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Original Research Article

Metformin Improves Insulin Secretion and Reduces Insulin Resistance in People at High Risk for Development of Type 2 Diabetes Mellitus and Cardiovascular Disease

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Abstract

The aim of the study was to investigate the effect of metformin on insulin secretion and insulin resistance in hyperinsulinaemic normal glucose tolerant people with metabolic syndrome who represent a high-risk group for development of type 2 diabetes mellitus and cardiovascular disease. Fifty two participants of mean age 40.1±14.2 yrs were included in an open-label prospective one year observational clinical study in which plasma glucose, serum insulin during a 3-h oral glucose tolerance test, Glucose/Insulin ratio (G/I), Quantitative Insulin Sensitivity Check Index (QUICKI) and Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) at three months intervals following metformin treatment were evaluated. The results showed that fasting serum insulin, 3-h post glucose load (PGL) serum insulin and HOMA-IR significantly reduced at 6, 9 month and at 1 year. Fasting plasma glucose, 1-h and 2-h PGL serum insulin significantly decreased at 3, 6, 9 month and at 1 year. Fasting G/I significantly increased at 9 month and at 1 year. 1-h G/I and QUICKI significantly increased at 3, 6, 9 month and at 1 year. 2-h and 3-h G/I significantly increased at 6, 9 month and at 1 year of metformin treatment (all p<0.001). In conclusion, metformin restores physiological insulin secretion and reduces insulin resistance in hyperinsulinaemic normal glucose tolerant people with metabolic syndrome and could be considered as a therapeutic option for prevention of type 2 diabetes mellitus and cardiovascular disease.

Key Words: Hyperinsulinaemia, Insulin Secretion, Insulin Resistance, Metabolic Syndrome, Metformin, Normal Glucose Tolerance, Type 2 Diabetes Mellitus

INTRODUCTION

Metabolic syndrome (MS) is a cluster of cardiometabolic risk factors that defines an elevated risk of developing type 2 diabetes mellitus (T2DM) and cardiovascular disease (CVD) (Wilson and Meigs, 2008; Lucacova-Zib and Gopalacrishnan, 2010; Kassi et al., 2011). Nowadays, T2DM affects over 382 million people worldwide and approximately a half of million people in Bulgaria. Patients with T2DM without a previous myocardial infarction (MI) have as high a risk of having a MI as patients with no T2DM and with a previous MI. This observation is also true for stroke and CV death (Haffner et al., 1998). Patients with T2DM without prior CVD have a similar CV mortality rate to patients with no T2DM and with a previous CVD showing that T2DM is a coronary heart disease risk equivalent (Malmberg et al., 2000). T2DM is a complex metabolic disorder, characterized by hyperglycaemia resulting from both impaired insulin secretion and insulin resistance. Insulin resistance or decreased insulin sensitivity can be generally defined as a subnormal tissue response to normal insulin

concentrations. By this definition, it may refer to many metabolic actions of insulin in many tissues of the body. In clinical practice, however, insulin resistance refers to a state in which a given concentration of insulin is associated with a subnormal glucose response. As a result higher levels of insulin are needed in order for insulin to keep blood glucose at a normal level (Moller and Flier, 1991). Under most circumstances, insulin resistance is considered as the leading pathogenetic defect of T2DM and compensatory hyperinsulinaemia due to insulin resistance as the earliest stage for developing T2DM. Initially, enhanced insulin secretion can compensate for the insulin resistance but early phase insulin secretion is impaired. In the transition from normal to impaired and diabetic glucose tolerance, insulin sensitivity worsens about 40% whereas insulin secretion worsens 3-4 fold. At the time of diagnosis 50% of the individuals already have some manifestations of CVD (Groop, 2000). Prevention of T2DM requires treatment pointed at defects of both insulin secretion and insulin resistance.

The main components of the MS are insulin resistance, central (visceral) obesity, dyslipidaemia, raised arterial blood pressure and dysregulated glucose homeostasis. The answer of the question of what is the core defect of MS remains controversial. Some consider as the metabolic antecedent insulin resistance and the others think that it is obesity. From historical point of view, Gerald Reaven was the first to put forward the concept of “syndrome X”, hypothesizing that target tissue resistance to insulin action is a central feature for the development of T2DM and CVD (Reaven, 1988). Ten years later insulin resistance defined with the “gold standard” hyperinsulinaemic euglycaemic clamp technique or with its surrogate measure homeostasis model assessment of insulin resistance (HOMA-IR) is a necessary requirement in the first official definition for the MS of World Health Organisation (Alberti and Zimmet, 1998). Fasting hyperinsulinaemia considered as the best marker of insulin resistance in nondiabetic individuals, is a necessary requirement of the MS defined as insulin resistance syndrome by the European Group for the Study of Insulin Resistance (EGIR) (Balkau and Charles, 1999). International Diabetes Federation (IDF) introduced central obesity measured with waist circumference as a prerequisite for the MS to be diagnosed (Alberti and Zimmet, 2005). Hyperinsulinaemia is a metabolic antecedent or cause rather than consequence of obesity and dietary and pharmacologic approach that reduce high insulin levels could promote weight loss (Mogul et al., 2001). Mechanism responsible for prevention of T2DM and CVD refers to the treatment of insulin resistance and hyperinsulinaemia.

Metformin has been established like a first-line therapy in guidelines for treatment of T2DM because it reduces hyperglycaemia and targets CVD risk factors (Inzucchi et al., 2015). 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 (Diabetes Prevention Program Research Group, 2002; Diabetes Prevention Program Research Group, Knowler at al., 2009; Andreadis at al., 2009; Fontbonne et al., 2009; Diabetes Prevention Program Outcomes Study Research Group, Orchard et al., 2013). At present, metformin is one of the main therapeutic options in the polycystic ovary syndrome (PCOS), an insulin resistant state, because of reducing insulin resistance, hyperinsulinaemia and CVD risk factors (Krstevska et al., 2006; Cheang et al., 2009; Oppelt et al., 2010; Otta et al., 2010; Saxena et al., 2010). Less is known about the effect of metformin on insulin resistance and hyperinsulinaemia in individuals with normal glucose tolerance at high risk for development of T2DM and CVD.

The aim of the study was to investigate the effect of metformin on insulin secretion and insulin resistance in hyperinsulinaemic normal glucose tolerant people with MS who represent a high-risk group for development of T2DM and CVD.

MATERIALS AND METHODS

Study participants

Fifty two participants attending Department of Diabetology of Clinical Center of Endocrinology and Gerontology participated in the study. The inclusion criteria were: 1) age-between 18-59 years; 2) MS according to the IDF definition (Alberti et al., 2005); 3) 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 (PGL) plasma glucose < 7.8 mmol/l; 4) hyperinsulinaemia during OGTT defined as fasting serum insulin > 25 mIU/l and/or 2-h PGL serum insulin > 3 times from baseline; 5) no presence of CVD or diseases of the endocrine system that are post related with MS; 7) no family history for diabetes; 8) no contraindications for metformin treatment. Characteristics of subjects with hyperinsulinaemia, normal glucose tolerance and MS according to the IDF definition are presented in Table 1.

Study Procedure

At baseline visit case history, physical examination and blood measurements of 90 people were performed and 52 of them fulfilling the inclusion criteria were involved in an open-label prospective one year observational clinical study. Participants were admitted to the Department of Diabetology of Clinical Center of Endocrinology and Gerontology at baseline visit and at 3, 6, 9 month and at 1 year visits to perform blood measurements and to check drug administration. Side effects of metformin

Table 1. Characteristics of subjects with hyperinsulinaemia, normal glucose tolerance and metabolic syndrome according to the IDF definition; LDL= low density lipoprotein, HDL= high density lipoprotein

Variables	Mean ± SD
Sex (men / women)	20 / 32
Body Mass Index (kg/m^2)	32.3 ± 5.2
Waist circumference (cm)	102.8 ± 14.3
Systolic blood pressure (mm Hg)	131 ± 18
Diastolic blood pressure (mmHg)	85 ± 11
Fasting plasma glucose (mmol/l)	5.40 ± 0.53
Total cholesterol (mmol/l)	5.78 ± 0.76
LDL cholesterol (mmol/l)	3.61 ± 0.76
HDL cholesterol (mmol/l)	1.10 ± 0.34
Triglycerides (mmol/l)	2.60 ±1.74

treatment were recorded at 3, 6, 9 month and at 1 year. The participants had on disposal a constant telephone contact with investigators for any questions and problems occurred during the study. OGTT with measurement of plasma glucose and serum insulin on fasting and at 1-h, 2-h and 3-h after 75 g glucose load, Glucose/Insulin ratio (G/I), Quantitave Insulin Sensitivity Check Index (QUICKI) and HOMA-IR at baseline and at 3, 6, 9 month and at 1 year of metformin treatment were followed.

All subjects gave their written informed consent to participate in the study. The study protocol was approved by the local Ethical Committee of the Clinical Center of Endocrinology and Gerontology.

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±0.2g, taken at breakfast, at lunch and at dinner in the middle of the meal. Participants were advised to keep on their usual diet and physical activity throughout the study. Individuals who were taking lipid lowering and antihypertensive drugs continued their use to the end of the observation.

Analytical Methods

Blood samples for glucose, insulin and routine biochemical parameters-serum lipids, full blood count, urea, creatinine, uric acid, liver enzymes and electrolytes were taken after a 12-hour overnight fast. They were immediately centrifuged and analysed. Plasma glucose was defined by a glucose oxidase method on biochemical analyzer (Cobas Integra, Roche Diagnostics, Switzerland). Serum insulin was estimated by an immunoradiometric method (Insulin IRMA kit, Immunotech, Beckman Coulter, Czech Republic, reference range 2-25 mIU/l) with analytical sensitivity 0.49 mIU/l and functional sensitivity 1.35 mIU/l. The assay exhibit extremely low cross reactivities with human proinsulin, C-peptide, Des-31,32 proinsulin, Lispro (Humalog®) and 55% cross-reactivity with Des-64,65 proinsulin. The intra-assay coefficient of variation was found below 4.0%, the inter-assay coefficient of variation was found below 4.8%. G/I was calculated as fasting plasma glucose (mg/dl) (1mmol/l=18 mg/dl) divided by serum insulin (mIU/l) (Legro et al., 1998), QUICKI was calculated according to the fasting serum insulin (mIU/l) and fasting plasma glucose (mg/dl) as $1/[\log(I_0) + \log(G_0)]$ (Katz et al., 2000). HOMA-IR was calculated as fasting plasma glucose (mmol/l) x fasting serum insulin (mIU/l) / 22.5 (Matthews et al., 1985).

Statistical Methods

Statistical analysis was done using statistical package for social science (SPSS, version 14 for Windows, Chicago, IL, USA). Data are presented as mean±SD. For evaluation of 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. Shapiro-Wilk test was used for normality. A level of $p<0.05$ was considered significant.

RESULTS

Fasting plasma glucose 5.40±0.53 mmol/l was significantly decreased at 3 month 5.07±0.52 mmol/l ($p=0.029$), at 6 month 5.04±0.40 mmol/l ($p=0.002$), at 9 month 4.88±0.52 mmol/l ($p<0.001$) and at 1 year 4.74±0.50 mmol/l ($p<0.001$). At 1 year it was significantly lower compared to that of 3 month ($p=0.036$). 1-h and 2-h

Table 2. Effect of metformin on fasting SI, 1-h, 2-h and 3-h PGL serum insulin at 3, 6, 9 month and at 1 year; SI= serum insulin; PGL= post glucose load serum insulin

Variables		Baseline	3 month	6 month	9 month	1 year
Fasting (mIU/l)	SI	24.1 ± 15.3	18.5 ± 12.6	17.2 ± 8.8	13.2 ± 6.9	11.6 ± 6.0
P			0.123	0.012*	<0.001*	<0.001*
1-h PGL (mIU/l)		136.8 ± 67.6	94.9 ± 52.2	93.8 ± 53.2	61.9 ± 34.1	54.5 ± 51.4
P			0.009*	0.003*	<0.001*	<0.001*
2-h PGL (mIU/l)		62.6 ± 43.2	45.1 ± 26.6	38.7 ± 29.0	26.1 ± 13.8	27.6 ± 21.6
P			0.040*	0.026*	0.004*	<0.001*
3-h PGL (mIU/l)		23.2 ± 11.7	18.3 ± 9.05	15.3 ± 7.1	11.4 ± 5.2	9.7 ± 5.8
P			0.132	<0.001*	<0.001*	<0.001*

*significant difference versus baseline

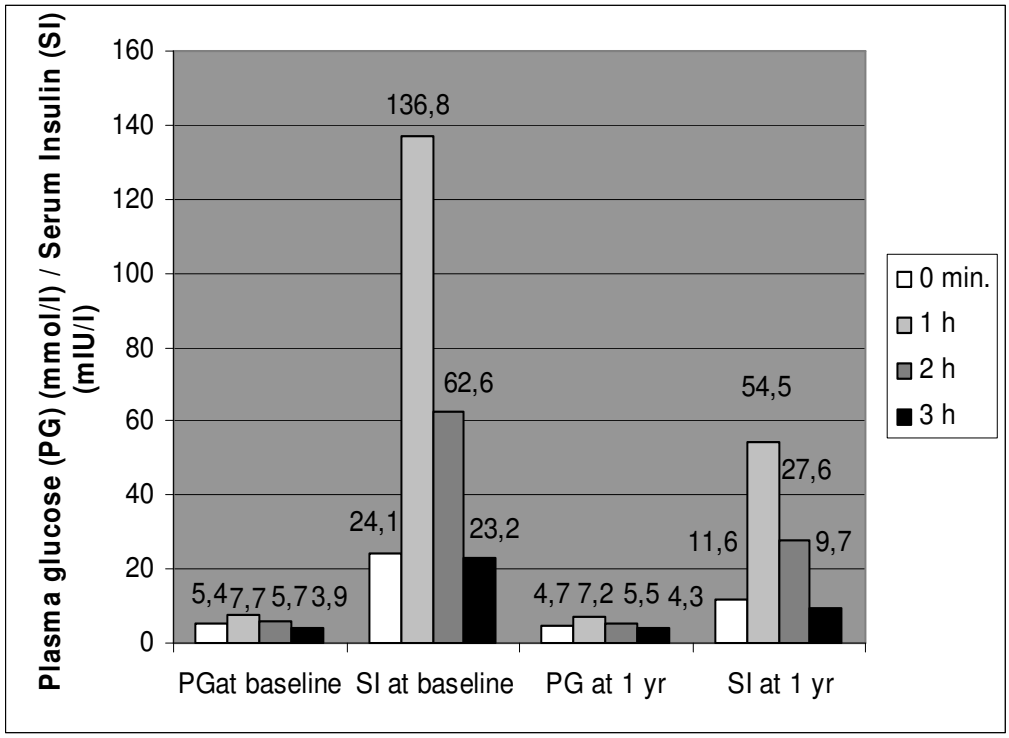


Figure 1. Mean values of Plasma Glucose and Serum Insulin at baseline and at 1 year of metformin tretment; PG=plasma glucose; SI= serum insulin (Insulin IRMA kit, Immunotech, Beckman Coulter, Czech republic)

plasma glucose were not changed during a 1 year treatment period. The effect of metformin on fasting serum insulin, 1-h, 2-h and 3-h PGL serum insulin is presented in Table 2. At 1 year fasting serum insulin was significantly lower in comparison to that of 6 month (p=0.007), 1-h PGL serum insulin was significantly lower compared to that of 3 month (p= 0.013) and 2-h PGL serum insulin was significantly lower in comparison to that of 3 month (p=0.024). The mean values of plasma glucose amd serum insulin during OGTT at baseline and at 1 year following metformin treatment is presented in Figure 1. Effect of metformin on fastng G/I, 1-h G/I, 2-h G/I and 3-h G/I is shown in Figure 2 a,b,c,d. Effect of metformin on QUICKI and HOMA-IR is presented in Figure 3 and Figure 4. At 1 year HOMA-IR was significantly lower in comparison to that of 6 month (p=0.006).

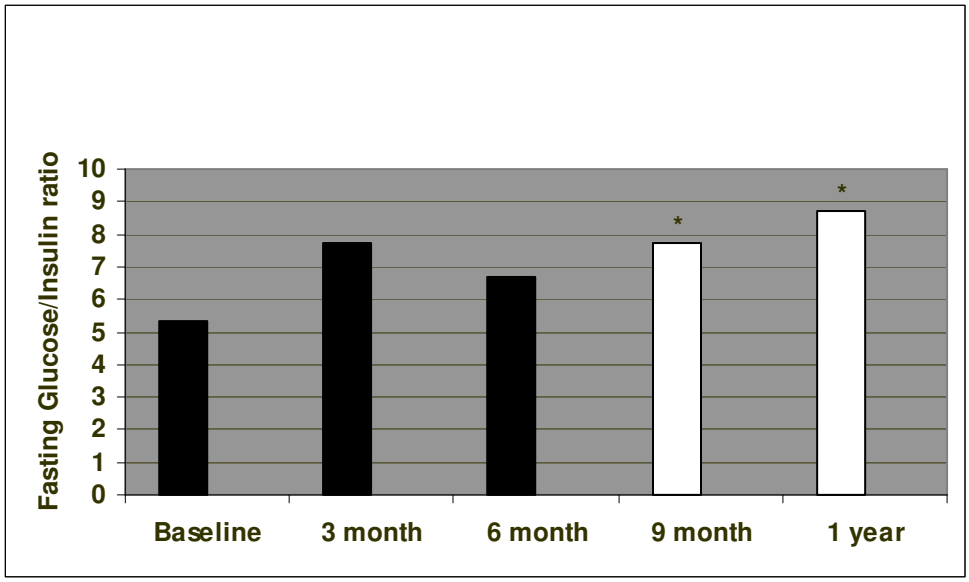


Figure 2a

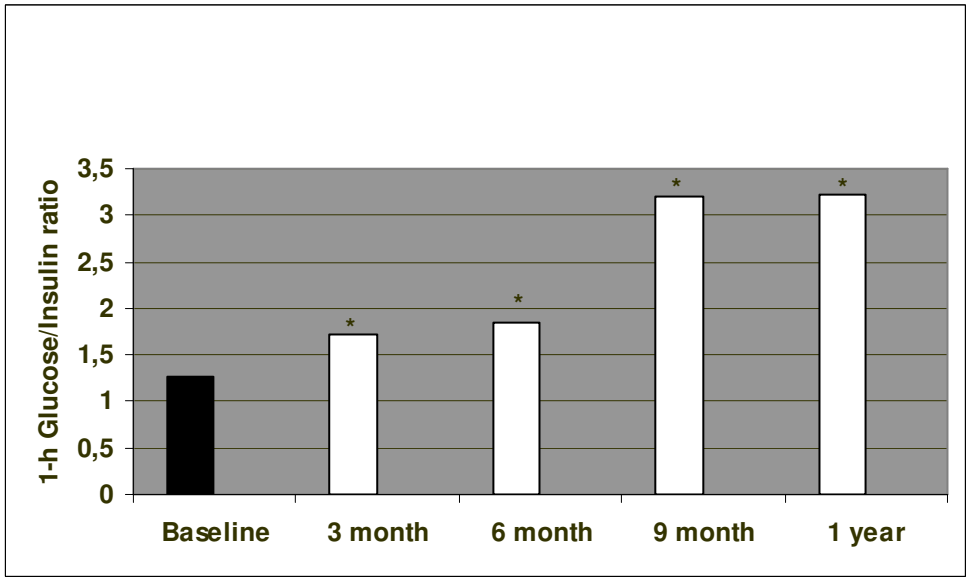
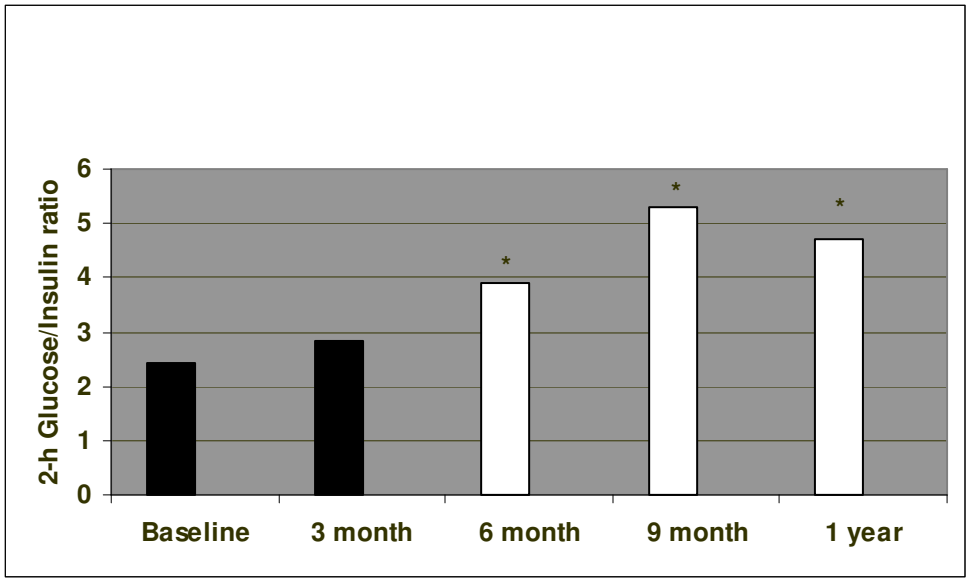


Figure 2b



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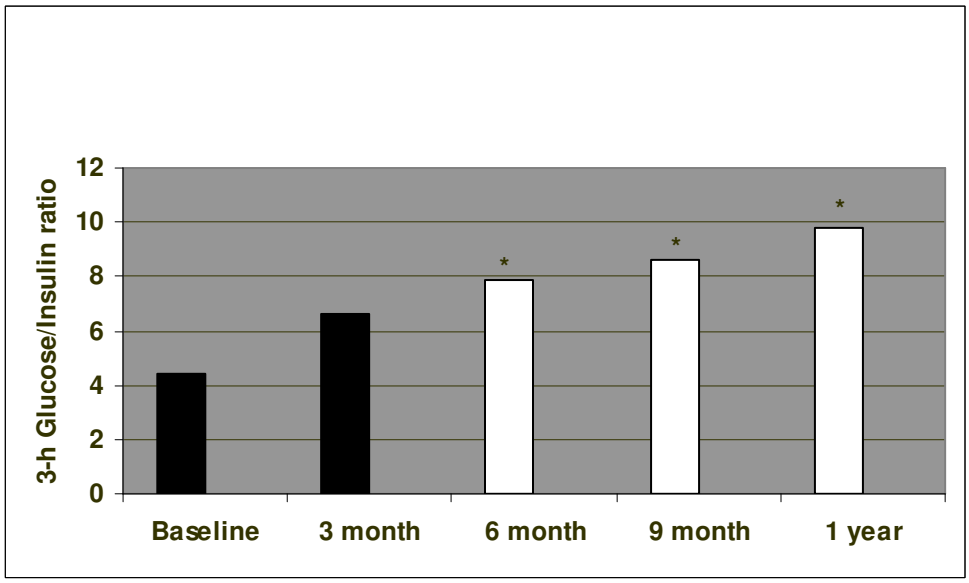

Figure 2d

Figure 2. Effect of metformin on Glucose/Insulin ratio. **2a.** Effect of metformin on Fasting Glucose/Insulin Ratio. Fasting G/I 5.33±3.03 significantly increased at 9 month 7.86±3.54 ($p=0.003$) and at 1 year 8.71±3.95 ($p<0.001$); **2b.** Effect of metformin on 1-h Glucose/Insulin Ratio. 1-h G/I 1.27±0.73 significantly increased at 3 month 1.72±0.96 ($p=0.049$), at 6 month 1.86±0.86 ($p=0.003$), at 9 month 3.19±1.86 mIU/l ($p<0.001$) and at 1 year 3.23±1.74 ($p<0.001$); **2c.** Effect of metformin on 2-h Glucose/Insulin Ratio. 2-h G/I 2.44±1.93 significantly increased at 6 month 3.93±2.49 ($p=0.01$), at 9 month 5.32±2.54 ($p<0.001$) and at 1 year 4.73±2.26 ($p<0.001$); 2**d.** Effect of metformin on 3-h Glucose/Insulin Ratio. 3-h G/I 4.41±4.05 significantly increased at 6 month 7.90±3.57 ($p=0.005$), at 9 month 8.61±4.34 ($p=0.001$) and at 1 year 9.80±4.09 ($p<0.001$); G/I = Glucose/Insulin ratio
*significant difference versus baseline

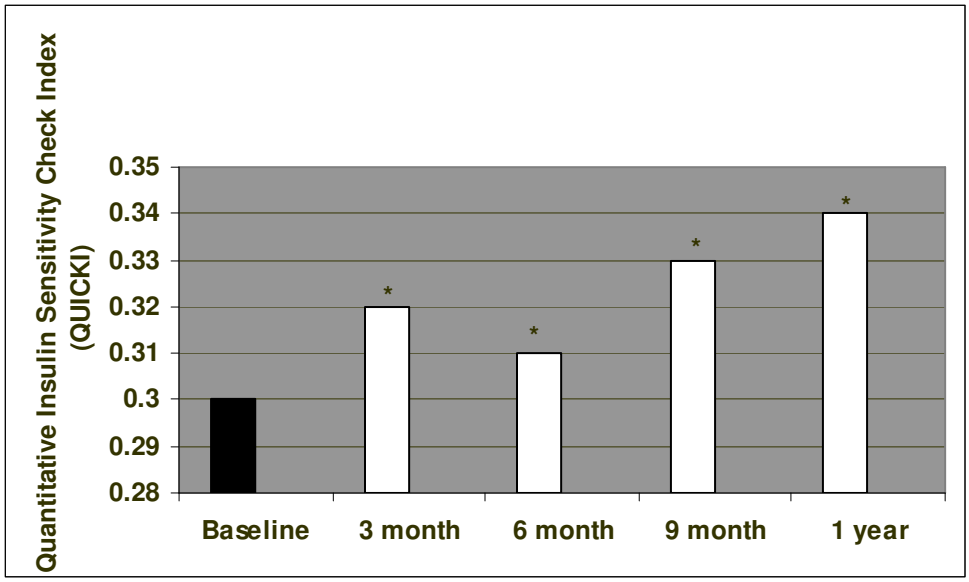

Figure 3. Effect of metformin on Quantitative Insulin Sensitivity Check Index. QUICKI 0.30±0.02 significantly increased at 3 month 0.32±0.03 (p=0.045)**.** at 6 month 0.32±0.02 (p=0.008), at 9 month 0.33±0.02 (p<0.001) and at 1 year 0.34±0.02 (p<0.001); QUICKI=Quantitative Insulin Sensitivity Check Index
*significant difference versus baseline

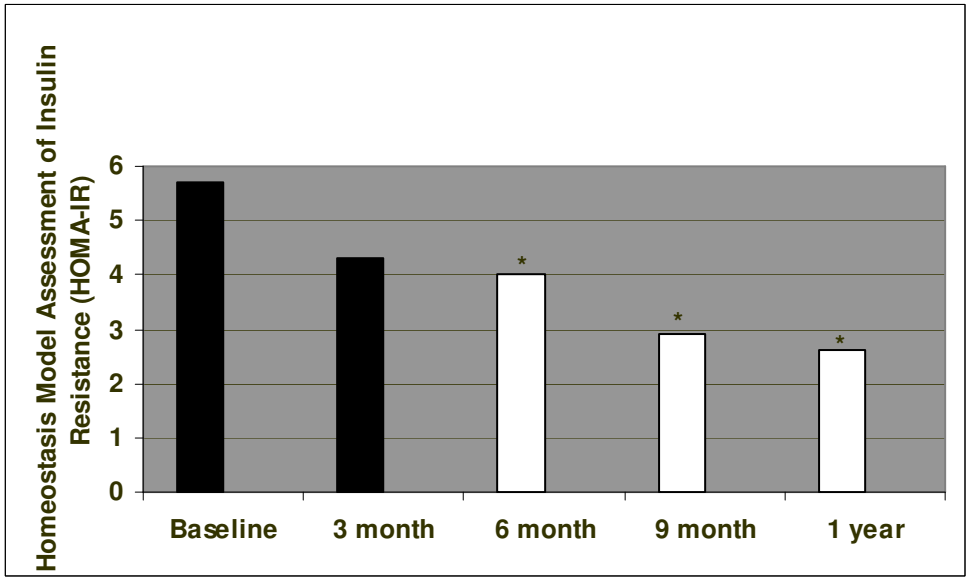

Figure 4. Effect of metformin on Homeostasis Model Assessment of Insulin Resistance. HOMA-IR 5.74±3.77 significantly reduced at 6 month 4.01±2.13 (p=0.01), at 9 month 2.97±1.49 (p<0.001) and at 1 year 2.58±1.40 (p<0.001); HOMA-IR= Homeostasis Model Assessment of Insulin Resistance
*significant difference versus baseline

DISCUSSION

Metabolic syndrome is a strong predictor of T2DM and CVD (Wilson and Meigs, 2008; Lucacova-Zib and Gopalacrishnan, 2010; Kassi et al., 2011). Insulin resistance is considered as the major common denominator of the components involved in the MS and it has been shown to be associated with increased risk of developing T2DM and CVD (Reaven, 1988; Alberti and Zimmet, 1998; Balkau and Charles, 1999; Groop, 2000).

T2DM and CVD affect increasing number of young and social active people, like those included in our study, so that the prevention of these diseases is a strategical aim of health systems all over the world (Ervin, 2009). Treatment of insulin resistance seems to have investigational and clinical relevance in order to prevent subjects at high risk for development of T2DM and CVD. Thus, agents that ameliorate insulin resistance and reduce hyperinsulinaemia, such as metformin, may provide a therapeutic option of the MS and could prevent T2DM and CVD. Metformin counteracts hyperglycaemia and hyperinsulinaemia primarily by suppressing hepatic gluconeogenesis and hepatic glucose production. It also increases peripheral insulin sensitivity in insulin sensitive tissues such as muscle and adipose tissue, promotes glucose uptake and enhances peripheral glucose utilization (Boyle, 2010).

Our study confirmed the antihyperglycaemic, but not hypoglycaemic action of metformin. The effect of metformin on fasting plasma glucose was increasing over the time of observation. Metformin significantly reduced fasting plasma glucose within the normoglycaemic range at 3 month, this effect continued to the end of the observation and it was the most pronounced at 1 year without reaching hypoglycaemic values. Effect of metformin on fasting plasma glucose at 3 month in first degree relatives of type 2 diabetics with normal glucose tolerance, MS and obesity is noticed (Kraemer de Aguiar et al, 2006; Lima et al, 2009). Metformin alone or added to diet reduces fasting plasma glucose in people with overweight, obesity, MS, normal glucose tolerance with risk factors for diabetes and prediabetes over a 1 year period (Andreadis et al, 2009; Fontbonne et al, 2009). Also a significant decrease in fasting plasma glucose level is detected in patients with MS taking metformin at a lower dose of 1g daily for a shorter period of 3 months but not in those on placebo (Vitale et al, 2005).

Our results indicated that metformin restores physiological pattern of insulin secretion by decreasing fasting and post glucose load hyperinsulinaemia. The effect of metformin on hyperinsulinaemia was increasing over the time of observation. The decrease in fasting serum insulin and 3-h PGL serum insulin was significant at 6, 9 month and at 1 year it was the most pronounced. The significant effect of metformin on 1 and 2-h PGL serum insulin was noticed at 3, 6, 9 month and at 1 year it was the most expressed. In concordance to our data, for the same period of 1 year, in obese impaired glucose tolerant and normal glucose tolerant people with risk factors for T2DM from DPP study, a significant decrease in fasting plasma glucose with no influence on 2-h PGL plasma glucose is observed. In contrast to our findings, there is no a significant effect of metformin on fasting and 2-h PGL serum insulin (Fontbonne et al., 2009). Physiologically, glucose stimulated insulin secretion during OGTT consists of a transient first phase at 30-60 min when it is increased 5-6 fold, followed by a sustained second phase at 60-120 min when it is increased 2-3 fold. Insulin secretion declines afterwords so that to reach the baseline level at 180 min. According to the immunoradiometric assay of serum insulin (Insulin IRMA kit, Immunotech, Beckman Coulter) the values of serum insulin during OGTT in healthy subjects are as follows: 0 min. 8.8±3.1, 60 min. 44.4±14.1, 120 min. 17.6±7.2 mIU/l. As shown in Figure 1, at the end of a 1 year study period, dynamics of insulin release during OGTT resembles physiological pattern of insulin secretion after glucose stimulus.

Hyperinsulinaemic euglycaemic clamp technique is regarded as the “gold standard” for an accurate assessment of in vivo insulin sensitivity in humans. However, this method is labour extensive, expensive and therefore unsuitable for routine clinical practice. Fasting glucose and insulin levels contain sufficient information to precisely determine insulin sensitivity in vivo over a wide range in a diverse population. We applied G/I, QUICKI and HOMA-IR as the most frequently used surrogate measures of insulin sensitivity/insulin resistance (Matthews et al., 1985; Legro et al., 1998; Katz et al, 2000; Bonora et al., 2000).

In women with PCOS, a significant correlation of insulin sensitivity index from the frequently sampled intravenous glucose tolerance test with fasting G/I (r=0.73) and 2-h G/I (r=0.74) is found. Among fasting plasma glucose, insulin level and area under the curve for glucose and insulin during OGTT, only fasting G/I is found to be significantly predictive of insulin sensitivity index. As a screening test for insulin resistance in PCOS has been set a value of the fasting G/I of less than 4.5 (legro et al., 1998). A mean value of fasting G/I in subjects included in our study was 5.33, at the end of the observation it reached the values of 7.86 and 8.71 at 9 month and at 1 year respectively, indicating improved insulin sensitivity. 1-h G/I significantly increased at 3, 6, 9 month and at 1 year of metformin treatment, 2-h and 3-h G/I significantly increased at 6, 9 month and 1 year of metformin treatment, showing improved insulin action after glucose stimulus. At the end of the observation, 3-h G/I reached the values of 8.61 and 9.80 at 9 month and at 1 year respectively, similar to the fasting G/I levels at the same time period.

QUICKI and index of insulin sensitivity derived from the clamp technique are highly correlated for nonobese, obese and diabetic subjects (r=0.78). QUICKI has substantially better correlation with insulin sensitivity from the clamp than the correlation between insulin sensitivity from the clamp and insulin sensitivity from the frequently sampled intravenous glucose tolerance test (Katz et al., 2000). We used QUICKI as an accurate and reproducible method for determining insulin sensitivity in people at high risk for development of T2DM and CVD. As shown in Figure 3, there was a significant increase in QUICKI at 3 month of metformin treatment continuing to the end of the study, from 0.30 at baseline to 0.34 at

1 year, that denotes increased insulin sensitivity.

A valuable alternative to more sophisticated techniques in the evaluation of in vivo insulin sensitivity/insulin resistance in man is HOMA-IR. With this homeostasis model of insulin resistance, high HOMA values denote low insulin sensitivity (insulin resistance) (Matthews, 1985; Bonora et al., 2000). HOMA-IR is strongly correlated with insulin sensitivity, assessed by the glucose clamp technique in both nondiabetic and diabetic subjects (r=0.83 and -0.92, respectively) (Matthews at al., 1985). The significant correlation (r=-0.82) between HOMA-IR and total glucose disposal rate during glucose clamp technique is observed, with no substantional differences between men and women, younger and older subjects, nonobese and obese subjects, nondiabetic and diabetic subjects and normotensive and hypertensive subjects (Bonora et al, 2000). According to our previous data, as a screening test for insulin resistance in subjects with normal glucose tolerance and overweight or obesity could be considered a value of HOMA-IR of ≥5.64 (Kamenova, 2006). The mean value of HOMA-IR in subjects included in our study was 5.74, which indicate a presence of insulin resistance. Our results showed, that effect of metformin on HOMA-IR, such as on hyperinsulinaemia, were increasing over the time of observation. The decrease in HOMA-IR was significant at 6, 9 month and at 1 year it was the most pronounced declining to a value of 2.58, that indicates a reduced insulin resistance. Metformin decreases insulin resistance compared with placebo (HOMA-IR from 3.39 to 2.5 vs.3.42 to 3.37, p=0.01) in people with MS after 3 months at a lower dose of 1g daily (Vitale et al., 2005). Similarly to our findings, the significant increase in insulin sensitivity derived from the clamp technique and QUICKI and a significant decrease in fasting serum insulin, 2-h PGL serum insulin and HOMA-IR are noticed at 6 month in obese hyperinsulinaemic adolescents between 9 and 17 years old, having in mind that metformin has been added to an individual diet and physical activity (Atabek and Pirgon, 2008). In patients with heart failure and insulin resistance, defined by fasting insulin resistance index (FIRI), metformin reduces insulin resistance in comparison to placebo for a shorter period of 4 months (Wong et al., 2012). In 19 individuals with MS and T2DM, metformin treatment at a lower dose of 1.7 g daily for a period of 6 weeks does not have a significant effect on HOMA-IR and fasting plasma glucose (Cabezas et al., 2012).

Generally, the metformin treatment was well tolerated. We did not observe serious side effects, hypoglycaemias and changes in routine biochemical parameters. Some people 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 them.

According to the updated Position Statement of the American Diabetes Association and the European Association for the Study of Diabetes, metformin is a first-line therapy for T2D (Inzucchi et al, 2015). Despite an increased number of medications for treating hyperglycaemia, only it has been shown to improve prognosis as a primary end point in a randomized-controlled trial (UK Prospective Diabetes Study (UKPDS) Group, 1998). Having in mind the role of metformin for diabetes prevention, the American Association of Clinical Endocrinologists has recommended metformin for treatment of high-risk individuals with impaired glucose tolerance and impaired fasting blood glucose (Lukacova-Zib and Gopalakrishman G, 2010). Reduction of factors leading to the cardiovascular complications like systolic blood pressure, diastolic blood pressure and triglycerides and improvement of HDL cholesterol and endothelial function leads to the conclusion that metformin could be applied for the treatment of MS (Vitale et al., 2005; Meaney et al., 2008; Cheang et al., 2009).

CONCLUSION

Insulin resistance and resulting hyperinsulinaemia are involved in the pathogenesis of both-T2DM and CVD. The data about the effect of metformin on insulin secretion and insulin resistance in subjects with normal glucose tolerance at high risk for developing T2DM and CVD are inconclusive and demanding more investigations. Our open-label one year prospective observational clinical study shows that treatment with metformin alone, without intensive diet and physical activity, in people with hyperinsulinaemia, normal glucose tolerance and MS, restores physiological insulin secretion and reduces insulin resistance and supports the hypothesis that metformin could be applied for prevention of T2DM and CVD. As this study has some limitations referred to a small sample size and lack of a control group, further studies should be carried out aimed to a prevention of T2DM and CVD.

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