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EFFECTS OF METFORMIN ON BODY WEIGHT MANAGEMENT AND MARKERS OF THE METABOLIC SYNDROME IN PERSONS WITH NORMAL GLUCOSE TOLERANCE

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Abstract

Treatment of the metabolic syndrome (MS) is essential for prevention of type 2 diabetes mellitus (T2DM) and cardiovascular disease (CVD). The purpose of this open-label prospective one year observational clinical study was to examine the effects of metformin 2.55±0.3 g/d on body weight management and markers of the MS in normal glucose tolerant persons with hyperinsulinaemia. Body weight was reduced by 6.8% at 6 months and by 11.1% at 1 year. The body weight reduction was 7.2±3.4 kg at 6 months and 11.7±4.7 kg (mean±SD) at 1 year. We found a significant correlation of reduction of body weight at 1 year with initial body weight, body mass index, waist circumference and homeostasis model assessment of insulin resistance (HOMA-IR), all $p < 0.001$. At 1 year of metformin treatment HOMA-IR, total cholesterol, low-density lipoprotein cholesterol, triglycerides, systolic and diastolic blood pressure were significantly reduced, all $p < 0.001$ and high-density lipoprotein cholesterol was significantly increased, $p = 0.004$. Our study shows that treatment with metformin alone, without intensive diet and physical activity, could reduce visceral obesity, insulin resistance, dyslipidaemia and arterial hypertension and supports the hypothesis that it could be applied for prevention of T2DM and CVD.

Key words: metabolic syndrome, obesity, metformin

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Introduction. Metabolic syndrome (MS) is determined as a cluster of cardiometabolic risk factors mainly generalized and central (visceral) obesity, insulin resistance and hyperinsulinaemia, dyslipidaemia, arterial hypertension and dysregulated glucose homeostasis that have been found to associate with an increased risk of type 2 diabetes mellitus (T2DM) and cardiovascular disease (CVD) [1]. The International Diabetes Federation (IDF) Diabetes Atlas showed that in 2017 there were 451 million (age 18–99 years) people with diabetes worldwide and these figures were expected to increase to 693 million by 2045. According to the National Diabetes Registry, there are over a half million people with diabetes in Bulgaria. At the beginning of the 21st century T2DM is considered a cardiovascular disease risk equivalent. There is an increasingly urgent need for governments to implement policies to decrease the risk for T2DM the main part of which is treatment of the MS. There is no definitive therapy for the MS besides reduction of the cardiometabolic risk factors such as visceral obesity, insulin resistance, dyslipidaemia, arterial hypertension and hyperglycaemia [1]. There is a close relationship between obesity and risk of developing T2DM. For each kilogram of weight gained annualy over a period of 10 years there is an associated 49% increase in the diabetes risk in the next 10 years. Conversely, for each kilogram of weight lost annually over 10 years, there is an associated 33% decrease in the diabetes risk in the next 10 years [2]. The change in lifestyle aimed at reduction of body weight is the first and most important step for diabetic prevention, but in individuals who do not get the desirable result, the addition of medical treatment is the helpfull alternative [1,3,4]. Hyperinsulinaemia is a metabolic antecedent or cause rather than consequence of obesity and dietary and pharmacologic approaches that reduce hyperinsulinaemia could promote weight loss [3].

Metformin has been established as a drug of first choice in guidelines for treatment of T2DM and metformin has been shown to reduce the incidence of T2DM and CVD risk factors in individuals with impaired fasting blood glucose and impaired glucose tolerance [4–6]. The American Diabetes Association has recommended metformin for prevention of T2DM in persons with prediabetes, especially for those with BMI ≥ 35 kg/m^2, those aged $<$60 years, women with prior gestational diabetes mellitus, and/or those with rising glycated hemoglobin despite lifestyle intervention [7]. The data about the effect of metformin on CVD risk factors in normal glucose tolerant persons with MS are inconclusive and demanding more investigations. The purpose of this study was to examine the effects of metformin on body weight management and markers of the MS in normal glucose tolerant persons with hyperinsulinaemia who are at high risk for development of T2DM and CVD.

Materials and methods. Sixty-eight persons (24 males, 44 females) aged 39.8$\pm$13.6 yrs were involved in an open-label prospective one year observational clinical study. The inclusion criteria were: 1) MS according to the IDF definition with a necessary requirement central obesity defined as waist circumference

$\geq$ 80 cm for women and $\geq$ 94 cm for men and two of the following: triglycerides $\geq$1.7 mmol/l and/or high-density lipoprotein (HDL) cholesterol $<$ 1.03 for men and $<$ 1.29 mmol/l for women and/or specific treatment, systolic blood pressure $\geq$ 130 mmHg and/or diastolic blood pressure $\geq$ 85 mmHg and/or specific treatment, fasting plasma glucose $\geq$ 5.6 mmol/l; 2) normal glucose tolerance during 75 g oral glucose tolerance test (OGTT) defined as fasting plasma glucose $<$ 6.1 mmol/l and 2-h post glucose load plasma glucose $<$ 7.8 mmol/l; 3) hyperinsulinaemia during OGTT-fasting serum insulin $>$ 25 mIU/l and/or 2-h post glucose load serum insulin $>$ 3 times from baseline; 4) failure to loose weight with conventional medical care – caloric restriction plus participation in regular exercise at a minimum level of 150 min moderate-intensity sessions per week in prior year.

Study procedure. Participants were admitted to the Division of Diabetology of University Specialized Hospital for active treatment in Endocrinology at baseline visit, at 6 months and at 1 year of metformin treatment to perform case history, physical examination and blood measurements. All persons included in the study have signed an informed consent according to the respective requirements from the Code of Ethics of the World Medical Association (Declaration of Helsinki). The study protocol was approved by the Ethics Committee of the University Specialized Hospital for active treatment in Endocrinology. Body weight, BMI, waist circumference, systolic blood pressure, diastolic blood pressure, HOMA-IR, serum lipids-total cholesterol, HDL cholesterol, low-density lipoprotein (LDL) cholesterol and triglycerides at baseline, at 6 months and at 1 year were followed. The body weight was measured to the nearest 0.1 kg, height was measured to the nearest 0.1 cm and BMI was calculated as body weight (kg) divided by squared height (m^2). Waist circumference was measured using a non-elastic tape to the nearest 0.1 cm in the middle between lowest rib and the iliac crest in inspiration and expiration position and the mean value was taken**.** Systolic and diastolic blood pressure was measured with the use of manual sphygmomanometer on the left arm in a sitting position after at least 10 min of rest. Blood samples for glucose, insulin and lipids were taken after a 12-hour overnight fast. They were immediately centrifuged and analysed. Plasma glucose was defined by a glucose oxidase method and serum lipids-total cholesterol, triglycerides and HDL cholesterol were measured by an enzymatic method on biochemical analyzer (Cobas Integra, Roche Diagnostics, Switzerland). LDL cholesterol was calculated using Friedewald equation. Serum insulin was estimated by an immunoradiometric method (Insulin IRMA kit, Immunotech, Beckman Coulter, Czech Republic, reference range 2–25 mIU/l). HOMA-IR was calculated as fasting plasma glucose (mmol/l) $\times$ fasting serum insulin (mIU/l)/22.5.

Drug administration. It was an open-label study in which metformin, tablets of 1000 mg, was applied at an initial dose of 500 mg in the middle of the dinner for 5 days, titrated in 5 days intervals by 500 mg at lunch, at breakfast and at dinner consecutively to the maximal of 3 g or until side effects occurred,

when the previous well tolerated dose was kept constant during the follow-up. The mean dose of metformin was 2.55±0.3 g, taken at breakfast, at lunch and at dinner in the middle of the meal. Participants were advised to keep on their usual diet, physical activity and medication throughout the study.

Statistical methods. Statistical analysis was performed using statistical package for social science (SPSS for Windows, Chicago, Il, USA). Data are presented as mean±SD and as percentages. To evaluate differences between baseline and follow-up variables one-way analysis of variance (ANOVA) with repeated measures or Friedman test according to a normal or a nonparametric distribution of the tested variable were used. To determine differences between variables of two groups, two-way ANOVA was used. To assess correlation between two variables Pearson correlation analysis was done. Shapiro–Wilk test was used for normality. A level of $p<0.05$ was considered significant.

Results. The significant effect of metformin on body weight (Fig. 1), BMI (Fig. 2) and waist circumference (Fig. 3) was noticed at 6 months and at 1 year of metformin treatment.

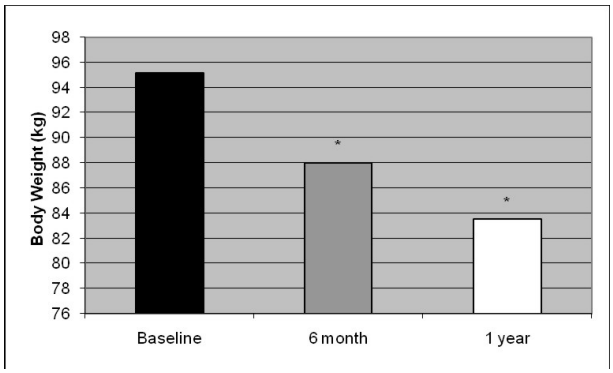

Fig. 1. Effect of metformin on body weight. Body weight 95.2±18.8 kg significantly reduced at 6 months 88.0±17.2 kg ($p = 0.02$) and at 1 year 83.5±16.6 kg ($p = 0.001$)
* significant difference versus baseline

There was no statistically significant difference between body weight, BMI and waist circumference at 1 year compared to the 6th month. Body weight was reduced by 6.8% at 6 months and by 11.1% at 1 year of metformin treatment. The body weight reduction was 7.2±3.4 kg (from 1.7 to 20 kg) at 6 months and 11.7±4.7 kg (from 4 to 22 kg) at 1 year. We found a significant correlation of reduction of body weight at 1 year with initial body weight $r = 0.641$, BMI $r = 0.532$, waist circumference $r = 0.597$ and HOMA-IR $r = 0.489$, all $p < 0.001$.

The body weight of men 106.4±15.7 kg was significantly higher than that of women 89.1±17.7 kg, the waist circumference of men 110.3±9.2 cm was significantly higher that that of women 97.0±15.3 cm, both $p < 0.001$; the homeostasis

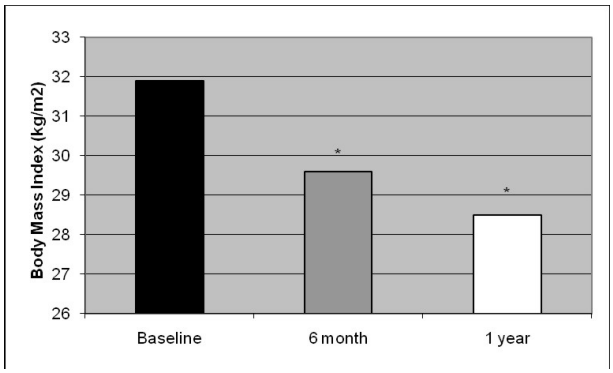

Fig. 2. Effect of metformin on BMI. BMI 32.0±5.1 kg/m^2 significantly reduced at 6 months 29.6±4.8 kg/m^2 (p = 0.006) and at 1 year 28.5±4.6 kg/m^2 ($p < 0.001$); BMI= Body Mass Index * significant difference versus baseline

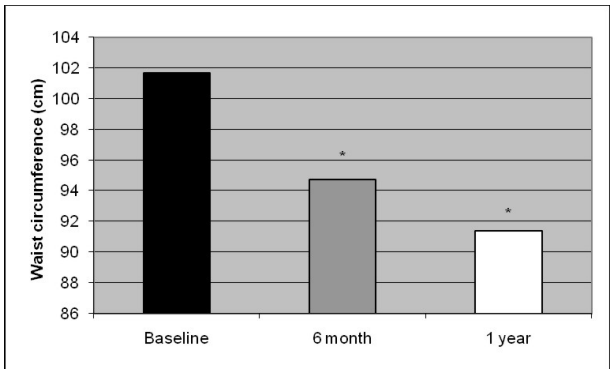

Fig. 3. Effect of metformin on waist circumference. Waist circumference 101.7±14.8 cm significantly reduced at 6 months 94.7±12.9 cm (p = 0.007) and at 1 year 91.4±11.9 cm ($p < 0.001$) * significant difference versus baseline

model assessment of insulin resistance (HOMA-IR) of men 6.84±4.42 was significantly higher compared to that of women 4.34±2.74,p=0.016. The body weight reduction in men 13.5±4.4 kg was significantly higher compared to that of women 10.8±4.6 kg (p = 0.025) at the end of 1 year treatment period. HOMA-IR was significantly reduced at 6 months and at 1 year of metformin treatment. At 1 year it was significantly lower in comparison to that of 6 months (p = 0.005). The effect of metformin on HOMA-IR, total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, systolic and diastolic blood pressure is presented in Table 1.

Discussion. People with hyperinsulinaemia, normal glucose tolerance and MS represent a high-risk population for development of T2DM and CVD. The IDF emphasizes the role of central obesity as a cornerstone of the MS. Indeed, the main

Table 1

Effect of metformin treatment on HOMA-IR, Total cholesterol, LDL cholesterol, HDL cholesterol, Triglycerides, Systolic BP and Diastolic BP at 6 months and at 1 year

HOMA-IR = Homeostasis Model Assessment of Insulin Resistance; LDL = Low density lipoprotein; HDL = High density lipoprotein; BP = blood pressure; * significant difference versus baseline

Variables	Baseline	6 month	1 year
HOMA-IR	5.22 ± 3.60	3.87 ± 2.06	2.61 ± 1.34
p		0.020*	<0.001*
Total cholesterol (mmol/l)	5.66 ± 0.85	5.22 ± 0.98	4.79 ± 0.80
p		0.048*	<0.001*
LDL cholesterol (mmol/l)	3.53 ± 0.83	3.40 ± 0.98	2.84 ± 0.84
p		0.595	<0.001*
HDL cholesterol (mmol/l)	1.20 ± 0.39	1.22 ± 0.29	1.44 ± 0.31
p		0.808	0.004*
Triglycerides (mmol/l)	2.24 ± 1.63	1.94 ± 0.90	1.36 ± 0.64
p		0.306	<0.001*
Systolic BP (mm Hg)	129 ± 21	122 ± 15	117 ± 14
p		0.041*	<0.001*
Diastolic BP (mm Hg)	84 ± 12	80 ± 10	75 ± 8
p		0.053	<0.001

concern of persons, included in our study which pointed them to the physician was trouble with body weight. Some of them had gained a lot of kilograms – between 10 and 30 for a short period of time up to 1 year, others had noticed a gradual increase in body weight up to 50 kilograms for a longer period. Usually they thought that their weight did not correspond to their food intake and physical activity. All of them had kept a hypocaloric diet and had increased their physical activity, but the result on body weight was unsatisfactory or temporary, so that they were not motivated to keep on the lifestyle modification. A majority of persons had experienced episodes of tremor, increased sweating and tachycardia on fasting or after ingestion of sugar or carbohydrate food. Tachycardia at rest, peripheral oedema or unmotivated nervousness were their other complaints. Some of the women had an irregular menstrual cycle and/or impossibility to become pregnant.

Our results indicated that a significant effect of metformin on body weight, BMI and waist circumference was observed at the 6th month. It was continued to the end of the observation and it was no more pronounced at 1 year compared to the 6th month. Data about the effect of metformin on anthropometric parameters are not convincing and depend on the treatment duration, the dose of metformin and manner of treatment, alone or added to the lifestyle modification. In concor-

dance with our data, the significant decrease in BMI is observed at 6 months of treatment with metformin from 28.5±3.4 to 26.7±4.0 kg/m^2 ($p < 0.001$) in obese hyperinsulinaemic adolescents between 9 and 17 years old, bearing in mind that it is added to an individual diet and physical activity [8]. Some of metformin's diabetes prevention effect is attributed to weight loss which is durable over the time in the DPP/DPP Outcomes Study [4,6]. Weight reduction with metformin explains 64% of its beneficial effect on diabetes risk at the end of the DPP. Favourable changes are also observed in other parameters of adiposity (waist circumference and waist-hip-ratio). While no single covariate completely explains the beneficial effect of metformin vs. placebo, the combination of weight, fasting insulin and proinsulin levels, and other metabolic factors explains 81% of the favourable outcomes of metformin. Improvements in FPG and estimated insulin sensitivity with metformin may be owing to a combination of weight loss and other direct effects on the liver and other tissues [9].

Following metformin treatment, the mean body weight reduction at 6 months of 7.2 kg and at 1 year of 11.7 kg in our study was greater than described in the DPP by both-lifestyle intervention and metformin. The average weight loss at 6 months is 2.1 and 5.6 kg in metformin and lifestyle intervention group and makes the lifestyle intervention superior compared to metformin. However, the intensive diet and 150 minutes physical exercise per week led to a mean body weight reduction of 6.8 kg in the first year [4]. Metformin in combination with carbohydrate-modified hypocaloric diet led to a body weight loss at 6 months of 7.5 kg and at 1 year of 10.7 kg in non-diabetic women with hyperinsulinaemia [3].

Our results indicated, that the effect of metformin on insulin resistance was increasing over the time of observation, which could explain its durable effect on body weight. Even after 10 years of metformin treatment the reduction in body weight has kept constant and the incidence of diabetes has been reduced by 18% in comparison to placebo [4]. In patients with heart failure and insulin resistance, defined by FIRI≥2.7, metformin 2 g/daily has reduced insulin resistance (from 5.8±3.8 to 4.0±2.5, $p < 0.001$) and resulted in a weight loss of 1.9 kg ($p < 0.001$) for a shorter period of 4 months [10]. Similarly to our data, as effect on BMI, metformin significantly decreases HOMA-IR at a dose of 1.7 g/d in adolescents aged 9–17 years given in combination with individual diet and physical activity [8]. Metformin reduces insulin resistance compared with placebo (HOMA-IR from 3.39 to 2.5 vs.3.42 to 3.37, $p = 0.01$) in persons with MS after 3 months at a lower dose of 1 g/daily [11]. Metformin treatment at a dose of 1.7 g daily for a period of 6 weeks did not have a significant effect on HOMA-IR [12].

A 1 year metformin treatment resulted in a significant decrease in total cholesterol, LDL cholesterol, triglycerides, systolic and diastolic blood pressure and in significant increase in HDL cholesterol. Total cholesterol and systolic blood pressure were significantly reduced even at 6 months. Metformin significantly reduced total cholesterol, LDL cholesterol, Cholesterol:HDL cholesterol ratio and systolic

blood pressure and it significantly increased HDL cholesterol in double-blind randomized controlled studies in first line relatives of type 2 diabetics with normal glucose tolerance and MS for a period of 3 months [13, 14]. A 1 year metformin treatment significantly reduced systolic blood pressure, total and LDL cholesterol with no effect on body weight, HDL cholesterol and triglycerides in persons with normal and impaired glucose tolerance and impaired fasting blood glucose in a BIGPRO1 Trial [15]. In the Carmos study, metformin reduced the incidence of T2DM in overweight and obese non-diabetic adults while also decreasing the rate of MS by improving the CVD risk factors. After 1 year of follow-up, the prevalence of T2DM in the metformin group is 1.1% and 8.1% in the non-metformin group ($p = 0.012$). Incidence of MS decreased from 38.9% to 21.1% in the metformin group and from 36.2% to 32.8% in the non-metformin group ($p = 0.035$). The statistically significant decrease in the prevalence of the MS in the metformin group is not correlated with waist circumference, triglyceride, or blood pressure levels. The percentages of persons with low HDL cholesterol levels is decreased by 5.6% in the metformin group and by 3.0% in the non-metformin group ($p = 0.046$). HDL cholesterol is increased by 3.1 mg/dl from baseline in the metformin group vs. 1 mg/dl in the non-metformin group ($p = 0.001$) [16].

A 10 year analysis of effectiveness of three therapeutic regimens (metformin, lifestyle change and placebo) in the programme of diabetes prevention has shown a significant reduction in systolic blood pressure, diastolic blood pressure, LDL cholesterol and triglycerides and a significant increase in HDL cholesterol in all treatment groups similarly and less medicaments for dyslipidaemia and hypertension was observed in the group with intensive lifestyle change [4]. At the beginning of our study, 25 of 68 persons with MS were taking antihypertensive drugs. At 1 year of metformin treatment, 12 persons reduced the number of antihypertensive drugs and 11 stopped them. At the end of the study all 7 persons who were taking drugs for dyslipidaemia discontinued their use.

Generally, the metformin treatment was well tolerated. We did not observe serious side effects, hypoglycaemias and changes in routine biochemical parameters. Some persons complained of mild gastrointestinal symptoms like diarrhoea, flatulation or nausea at the beginning of the treatment, that dissapeared during titration period and did not cause discontinuation of the treatment in any of the individuals.

Conclusion. People who have MS are at high risk for development of T2DM and CVD, that makes the treatment of cardiometabolic risk factors mandatory. In routine clinical practice we treat the most common cardiometabolic risk factors – obesity with lifestyle intervention, lipid abnormalities with diet, fibrates and statins and hypertension with antihypertensive drugs. Our study shows that treatment with metformin alone, without intensive diet and physical activity could reduce cardiometabolic risk factors as visceral obesity, insulin resistance, dyslipidaemia and arterial hypertension and supports the hypothesis that metformin

could be applied for prevention of T2DM and CVD. As it has some limitation concerning lack of a control placebo group, further prospective population-based studies and randomized clinical placebo-controlled trials especially concerning the dose of metformin and duration of treatment are needed.

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