_2 was associated in a number of statin trials with higher cardiovascular risk, which led to an investigation of their role in the development of atherosclerotic plaque in several studies.[6] On the other hand, several clinical trials have been initiated to inhibit Lp-PLA_2 in patients with angina to reduce lipid oxidation and atherosclerotic burden. Both studies failed owing to lack of clinical significance.[6,7]

Cholesteryl ester lipase (CEL) is another lipase that may be involved in the atherosclerotic process, but its role remains unknown. It is known that it can oxidize LDLs (oxLDLs) as well as hydrolyze proatherogenic ceramides.[8-10]

In our previous research, we did not observe any effect of adjunctive metformin use (in young type 1 diabetes patients treated with insulin) on the amount of oxLDL. Also, we had no possibility of determining any relationship between these treatments and cardiovascular risk.

In our current study, we aimed to determine the influence of additional metformin use in young type 1 diabetes patients with excess body fat on the concentrations of atherogenic lipid fractions, with particular focus on the activity and the amount of Lp-PLA_2 and CEL. We also aimed to find a possible link between additional metformin use and the intima–media thickness (IMT) of the common carotid artery in this population of patients.

PATIENTS AND METHODS

The study protocol was registered at clinicaltrials.gov (NCT01889706) and approved by an institutional review board. It was conducted in accordance with the guidelines stated in the Declaration of Helsinki and received approval from a local bioethics committee. All subjects were informed about the aim of the study and gave their written informed consent.

It was an open-label, prospective, randomized study of 6-month duration. A total of 84 people with metabolic decompensation (HbA_{1c} >7.5%, >58.5 mmol/mol) of type 1 diabetes were included. Type 1 diabetes was diagnosed according to the 2010 American Diabetes Association criteria and the presence of positive autoimmune antibodies. All patients underwent intensive insulin treatment. The main inclusion criterion was excess body fat diagnosed by electric bioimpedance (Tanita BC418MA device, Tanita Corporation of America, Inc., Arlington Heights, Illinois, United States). Reference body fat level was estimated according to the guidelines by Gallagher et al.[11]

A total of 42 patients were randomized to the arm receiving adjunctive metformin at a dose of 1000 ±500 mg/d (insulin-plus-metformin group). The control group comprised another 42 people randomly assigned to the insulin-only arm (control group, insulin group).

The study was introduced after screening hospitalization, where optimization (screening for complications, re-education in diabetes self-care, and assessment of patients' ability to comply with the study protocol) of the therapy was performed. The outcome visit was conducted no earlier than after 6 months of treatment.

During follow-up visits, taking place every 8 weeks, information was collected concerning insulin dosage, number of returned pill containers, as well as missed tablets and side effects. Measurements of anthropometric and biochemical parameters were performed as described previously.[1]

The IMT of the right common carotid artery was determined using high-resolution ultrasonography (Accuson Cv 70, Siemens, Erlangen, Germany) with a 10-MHz transducer. One longitudinal anterolateral projection was assessed. Images were captured at 16 frames per second for 5 seconds. The distal 1 cm of the common carotid artery just proximal to the bulb was measured and calculated automatically using the Carotid Analyzer for Research (CAD 5) program (Medical Imaging Applications LLC, Coralville, Iowa, United States). The result was the average of 100 automated computer measurements. IMT measurements were blinded with respect to patients' names and the study group.

Inclusion criteria

Inclusion criteria required subjects to be aged between 18 and 60 years, have at least a 5-year history of diabetes, HbA_{1c} levels over 7.5% (>58.5 mmol/mol) despite previous participation in the World Health Organization education program, and undergo intensive insulin therapy.

Exclusion criteria

Potential subjects were excluded if any of the following had been observed: decompensation of diabetes with acetonuria, hypoglycemic unawareness or recurrent severe hypoglycemia in the past 3 months, recurrent diabetic ketoacidosis (more than 2 episodes in the past year), and pregnancy or sexual activity in women who refused to take birth control. Additionally, patients with renal impairment (with glomerular filtration rate below 60 ml/min/1.73 m^2, as estimated by the Modification of Diet in Renal Disease formula) and elevated aminotransferase levels (more than twice the upper normal limit).

Laboratory tests

Laboratory tests were performed using routine laboratory techniques, as described in our previous article.[1] Plasma samples

TABLE 1 Characteristics of the study group

Parameter	All patients (n = 84)	Metformin + insulin (n = 42)	Insulin alone (n = 42)
male, %	54	45	68
age, y	33.2 ±11.5	35.2 ±11.0	31.2 ±11.7
weight, kg	85.4 ±13.3	90 ±15	80.9 ±9.7
total cholesterol, mg/dl	199.9 ±41.7	204 ±31.5	195.3 ±51
triglycerides, mg/dl	121.2 ±64.3	130.1 ±72	111.9 ±54.4
HDL cholesterol, mg/dl	59.7 ±15.4	56 ±12.6	63.4 ±17
LDL cholesterol, mg/dl	121.1 ±37.7	122.2 ±31.9	119.9 ±43.3
non-HDL, mg/dl	142.2 ±40.1	150.5 ±35.6	126.1 ±44.3
HbA_{1c}, %, mmol/mol	8.5 ±1.7, 69 ±(–5)	8.6 ±1.7, 70 ±(–5)	8.5 ±1.7, 69 ±(–5)
FPG, mg/dl	177.3 ±71.3	177.9 ±65.7	176.8 ±77.3
PPG, mg/dl	189.8 ±61.9	197.7 ±57.6	181.9 ±65.7
average glycemia, mg/dl	158.5 ±36.2	162.7 ±36.1	154.3 ±36.3
dose of insulin at baseline, units	51.0 ±16.5	56.2 ±19	45.9 ±11.7
dose of insulin/body weight/day, units/kg/24 h	0. 6 ±0.16	0.6 ±0.19	0.56 ±0.13
carotid IMT, cm	0.56 ±0.12	0.59 ±0.1	0.53 ±0.13
hypertension, %	37	45	30
dyslipidemia, %	10.4	7.1	13
statin use, %	10.4	7.1	6.8

Data are presented as mean ± SD unless otherwise stated.

Conversion factors to SI units are as follows: for LDL, HDL, non-HDL, and total cholesterol [mg/dl]/38,67 = [mmol/l], for triglicerydes [mg/dl]/88.57 = [mmol/l]

Abbreviations: FPG, fasting plasma glucose; HbA_{1c}, glycated hemoglobin; HDL, high-density lipoprotein; IMT, intima–media thickness; LDL, low-density lipoprotein; PPG, postprandial glycemia

TABLE 2 Differences between patients randomized to the insulin-plus-metformin treatment versus those receiving insulin alone

Parameter	Metformin + insulin (n = 42)	Insulin alone (n = 42)	*P* value
CEL, pg/ml	117.1 ±33	46.1 ±26.9	<0.001
non-HDL, mg/dl	150.5 ±35.6	126.1 ±44.3	0.05
dose of insulin at baseline, units	56.2 ±19	45.9 ±11.7	0.003
weight, kg	90 ±15	81 ±9.7	0.001
maximum carotid IMT, cm	0.6 ±0.1	0.53 ±0.1	0.02

Data are presented as mean ± SD.

Abbreviations: CEL, cholesteryl ester lipase; others, see TABLE 1

were collected from patients after an overnight fast. Glycated LDL, oxLDL, Lp-PLA_2, and CEL were assessed using commercially available enzyme-linked immunosorbent assay kits: Glicacor (Exocell, Philadelphia, Pennsylvania, United States), Mercodia Kit (Uppsala, Sweden), as well as CEL and Lp-PLA_2 (Cusabio Biotech, Wuhan, China), respectively.

Statistical analysis Normality was tested by means of the Shapiro–Wilk test. The *t* test was used for variables with normal distribution (for 2 independent and dependent variables). Mann–Whitney test (for 2 independent variables) as well as the Sign test and Wilcoxon matched-pair test (for 2 dependent variables) were applied for variables with nonnormal distribution. The results were presented as mean ± SD. Statistical significance was established at a *P* value of less than 0.05. Statistical analysis was performed using the STATISTICA 8.0 software (Dell Statistica,Tulsa, Oklahoma, United States).

RESULTS The study included 84 patients (47 men, 37 women) at a mean age of 33.2 ±11.5 years. The characteristics of the group are shown in TABLE 1. Baseline differences between patients randomized to the insulin-plus-metformin arm

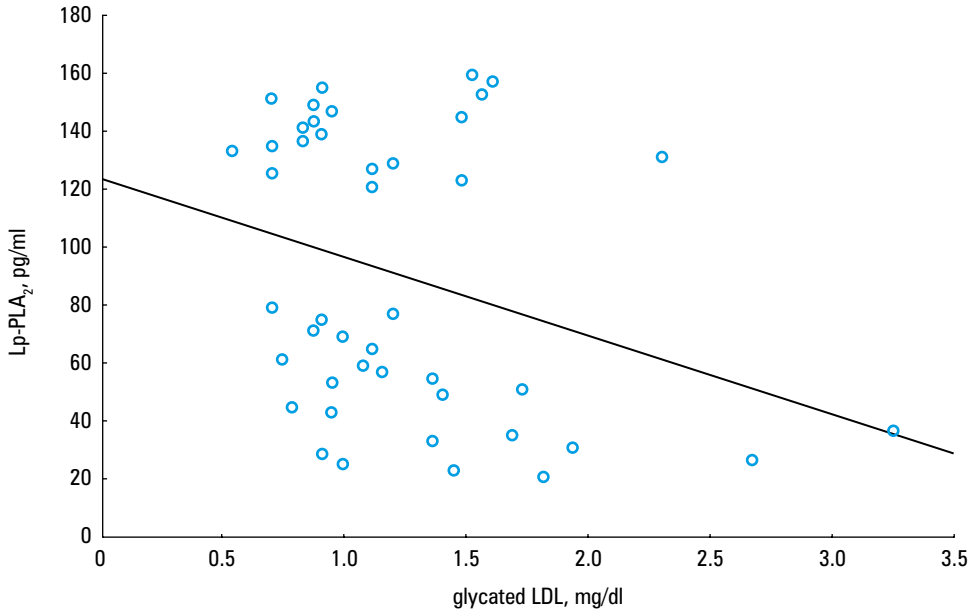

FIGURE 1 Significant inverse correlation between the concentrations of glycated low-density lipoprotein (LDL) and amount of lipoprotein-associated phospholipase A_2 (Lp-PLA_2) ($r = -0.31$; $P < 0.05$)

and those receiving insulin alone are presented in TABLE 2. The groups did not differ significantly in terms of age and duration of diabetes.

After 6 months of adjunctive metformin therapy, we observed a significant increase in the levels of CEL (117.1 ±33 pg/ml vs 118.2 ±33 pg/ml; $P < 0.001$), Lp-PLA_2 (82.4 ±45.6 pg/ml vs 83.4 ±45.6 pg/ml; $P < 0.001$), and a reduction in the levels of glycated LDL (1.5 ±1.6 mg/dl vs 1.0 ±0.5 mg/dl; $P = 0.006$) and triglycerides (130.1 ±72 mg/dl vs 105.5 ±65.2 mg/dl; $P < 0.001$). Furthermore, a reduction in the thickness of the carotid IMT (0.6 ±0.1 mm vs 0.53 ±0.1 mm; $P = 0.002$) was noticed. Simultaneously, we observed a significant improvement in fasting glucose levels (177.9 ±65.7 mg/dl vs 123.8 ± 38.3 mg/dl; $P < 0.001$), postprandial glycemia (197.7 ±57.6 mg/dl vs 133.9 ±44.4 mg/dl; $P < 0.001$), average glycemia (162.8 ±36.1 mg/dl vs 134.6 ±19.8 mg/dl; $P < 0.001$) and HbA_{1c} (8.6% ±1.8% vs 7.6% ±1.2%; 70 ±[–3.8] mmol/mol vs 60 ±[–10.4] mmol/mol; $P < 0.001$). However, it needs to be noted that the latter results will be addressed in detail in a different publication. No effect of metformin on LDL or non-high-density lipoprotein (HDL) concentrations was observed, although we noticed a trend towards increased HDL cholesterol levels (56 ±12.6 mg/dl vs 60.9 ±12.9 mg/dl; $P = 0.07$) and reduced body weight (90 ±15 kg vs 87 ±15 kg; $P = 0.054$).

After 6 months of follow-up in the insulin group, we observed a significant increase in the levels of CEL (46.1 ±26.9 pg/ml vs 47.1 ±26.9 pg/ml; $P < 0.001$), Lp-PLA_2 (78.7 ±47.9 pg/ml vs 114.5 ±242.4 pg/ml; $P < 0.001$) HDL cholesterol (62.8 ±16.6 mg/dl vs 67.8 ±15.4 mg/dl; $P = 0.02$), and a reduction in triglyceride levels (112.4 ±55 mg/dl vs 97.8 ±69.1 mg/dl; $P = 0.025$). In addition, we noticed an increase in the maximum IMT of the common carotid artery (0.53 ±0.14 cm vs 0.55 ±0.14 cm; $P < 0.001$). There was no significant reduction in HbA_{1c} concentrations, fasting plasma glucose levels, or postprandial glycemia. The mean glucose level was increased (154.3 ±65.6 mg/dl vs 185.9 ±42.1 mg/dl; $P < 0.001$). No effects of insulin therapy on the levels of LDL, non-HDL, total cholesterol, and oxLDL or on body weight were determined.

At the end of the follow-up, the study groups differed with respect to the extent of body weight reduction (insulin-plus-metformin, 1.7 ±4 kg; insulin, 0.4 ±10.4 kg; $P = 0.005$), IMT reduction (insulin-plus-metformin, 0.030 ±0.056 cm; insulin, 0.042 ±0.124 cm; $P < 0.001$), as well as in terms of CEL concentrations (insulin-plus-metformin, 118.1 ±33 pg/ml; insulin, 47.1 ±26.9 pg/ml), fasting plasma glucose (insulin-plus-metformin, 123.8 ±38.3 mg/dl; insulin, 194.6 ±77.5 mg/dl; $P < 0.001$), and mean glycemia concentrations (insulin-plus-metformin, 134.6 ±19.8 mg/dl; insulin, 185.9 ±42.1 mg/dl; $P < 0.001$).

There was a significant inverse correlation between glycated LDL and Lp-PLA_2 levels ($r = -0.31$; $P < 0.05$) (FIGURE 1) in the metformin-plus-insulin group, and a correlation between CEL and Lp-PLA_2 concentrations in the insulin group ($r = 0.33$, $P < 0.05$).

DISCUSSION Biguanides sensitize body cells to insulin, which may cause a reduction of atherogenic lipid fractions in patients with type 2 diabetes.[12-14] Still, very few reports have addressed the effect of metformin on plasma lipoprotein concentrations in obese patients with type 1 diabetes.[15] In the current study, we found that young overweight and obese patients with type 1 diabetes who received adjunctive metformin therapy had improved glycemic control, better tissue sensitivity to insulin, and reduced number of glycated LDLs in comparison with subjects treated with insulin alone. These results (obtained from a larger study group of subjects) corroborate the conclusions of our previous research. In both studies, metformin administration did not affect the levels of oxLDL. However, antioxidative properties

of the drug came as a surprise.[14] This finding interested us in the context of the metabolic effect of metformin and its potential impact on enzymes, which are known to be most likely involved in oxidative modification of LDL.[6-10,16] Likewise, the role of these enzymes in the process of atherosclerosis is still poorly understood. The objective of this study was also influenced by the fact that similar data concerning the dependencies between the use of metformin and CEL and Lp-PLA_2 levels are lacking, not only with respect to young type 1 diabetes patients, but also to any patient population.

Initially, we noticed much higher levels of CEL in patients randomized for treatment with insulin and metformin than in subjects who would receive insulin alone. This phenomenon is difficult to explain. However, one must bear in mind the genetic variability of the CEL gene.

Additionally, the mutagenesis of the CEL gene may cause an exocrine pancreatic insufficiency combined with diabetes: MODY8.[17,18] Therefore, it cannot be excluded that the insulin-only arm was characterized by such etiology of diabetes. This conclusion is only a speculation because the CEL gene analysis was not performed, even though the autoimmune etiology of diabetes was confirmed. Laboratory error may also account for substantial discrepancies in enzyme levels between the studied groups, notwithstanding the fact that CEL and LPA_2 assessments were performed by one technician using the same enzyme-linked immunosorbent assay kits under the same conditions.

Finally, the causes behind the phenomenon may lie in the simple progression of atherosclerosis (which would contradict further conclusions below), because both study groups had high or very high cardiovascular risk.

In the follow-up analysis performed after 6 months, a significant increase in CEL and Lp-PLA_2 concentrations was observed in each of the studied groups. This was accompanied by a varying degree of improvement in glycemic control and reduction of LDL and triglyceride levels. After the said period, a significant decrease in maximum carotid IMT was only observed in patients who received adjunctive metformin treatment. In contrast, an increase in the IMT was observed in the insulin group. We can only speculate that this beneficial effect was secondary to weight reduction and significant decrease in glycated LDL concentration, which was noted exclusively among individuals receiving metformin.

Glycated LDL is an LDL particle formed via the interaction of LDL with advanced glycation end products.[19] In experimental diabetic mouse models, glycated LDL may stimulate endoplasmic reticulum stress (which is associated with insulin resistance and diabetic cardiovascular complications) as a response to chronic hyperglycemia.[19] Glycated LDL in people with diabetes is therefore widely regarded as a particle with high proatherosclerotic activity.[20] Lowering glycated LDL levels reduces the inhibition of endothelial nitric oxide synthase. Consequently, it improves endothelial function and is considered by many authors to have antiatherogenic properties.[21] The reduction of the IMT in the metformin group should therefore be considered as a secondary effect to a decrease of glycated LDL levels. It remains unclear why a 6-month adjunctive metformin treatment led to an increase in the levels of enzymes responsible for the oxidative modification of LDL. Additionally, CEL and Lp-PLA_2 levels in these groups were significantly higher than in subjects treated only with insulin. Finally, an inverse correlation between serum levels of Lp-PLA_2 and glycated LDL was found in the metformin group. It was observed that the lower the levels of glycated LDL, the higher the amount of Lp-PLA_2. No equivalent data for patients with type 1 diabetes can be found in the literature published so far. In turn, one of the very few reports concerning observations among patients with type 2 diabetes stated that the concentration of Lp-PLA_2 is directly proportional to the amount of glycated LDLs, as well as oxidized and small dense LDL particles.[22] Our observations are thus contrary to previous findings. It is likely that our results may be further clarified by extrapolating data on pathophysiological characteristics of lipoprotein lipase. Plasma expression of this enzyme is reduced in diabetes, contributing to significant disturbances in LDL metabolism and accelerating the degradation of HDL.[23-25] Improvement in glycemic control increases the activity and the amount of lipase, while improving the lipoprotein plasma profile.[23,24] Lp-PLA_2 is an isoenzyme for lipoprotein lipase, and we may only speculate that it may be subject to similar processes.

The treatment of diabetes in both groups did not have a significant effect on the concentration of oxLDL. However, there was a tendency for oxLDL to decrease slightly in the metformin group in comparison to the insulin group where the concentration of oxLDL increased.

Our observations indicate a positive effect of 6-month metformin administration on the metabolism of most atherogenic lipid fractions in type 1 diabetes patients with excess body fat, with a clinical exponent of reduction in the maximum carotid IMT. It should be noted that those patients who required lipid-lowering therapy had been undergoing the therapy prior to and during the 6 months of the study, so this factor probably had a minor effect on the results. In addition, at the beginning of the study, there were no significant differences between the groups in the use of lipid-lowering therapy. We did not observe any episodes of hypoglycemia nor digestive side effects in the metformin group.

The primary limitation of the study is that only one center was involved,[26] and the study group was relatively small. On the other hand, systematic error was minimized due to the fact that all analyses were performed by the same person using the same methods and the same equipment.

In conclusion, adjunctive use of metformin in young people with type 1 diabetes and excess

body fat leads to a reduction in the IMT of the common carotid artery. This effect is probably due to the improvement of glucose metabolism, weight reduction, and the reduction of atherogenic plasma lipoprotein levels. Glycated LDL levels were inversely correlated with the concentration of Lp-PLA_2. The latter observation requires further clarification from biochemical and clinical points of view, as it has not been previously described in the literature.

Contribution statement PB and AZ contributed to conception, analysis, interpretation, and draft of the manuscript. DN and DZ-Z contributed to design, data analysis and interpretation, as well as critically revised the manuscript. JK and JM contributed to laboratory analyses. HW, BW-W, MG, and JR contributed to data interpretation and critically revised the manuscript.

Acknowledgments The project was supported by statutory funds (No. 502-01-023482-00-274; to BW-W) and the Poznan University of Medical Sciences. Special thanks to A. Wisniecki, K. Kempa, and S. Nowak for language and editing service.

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ARTYKUŁ ORYGINALNY

Związek między dodatkowym zastosowaniem metforminy u młodych pacjentów z cukrzycą typu 1 i nadmiarem tkanki tłuszczowej a zmniejszeniem grubości kompleksu błony środkowej i wewnętrznej w tętnicy szyjnej

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SŁOWA KLUCZOWE

fosfolipaza A_2 związana z lipoproteinami, lipaza estrów cholesterolowych, metformina w cukrzycy typu 1

STRESZCZENIE

WPROWADZENIE Fosfolipaza A_2 związana z lipoproteinami (*lipoprotein-associated phospholipase* A_2 – Lp-PLA_2) oraz lipaza estrów cholesterolowych (*cholesteryl ester lipase* – CEL) mogą utleniać lipoproteiny o małej gęstości (*oxidized low-density lipoprotein* – oxLDL).

CELE Celem badania było określenie wpływu metforminy zastosowanej u młodych pacjentów z cukrzycą typu 1 i nadmiarem tkanki tłuszczowej na metabolizm aterogennych frakcji lipidowych za pomocą oceny stężeń Lp-PLA_2 i CEL oraz ocena poprawy grubości kompleksu błony środkowej i wewnętrznej (*intima–media thickness* – IMT) w tętnicy szyjnej wspólnej.

PACJENCI I METODY Badanie miało charakter otwartej, randomizowanej próby klinicznej i trwało 6 miesięcy. Do badania włączono łącznie 84 osoby, u których stwierdzono metaboliczną dekompensację cukrzycy (glikowana hemoglobina >7,5%, >58,5 mmol/mol). U 42 chorych oprócz insuliny zastosowano dodatkowo metforminę, u kolejnych 42 pacjentów podawano wyłącznie insulinę. Stężenia glikowanego LDL, oxLDL, Lp-PLA_2 i CEL oceniano za pomocą komercyjnie dostępnych testów immunoenzymatycznych. IMT w tętnicy szyjnej mierzono za pomocą programu Carotid Analyser for Research. Parametry biochemiczne analizowano za pomocą rutynowych technik laboratoryjnych.

WYNIKI U młodych pacjentów z cukrzycą typu 1 stosujących metforminę obserwowano zmniejszenie średniej grubości IMT w tętnicy szyjnej wspólnej (0,6 ±0,1 cm *vs* 0,57 ±0,1 cm; p = 0,002). Efekt ten był najprawdopodobniej spowodowany redukcją masy ciała (90 ±16 kg *vs* 87 ±15 kg; p = 0,054) i zmniejszeniem stężenia aterogennego glikowanego LDL (1,5 ±0,5 mg/dl *vs* 1,6 ±1,046 mg/dl; p = 0,006). Podobnej zależności nie obserwowano u osób, u których stosowano tylko insulinę. Dodatkowo u pacjentów leczonych łącznie metforminą i insuliną stwierdzono ujemną korelację stężeń glikowanego LDL ze stężeniami Lp-PLA_2 (r = –0,31; p <0,05).

WNIOSKI Dodatkowe zastosowanie metforminy u młodych pacjentów z cukrzycą typu 1 i nadmiarem tkanki tłuszczowej prowadzi do zmniejszenia maksymalnego IMT w tętnicy szyjnej wspólnej. W obu badanych grupach stężenia CEL i Lp-PLA_2 istotnie wzrastały pomimo wyrównania metabolicznego cukrzycy.

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Praca wpłynęła: 12.05.2016.
Przyjęta do druku: 23.06.2016.
Publikacja *online*: 25.08.2016.
Nie zgłoszono sprzeczności interesów.
Pol Arch Med Wewn. 2016; 126 (7-8): 514-520
doi:10.20452/pamw.3527