ORIGINAL ARTICLE

Metformin added to intensive insulin therapy improves metabolic control in patients with type 1 diabetes and excess body fat

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KEY WORDS

insulin resistance, metformin, obesity, type 1 diabetes

ABSTRACT

INTRODUCTION Bad nutritional habits and administration of insulin in supraphysiological doses lead to the development of insulin resistance and poor metabolic control in patients with type 1 diabetes. Accumulation of visceral fat is the main cause of the decrease in insulin sensitivity.

OBJECTIVES We aimed to evaluate changes in anthropometric parameters, indirect measures of insulin resistance, and safety of treatment with metformin added to intensive insulin therapy in patients with type 1 diabetes and excess body fat.

PATIENTS AND METHODS We analyzed 114 patients (60 women and 54 men; median age, 31 years [range, 18–60 years]), with a median diabetes duration of 14 years (range, 10–20 years). Metformin was administered for at least 6 months in 74 patients, while 40 patients did not receive metformin. The study group was randomized in a 2:1 ratio. Total body fat assessment and laboratory tests were performed before the study and at 6-month follow-up.

RESULTS At 6 months, in the metformin group, compared with the non–metformin group, an improvement was noted for adiposity parameters (reduction in body mass index, –0.4 kg/m^2 vs 0.6 kg/m^2, $P = 0.006$; waist circumference, –5 cm vs 3.5 cm, $P = 0.02$; and total body fat, –1.7 kg vs 1.4 kg; $P < 0.001$; glycated hemoglobin A_{1c}: –0.6% vs 0.2%, $P < 0.001$), as well as for lipid parameters and blood pressure. An increase in the estimated glomerular filtration rate was greater in the metformin compared with the non–metformin group: 0.9 mg/kg/min vs –0.2 mg/kg/min, $P < 0.001$).

CONCLUSIONS In patients with type 1 diabetes and excess body fat, treated with intensive functional insulin therapy, the addition of metformin improves metabolic control of diabetes at 6 months. Metformin added to insulin therapy in patients with type 1 diabetes and excess body fat appears to be safe.

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INTRODUCTION The increasing prevalence of diabetes and its chronic complications is an important public health concern.[1] The major contributor to this epidemiological trend is the increasing prevalence of type 2 diabetes related to the epidemic of obesity and insulin resistance. Nevertheless, the prevalence of type 1 diabetes is also increasing, and the phenomenon of insulin resistance may also contribute to this trend and modify the clinical picture of the disease.[2] Apart from the autoimmune destruction of pancreatic β cells, the major pathogenic factor in type 1 diabetes, there is accumulating evidence that insulin resistance is also involved in this disease and may influence metabolic control and risk of chronic complications.[3-6] In patients with type 1 diabetes, insulin resistance may have genetic background (the concept of "double diabetes"), but often it is associated with unhealthy lifestyle (low physical activity, improper diet, smoking). Insulin therapy

may also contribute to decreased insulin sensitivity. The effect of insulin administered subcutaneously differs considerably from its release to the portal circulation and is less effective in suppressing hepatic gluconeogenesis. Also, the dosage and timing of administration, even using advanced continuous subcutaneous insulin infusion systems are different from the physiologic insulin secretion and may induce iatrogenic insulin resistance. This effect is particularly significant, often leading to obesity and other features of metabolic syndrome, when daily insulin dose is too high or treatment regimen is inappropriate.[7] Development of insulin resistance is more common in patients with poor metabolic control in the mechanism of glucotoxicity and lipotoxicity.[6]

Metformin has been used in the therapy of type 2 diabetes for over 50 years with the aim to improve insulin sensitivity. However, considering the role of insulin resistance in type 1 diabetes, add-on metformin therapy in overweight or obese patients with type 1 diabetes is being increasingly investigated.[8-11]

The aim of this study was to evaluate the parameters of metabolic control, measures of insulin resistance, and safety of treatment with metformin added to intensive insulin therapy in patients with type 1 diabetes and excess body fat.

PATIENTS AND METHODS This randomized prospective study was conducted in a group of 117 patients with type 1 diabetes, hospitalized in the Department of Internal Medicine and Diabetology, Poznan University of Medical Sciences, Poznań, Poland, in the years 2010 to 2014. All patients had type 1A diabetes and were treated with intensive insulin therapy. The study protocol was registered at clinicaltrials.gov (NCT01889706). It was conducted in accordance with the Declaration of Helsinki and received approval from a local bioethics committee. All subjects were informed about the aim and design of the study and gave their written informed consent. During the study, 77 patients received metformin and insulin therapy (metformin group), while the remaining 40 patients were treated with insulin alone (non–metformin group). Patients were randomized in a 2:1 ratio (two-thirds of the patients on metformin treatment).

The inclusion criteria were as follows: type 1 diabetes (positive for at least one of the autoantibodies: ilet cell antibodies, anti–glutamic acid decarboxylase antibodies, or anti–tyrosine phosphatase-like insulinoma antigen 2 antibodies), age above 18 years, duration of diabetes above 3 years, glycated hemoglobin A_{1c} (HbA_{1c}) >7.5%, increased total body fat content measured using the biopimpedance method (TANITA BC-418 MA, Tanita Corporation of America, Inc., Arlington Heights, Illinois, United States). The exclusion criteria were: concomitant acute disease (uncontrolled hypothyroidism, acute coronary syndrome, acute infection), metabolic decompensation of diabetes with acetonuria, lack of self-monitoring of blood glucose, hypoglycemia unawareness, at least 1 episode of severe hypoglycemia) in the past 3 months, recurrent diabetic ketoacidosis (more than 2 episodes in the past year), pregnancy or breastfeeding, chronic kidney disease stage 3B or higher (estimated glomerular filtration rate [eGFR] <45 ml/min/1.73 m^2), biochemical features of liver damage (alanine aminotransferase or aspartate aminotransferase activity higher than 3 times the upper limit of normal), history of drug or alcohol abuse, and prior use of metformin treatment. Early signs of intolerance (flatulence, abdominal pain, metallic taste in the mouth) resulted in discontinuation of metformin in 3 subjects. All patients underwent complete physical examination at baseline and at 6 months. Data concerning lifestyle, such as eating habits (daily intake of carbohydrates, frequency of meals), physical activity (type of exercise, weekly frequency of exercise), and occurrence of hypoglycemia (including severe hypoglycemia), were obtained using a questionnaire. The daily dose of insulin was calculated. Patients' height and weight, as well as hip and waist circumferences, were measured at baseline and at 6 months, and the mean value from the 3 measurements was used for analyses. Body mass index (BMI) and waist-to-hip ratio (WHR) were calculated. Hypertension and dyslipidemia were diagnosed according to the American Diabetes Association and Diabetes Poland guidelines.[12,13] Systolic and diastolic blood pressures were measured twice using a sphygmomanometer in a sitting position after 5-minute rest. All patients measured their fasting and 2-hour postprandial glycemia using their personal glucose meter. The average daily glucose levels were calculated from a 7-point daily glucose profile on the day of admission as well as at a follow-up visit. The value of HbA_{1c} was measured using the turbidimetric immunoinhibitory method (Cobas 6000, Roche Diagnostics, Indianapolis, United States). Alanine aminotransferase, aspartate aminotransferase, and lipid parameters (total cholesterol, high-density lipoprotein [HDL] cholesterol, and triglycerides) were measured by the enzymatic colorimetric method. Low-density lipoprotein (LDL) cholesterol concentrations were calculated using the Friedewald formula (with its exceptions). Non–HDL cholesterol levels were calculated by subtracting the HDL cholesterol from the total cholesterol concentration; the ratio of triglycerides to HDL cholesterol was also calculated. The eGFR was calculated using the Modification of Diet in Renal Disease study equation. The presence of ketones in urine was assessed at baseline and at follow-up, using a KetoDiastix strip (Legal's reaction). Total body fat and visceral fat content was estimated using the electrical bioimpedance method (TANITA BC-418 MA, TANITA AB-140 ViScan analyzer) according to the World Health Organization criteria, adjusted for age and sex.[14] The estimated glucose disposal rate (eGDR) was calculated using the following

TABLE 1 Clinical characteristics of the study group (n = 114)

Variable		Value
Sex, female/male, n (%)		60 (53) / 54 (47)
Age, y		31 (18–60)
Diabetes duration, y		14 (10–20)
Daily insulin dose, U/kg of body weight		0.6 (0.5–0.7)
BMI, kg/m^2		28.4 (26.7–30.7)
Total body fat, kg	Women	28.2 (25.5–33.0)
	Men	22.1 (19–26.8)
Visceral body fat[a], n		7 (5–9)
Trunk body fat[b], %		38.5 (34.4–42.4)
Abdominal visceral body fat[b], n		9.5 (7–13)
WC[b], cm		97 (94.5–103.5)
WC, cm	Women	92 (86.5–96.0)
	Men	103 (100–108)
WHR	Women	0.8 (0.8–0.9)
	Men	1 (0.9–1.0)
TG/HDL-C ratio, mmol/l		2.1 (1.4–2.8)
SBP, mm Hg		120 (110–130)
DBP, mm Hg		80 (70–85)
HbA_{1c}, %		8.5 (7.5–9.5)
FPG, mmol/l		9.2 (7.1–11.5)
PPG, mmol/l		10.6 (8.4–13.5)
MPG, mmol/l		8.7 (7.6–10.3)
Total cholesterol, mmol/l		5.8 (4.5–6.1)
TG, mmol/l		1.3 (0.9–1.6)
LDL-C, mmol/l		3.1 (2.5–3.9)
HDL-C, mmol/l		1.5 (1.2–1.7)
Non–HDL-C, mmol/l		3.6 (3.1–4.7)
ALT, U/l		18 (13.5–26)
AST, U/l		18 (15–23)
Creatinine, µmol/l		73,8 (65.4–84)
EGFR, ml/min/1.73 m^2		92 (83.7–105)
EGDR, mg/kg/min		7 (4.7–8.3)
SBP, mm Hg		120 (110–130)
DBP, mm Hg		80 (70–85)

Data are presented as median (interquartile range) unless otherwise stated.

a Measured using TANITA BC-418 MA (see the Methods section)

b Measured using TANITA AB-140 ViScan (see the Methods section)

Abbreviations: ALT, alanine aminotransferase, AST, aspartate aminotransferase; BMI, body mass index; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; eGDR, estimated glucose disposal rate; FPG, fasting plasma glucose; HbA_{1c}, glycated hemoglobin A_{1c}; HDL-C, high-density lipoprotein cholesterol; LDL-C, low--density lipoprotein cholesterol; MPG, mean plasma glucose; PPG, postprandial plasma glucose; SBP, systolic blood pressure; TG, triglycerides; TBF, total body fat; WC, waist circumference; WHR, waist-to-hip ratio

formula: 24.31–12.22 (WHR) – 3.29 (arterial hypertension 0/1) – 0.57 [HbA_{1c}%]) and expressed as mg/kg/min.[15] Subjects with an eGDR value below 7.5 mg/kg/min were considered as having insulin resistance.[16]

All the above parameters were measured before introduction of metformin and at 6-month follow-up. We calculated the difference between the result at baseline and that at 6 months of treatment (Δ parameter). The mean metformin dose was 1000 mg/d (range, 500–2550 mg/d). In overweight patients, the dose ranged from 500 to 1500 mg/d, and in obese individuals, from 1500 to 2550 mg/d according to drug tolerance. Patients were treated with the original metformin formulation. Gastrointestinal side effects were analyzed using a questionnaire. Early side effects were defined as those occurring within 7 days from the first metformin administration.

Statistical analysis Statistical analysis was performed using the Statistica PL software version 8.0. Normal distribution of variables was tested using the Kolmogorov–Smirnov test with Lillefors correction. Due to nonnormal distribution, nonparametric tests were used. For quantitative data, the intergroup differences were analyzed using the Mann–Whitney test, while the Wilcoxon signed-rank test was used for comparison of repeated measurements. Differences in qualitative data were evaluated using the χ^2 test. The results were presented as numbers and percentages or as median and interquartile range. A *P* value of less than 0.05 was considered significant.

RESULTS The median age of participants was 31 years (range, 18–60 years) and median duration of diabetes was 14 years (range, 10–20 years). The median daily insulin dose was 0.6 U/kg of body weight (range, 0.5–0.7 U/kg of body weight), and total body fat was 26.3 kg (range, 22.1–30.5 kg) (men, 22.1 kg [range, 19–26.8 kg]; women, 28.2 kg [range, 25.5–33 kg]). Detailed characteristics of the study group are presented in TABLE 1. All individuals treated with metformin reported administration of the drug according to recommendations. The groups did not differ in terms of sex, age, duration of diabetes, total body fat, presence of chronic complications of diabetes, or parameters of metabolic control of diabetes (current HbA_{1c} value, serum LDL cholesterol and triglyceride concentrations). At baseline, a significantly higher daily insulin dose was noted in the non–metformin group. Patients in the metformin group had higher BMI, and women in this group had higher WHR, compared with the non–metformin group. Also, in the metformin group significantly higher non–HDL cholesterol concentrations, ratio of triglycerides to HDL cholesterol, and lower eGDR and HDL cholesterol concentrations were noted (TABLE 2).

At baseline and at 6 months, the metformin and non–metformin groups did not differ significantly in lifestyle parameters, including eating habits and physical activity.

At 6 months, in the metformin subgroup, compared with the non–metformin group, a significant improvement was noted in adiposity parameters, glycemic control, lipid parameters, and blood pressure. The eGDR value significantly increased in the metformin compared with the non–metformin group. The results are presented in TABLE 3.

TABLE 2 Baseline clinical characteristics of the study groups treated and not treated with metformin

Variable		Metformin (n = 74)	Non–metformin (n = 40)	*P* value
Sex, female/male, n (%)		35 (47)/39 (52)	25 (63)/15 (37)	0.1
Age, y		32 (27–39)	27.5 (23–39)	0.4
Diabetes duration, y		13 (7–20)	15 (12–19.5)	0.1
Retinopathy, n (%)		23 (29.5)	16 (40)	0.1
Diabetic nephropathy, n (%)		6 (8.1)	8 (20)	0.9
Neuropathy, n (%)		11 (14.1)	3 (7.5)	0.2
Arterial hypertension, n (%)		27 (36.5)	10 (25)	0.2
Macroangiopathy, n (%)		1 (1.5)	2 (5)	0.4
Dyslipidemia, n (%)		1 (1.5)	4 (8.3)	0.6
Smoking, n (%)		9 (10.3)	9 (18.8)	0.1
Daily insulin dose, U/kg of body weight		0.5 (0.5–0.6)	0.6 (0.5–0.6)	0.02
BMI, kg/m^2		28.8 (27.6–31.5)	27.5 (25.7–29.2)	0.003
Total body fat, kg	Women	30.6 (27.7–33.9)	26.3 (25.0–28.6)	0.01
	Men	22.4 (20.4–27.5)	20.1 (18.2–22.3)	0.03
Trunk body fat[a], %		37.6 (34.4–45.2)	39 (34.3–41.8)	0.1
Abdominal visceral body fat[a], n		11.5 (8–18)	9.5 (6.5–12)	0.1
WC[a], cm		102 (96–107)	96 (92–101)	0.1
WC, cm	Women	93 (88–97)	90 (86–93)	0.1
	Men	104 (101–109)	102 (96–105)	0.1
WHR	Women	0.9 (0.8–0.9)	0.8 (0.8–0.9)	0.02
	Men	0.9 (0.9–1)	1 (0.9–1)	0.8
EGDR, mg/kg/min		6.9 (4.3–7.9)	7.6 (5.3–8.9)	0.03
SBP, mm Hg		120 (120–130)	124 (115–130)	0.8
DBP, mm Hg		80 (70–80)	80 (70–85)	0.9
HbA_{1c}, %		8.6 (7.8–9.6)	8.2 (7.2–9.3)	0.2
FPG, mmol/l		9.3 (7.2–11.3)	9.1 (6.5–12.5)	0.9
PPG, mmol/l		10.7 (8.8–11.4)	9.4 (7.5–9.3)	0.1
MPG, mmol/l		9.2 (7.9–10.4)	9.5 (7.8–12.4)	0.1
Total cholesterol, mmol/l		5.2 (4.7–6.1)	4.9 (4.3–6.0)	0.1
TG, mmol/l		1.4 (1.0–1.7)	1.1 (0.87–1.5)	0.1
LDL-C, mmol/l		3.1 (2.6–3.8)	3.2 (2.4–4.0)	0.8
HDL-C, mmol/l		1.4 (1.1–1.7)	1.6 (1.3–1.8)	0.008
Non–HDL-C, mmol/l		4.4 (3.2–4.8)	3.1 (2.7–3.4)	0.001
TG/HDL-C ratio		2.2 (1.5–2.9)	1.6 (1.3–2.5)	0.1
ALT, U/l		18 (14–27)	17.5 (12–25)	0.9
AST, U/l		17 (14–22)	19 (16–24)	0.7
EGFR, ml/min/1.73 m^2		99.7 (88.3–105.9)	90 (81.8–92.9)	0.04

Data are presented as median (interquartile range) unless otherwise stated.

a Measured using TANITA AB-140 ViScan (see the Methods section)

Abbreviations: see TABLE 1

In the metformin group, adverse gastrointestinal effects (diarrhea and flatulence, metallic taste in the mouth) occurred in 9 patients. In 8 patients, these symptoms resolved spontaneously within 7 days, and in 1 patient, they persisted but were mild and did not lead to metformin withdrawal.

During follow-up, a single episode of diabetic ketoacidosis occurred in a patient from the non–metformin group, who developed gastroenteritis. One patient in the metformin group developed temporary skin rash, which resolved spontaneously despite uninterrupted metformin treatment (TABLE 4).

DISCUSSION The increase in body weight and visceral adiposity may enhance inflammation and increase the risk of chronic complications of the disease.[17,18] In a study of Lund et al,[19] conducted in patients with type 1 diabetes, 12-month metformin treatment was associated with a weight loss of 1.6 kg. Jansen et al[20] reported that a mean weight loss in subjects with type 1 diabetes on 6-month add-on metformin therapy was 3 kg, with a mean 0.8-kg increase in the control group. In a study by Sharma et al,[21] weight gain was smaller in the metformin than in the placebo group. A significant weight loss on metformin therapy in type 1 diabetes was also reported by Urakami et al[22] and Jacobsen et al.[23] In our study, in patients with type 1 diabetes treated with metformin (as add-on to intensive insulin therapy) for 6 months, a significant improvement in parameters that reflect general and visceral adiposity were noted (BMI, waist circumference, WHR, total body fat content), compared with the nontreated group. Other studies with a follow-up shorter than 6 months showed no significant effects on BMI or body composition.[9,24] In contrast, Nadeau et al[25] reported a significant decrease of BMI and waist circumference after 3 and 6 months of metformin treatment in a randomized controlled trial including adolescent patients. These discrepancies may result from different duration of the studies or employed measuring instruments. In our study, the reduced adiposity was documented objectively using a noninvasive TANITA AB-140 ViScan device, which also measures visceral fat content. Precision of the obtained results is comparable to that of magnetic resonance imaging.[26]

Insulin dose is increasingly considered as an important factor in assessment of the risk of diabetic complications. Overinsulinization induces important metabolic effects that result in weight gain and insulin resistance.[20] A study in patients with type 2 diabetes also suggested an increased risk of carcinogenesis in overinsulinized patients.[27] Therefore, the effect of metformin on reducing the dose of exogenous insulin was addressed and confirmed in some studies in patients with type 1 diabetes.[9,28,29] In a study by Moon et al,[30] daily insulin dose was reduced on metformin treatment in patients treated with personal insulin pumps. Reduced insulin requirement following use of high metformin doses (2550 mg/d) in patients with type 1 diabetes was also documented in a study by Pagano et al.[30] Furthermore, a meta-analysis by Khalifah et al[31] showed that add-on metformin treatment reduced total daily insulin dose and BMI in children.

TABLE 3 Differences in variables (Δ) before and after 6 months of treatment in the groups treated and not treated with metformin

Variable		Metformin (n = 74)	Non–metformin (n = 40)	*P* value
ΔDaily insulin dose, U/kg of body weight		–0.04 (0 to –0.15)	–0.02 (–0.1 to 0.07)	0.004
ΔBMI, kg/m^2		–0.4 (0 to –1.4)	0.6 (–0.1 to 1.4)	0.006
ΔWC, cm	Women	–6 (–2 to –9)	4 (0–6)	<0.001
	Men	–5 (–2 to –8)	2 (–2 to 7)	<0.001
ΔWHR	Women	–0.03 (–0.01 to –0.05)	0.03 (–0.004 to 0.07)	<0.001
	Men	–0.005 (0.03 to –0.03)	0.001 (–0.009 to 0.1)	0.3
ΔSBP, mm Hg		–10 (0 to –20)	10 (0.5–20)	<0.001
ΔDBP, mm Hg		–5 (0 to –10)	10 (0–15)	<0.001
ΔTBF, kg	Men	–1.8 (0 to –3.2)	0,65 (–0.4 to 2.3)	<0.001
	Women	–1.65 (0 to –3.5)	2,05 (–0.2 to 3.65)	<0.001
ΔTrunk body fat[a], %		–4.3 (–0.5 to –8.6)	2.3(–0.2 to 6.8)	<0.001
ΔAbdominal visceral body fat[a], n		0 (0 to –1)	0 (0 to 1)	0.001
ΔWC, ViScan, cm		–5 (–12 to 7)	3.5 (–3 to 6)	0.02
ΔEGDR, mg/kg/min		0.9 (0.06 to 1.4)	–0.2 (–1.2 to 0.2)	<0.001
ΔHbA_{1c}, %		–0.6 (–1.5 to –0.2)	0.2 (–0.4 to 0.6)	<0.001
ΔFPG, mmol/l		–2.2 (–4.4 to –0.6)	0.6 (–1.3 to 4.2)	<0.001
ΔPPG, mmol/l		–3.4 (–6.8 to –1.2)	2.5 (–2.6 to 3.1)	<0.001
ΔMPG, mmol/l		–1.7 (–2.8 to –0.03)	1.7 (0.3 to 2.7)	<0.001
ΔTotal cholesterol, mmol/l		–0.3 (–0.8 to –0.03)	–0.1 (–0.5 to 0.5)	0.03
ΔTG, mmol/l		–0.3 (–0.6 to –0.1)	–0.2 (–0.5 to 0.1)	0.16
ΔLDL-C, mmol/l		–0.3 (–0.7 to 0.1)	–0.2 (–0.7 to 0.2)	0.3
ΔHDL-C, mmol/l		0.1 (–0.05 to 0.4)	0.1 (–0.05 to 0.2)	0.5
ΔNon–HDL-C, mmol/l		–0.4 (–1 to 0.02)	–0.1 (–0.4 to 0.5)	0.02
ΔTG/HDL-C ratio		–0.6 (–1.4 to –0.1)	–0.5 (–1 to 0.09)	0.12
ΔALT, U/l		–1 (–5 to 2)	0 (–2.5 to 2)	0.7
ΔAST, U/l		0 (–3 to 2)	–1 (–4.5 to 1)	0.26
ΔEGFR, ml/min/1.73 m^2		–8.1 (–22.6 to 6.2)	2.2 (–15.9 to 27.2)	0.001

Data are presented as median (interquartile range).

a Measured using TANITA AB-140 ViScan (see the Methods section)

Abbreviations: see TABLE 1

TABLE 4 Comparison of safety and tolerance of metformin therapy in a 6-month follow-up between the groups treated and not treated with metformin

Variable	Metformin (n = 74)	Non–metformin (n = 40)	*P* value
Acetonuria	3 (4.1)	7 (17.5)	0.02
Hypoglycemia	28 (37.8)	14 (35)	0.2
Severe hypoglycemia	1 (1.5)	8 (20)	<0.001
Ketoacidosis	0 (0)	1 (2.5)	0.17
Early gastrointestinal side effects	9 (11.5)	0 (0)	1
Gastrointestinal side effects	1 (1.1)	0 (0)	1
Skin side effects	1 (1.1)	0 (0)	1

Data are presented as number (percentage) of patients.

In our study, insulin resistance was assessed using an indirect method, with calculation of eGDR, the parameter that correlates with insulin resistance measured with the reference euglycemic-hyperinsulinemic clamp method.[32] In the metformin group, a significant increase in eGDR during 6-month follow-up was documented (higer ΔeGDR), compared with the group not treated with metformin. In patients with type 1 diabetes, a reduced eGDR value is linked to the development of microvascular complications.[33,34] In the metformin-treated subgroup, HbA_{1c} decreased by 0.5%. In contrast, in the non-treated group, HbA_{1c} value increased significantly. This is in line with the study by Sarnblad et al,[10] where the reduction in HbA_{1c} in the metformin-treated group was as high as 1%.[10] However, this effect was not confirmed by Meyer et al[35] in a 6-month follow-up. In our study, a significant reduction of serum cholesterol and non–HDL cholesterol levels was observed in the metformin group during 6 months of follow-up. Also Lund et al[19] confirmed the reduction of serum total cholesterol and LDL cholesterol levels in the group treated with insulin combined with metformin, compared with patients on insulin monotherapy.[19] A similar trend towards improvement of lipid parameters was also observed by Khan et al,[28] yet the difference was not significant. In both subgroups of patients (metformin and non–metformin), serum triglyceride concentrations decreased and HDL cholesterol concentrations increased, which is in line with a study by Ziaee et al.[36]

Hypoglycemia is the most common complication of insulin therapy in type 1 diabetes. High frequency of hypoglycemia is associated with high glycemic variability, reflecting poor metabolic control and high risk of chronic complications and acute cardiovascular events.[37] Moreover, increased frequency of symptomatic or subclinical hypoglycemia is associated with episodes of excessive appetite, uncontrolled weight gain, and, consequently, metabolic abnormalities leading to the development of insulin resistance.[38-40] Reduction of insulin requirement after addition of metformin may necessitate a reduction of the exogenous insulin dose. In the study by Jacobsen et al,[23] a significant increase in the frequency of episodes of hypoglycemia was observed in patients on metformin, compared with the nontreated group.[23] In a study by Nwosu et al,[41] the prevalence of hypoglycemia was similar between placebo and metformin groups. In our study, all patients were advised to reduce the daily insulin dose after a few days of treatment. Therefore, the frequency of hypoglycemia was higher in the non–metformin group. Similar results were obtained by other authors.[9,28,35] Acetonuria was also more frequently observed in the control group. In our study, gastrointestinal symptoms were reported only incidentally. In the study by Hamilton et al,[9] 11 of 27 patients presented gastrointestinal symptoms, but only 1 patient did not complete the study. In our study, only 3 subjects from the metformin group were excluded because of these symptoms. Contrary to other studies, in our study eGFR decreased significantly in the metformin group during follow-up. This may be associated with a greater reduction of

hyperglycemia in the metformin group compared with the non–metformin group and a resulting decrease of hyperfiltration, and is unlikely to be a direct adverse effect of metformin treatment.

Our results show a positive effect of metformin on the reduction in BMI, daily insulin dose, and lipid profile in patients with type 1 diabetes. In contrast, Steals et al[42] did not confirm the beneficial effect of metformin as adjunctive therapy in patients with type 1 diabetes on BMI and daily insulin dose. Moreover, metformin added to insulin treatment in young patients with type 1 diabetes with excess body fat leads to a significant reduction of the mean intima–media thickness of the common carotid artery, and may decrease the risk of chronic complications of diabetes.[43-45]

In patients with type 1 diabetes and excess body fat, treated with intensive functional insulin therapy, the addition of metformin leads to better metabolic control of diabetes at 6 months. Metformin added to insulin therapy in patients with type 1 diabetes and excess body fat appears to be a safe therapeutic option.

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CONTRIBUTION STATEMENT AZ, BW-W, and DZ-Z conceived the concept of the study. DN, PB, and MG contributed to the design of the research. All authors were involved in data collection. PN, AZ, and SP analyzed the data. AZ and BW-W coordinated funding for the project. All authors edited and approved the final version of the manuscript.

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