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EFFECT OF INSULIN SENSITIZERS ON GLYCEMIC AND LIPID PROFILE IN PATIENTS WITH POLYCYSTIC OVARY SYNDROME (PCOS)

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ABSTRACT

Introduction: Polycystic ovary syndrome (PCOS) is associated with increased cardiovascular risk later in life. Insulin resistance, common in PCOS, heightens the risk of type 2 diabetes, dyslipidemia, hypertension, and cardiovascular disease. This study explored whether insulin sensitizers could modify traditional cardiovascular risk factors, through influence on insulin resistance.

Objectives: To evaluate the impact of Metformin and Myoinositol therapy on glycemic and lipid profiles in PCOS patients, based on body mass index (BMI).

Methods: A prospective, randomized clinical study was conducted at the UC for Endocrinology in Skopje (2022–2023). Women aged 18–40 with PCOS (Rotterdam 2003 criteria) were assigned to either Metformin (1500 mg XR) or Myoinositol (2 g + 200 mg folic acid TID) for 6 months. Parameters monitored included BMI, fasting plasma glucose (FPG), HOMA-IR, total cholesterol, LDL-C, HDL-C, triglycerides, lipid accumulation product (LAP), and TG/HDL ratio.

Results: Baseline BMI significantly influenced HDL, triglycerides, TG/HDL, and LAP. Myoinositol significantly improved cholesterol regardless of BMI. Among patients with BMI ≥25 kg/m², Metformin significantly reduced FPG (4.65 ± 0.5 vs 5.01 ± 0.3 mmol/L) and HOMA-IR (2.25 ± 0.6 vs 2.94 ± 1.1 mmol/L). HOMA-IR positively correlated with TG/HDL ratio (R=0.2086, p=0.016).

Conclusion: Myoinositol improved cholesterol in PCOS patients regardless of BMI. Metformin significantly affected glycemic control in overweight patients. The TG/HDL ratio may serve as a predictive marker for insulin resistance in PCOS.

Keywords: PCOS, Metformin, Myoinositol, Lipid profile, Glycemic profile, Insulin resistance

INTRODUCTION

Polycystic Ovary Syndrome (PCOS) is one of the most common endocrine disorders, affecting 5-10% of women of reproductive age. In recent years, the importance of monitoring these patients has been increasingly emphasized, primarily due to the numerous comorbidities associated with the condition, such as: infertility, metabolic dysfunction, cardiovascular diseases, psychological and oncological complications. The metabolic dysfunction observed in Polycystic Ovary Syndrome (PCOS) leads to an increased risk of glucose intolerance, type 2 DM, and gestational diabetes, which leads to an increased cardiovascular risk in these women of reproductive age. [1] In addition, compensatory hyperinsulinemia directly affects the occurrence of reproductive dysfunction in these patients.

A large proportion of women with PCOS are overweight or obese. These patients have been shown to have a pronounced centripetal accumulation of adipose tissue, compared with control groups. Obesity, especially centripetal, plays a major role, independently , in the development and maintenance of PCOS, and has a significant impact on cardiovascular and metabolic risk in this group of patients. [2] Obesity is a clear risk factor for the development of impaired glucose tolerance, type 2 diabetes, metabolic syndrome, and dyslipidemia. Most meta-analyses of the impact of obesity in PCOS have shown that overweight and obesity are associated with elevated fasting glycemia(FPG), basal insulinemia, Homeostatic Model Assessment of Insulin Resistance (HOMA IR), and a worsening lipid profile. It remains debatable whether there is a cardiovascular risk in women with PCOS and normal body weight. These patients have been shown to have impaired fat tissue distribution and insulin resistance, reduced peripheral insulin sensitivity, muscle mitochondrial activity, impaired glucose utilization, relative postprandial hyperinsulinemia, and increased hepatic fat deposition have also been reported, compared to normal-weight controls. [3, 4]

Dyslipidemia is one of the main risk factors for the progression of atherosclerotic changes in blood vessels, and is directly related to cardiovascular diseases. There are a large number of studies on the relationship of dyslipidemia with cardiovascular events in postmenopausal women, but such data are limited when it comes to the female population in the reproductive period.

Atherosclerosis begins at a very early age, and PCOS as a syndrome ,is often associated with dyslipidemia and represents a condition that is associated with increased cardiovascular risk.

Insulin resistance is considered one of the most significant features of PCOS with a prevalence of 35-80%. [5] The risk of developing type 2 Diabetes mellitus is 5-10 times more common than in healthy controls. About 70% of these patients also have dyslipidemia. Most studies indicate reduced HDL (high-density lipoprotein) -C and elevated triglycerides in PCOS. [6] The syndrome is likely one of the most common causes of dyslipidemia in women under the age of 40. Studies have shown that dyslipidemia is more common in obese patients with PCOS, especially in terms of elevated triglycerides and decreased HDL cholesterol. However, regardless of BMI, it has been observed that patients with PCOS have poorer metabolic control and a higher degree of visceral adiposity, compared to the control group with a similar BMI. However, lipid profile and obesity have been shown to be significant predictors of the occurrence of metabolic syndrome in PCOS.

Also, lipoprotein indices, especially triglycerides(TG)/HDL-C, have been shown to be directly related to insulin resistance and as such can be used as predictors of glucose intolerance in women with PCOS. [5]

In recent years, indices that combine anthropometric parameters with lipid values, such as Visceral Adiposity Index (VAI) and Lipid accumulation product (LAP) index, have been increasingly used, which have shown high accuracy in identifying visceral obesity and as such are effective predictors of insulin resistance and metabolic syndrome and are positively associated with cardiometabolic risk in PCOS. [7]

Given the association of PCOS with possible long-term cardiovascular complications in older patients, there is increasing focus on the treatment of the syndrome, in order to avoid this risk. To this end, in our study we examine the implication of the use of insulin sensitizers on the glycemic and lipid profile in PCOS, as traditional cardiovascular risk factors.

OBJECTIVES

The study aimed to determine the impact of therapy with the insulin sensitizers, Metformin and Myoinositol, on the glycemic and lipid profile in patients with Polycystic Ovary Syndrome, depending on their BMI.

MATERIAL AND METHODS

The research conducted was a prospective, randomized, clinical study that was done at the University Clinic for Endocrinology, Diabetes and Metabolic Diseases in Skopje, in the period of 2022/2023. The study, in accordance with previously set inclusion and exclusion criteria, included total of 68 women of reproductive age from 18 to 40 years. The selection of the participants was done by a simple random sampling method.

All women, according to the 2003 Rotterdam criteria, had a clinical diagnosis of Polycystic Ovary Syndrome (PCOS), with varying duration of the disease, and without regular treatment for PCOS for at least three months prior to inclusion in the study. Inclusion in the study was preceded by a signed informed consent.

Inclusion criteria:

– patients aged 18-40 years

– diagnosis of PCOS (Rotterdam criteria, 2003)

– newly diagnosed patients or patients without treatment for PCOS for at least the last 3 months of the screening period

– HOMA IR> 2.2

Exclusion criteria:

– Known or suspected hypersensitivity to the test product or similar products

– Started treatment for PCOS (oral contraceptive therapy for example)

– Pregnancy, lactation

– Impaired hepatic or renal function (function tests)

– Irregular thyroid function

– Diabetes, prediabetes

– Hyperprolactinemia

– Presence of androgen-secreting tumor

– Other conditions leading to hypersecretion of androgen hormones – Cushing Syndrome, CAH

The diagnosis of PCOS based on the 2003 Rotterdam criteria implied the presence of two , out of three criteria: a) oligo and/or anovulation: oligomenorrhea defined as less than 9 cycles per year or three cycles with a duration of more than 36 days during the last year; b) clinical and/or biochemical signs of hyperandrogenism implying a clinical diagnosis based on the Ferriman-Gallwey (mFG) scale ≥8 or if the patient has moderate to severe acne and/or biochemically if she has a total testosterone level of >2.0 nmol/L or a free androgen index (FAI) of ≥6; c) polycystic ovarian morphology determined by ultrasound (8 MHz probe) – presence of 20 or more follicles in one ovary with a diameter of 2-9 mm and/or a volume >10 ml in one of both ovaries.

According to the treatment, the patients were divided into two groups of 34 patients. The first group of 34 female patients were placed on Metformin therapy at 750mg XR after a meal, with a gradual introduction of the total dose of 1500mg XR over two weeks. This was done to minimize side effects in the gastrointestinal tract (GIT). The second group of 34 patients was placed on therapy with Myoinositol 2gr, every 12 hours between meals. The monitoring of the subjects was at zero time before starting the therapy and 6 months after its start.

Blood samples were collected after 12 hours of fasting in the follicular phase of the cycle (between the 2nd and the 5th days) or randomly in a case of amenorrhea.

The parameters monitored: were BMI (Body Mass Index), FPG (fasting glycemia), HOMA-IR (homeostasis model assessment index), waist circumference (WR), total cholesterol, LDL (low-density lipoprotein) cholesterol, HDL (high-density lipoprotein) cholesterol, triglycerides (TG), lipid accumulation product (LAP) index, TG/HDL ratio.

Plasma glucose, TC, LDL, HDL and TG were measured immediately after sampling with photometric analyzer (Snibe, Biossay 240 Plus), according to the manufacturer's instructions.

– Assessment of HOMA-IR (homeostasis model assessment) index is calculated using the formula: [fasting insulin (mU/l) × fasting glucose (mmol/l)]/22.5; HOMA-IR values between 1.0 and 1.4 are generally considered within the normal range.

Lipid accumulation product (LAP) index is calculated using the formula, for women: (WC (cm) - 58) x TG (mmol/L). Studies have suggested cut-off values for LAP to identify individuals at higher risk of specific conditions, such as hypertension (e.g., 25.16 cm mmol/l for women and 20.10 cm mmol/l for men) or NAFLD (e.g., ≥42.7).

TG/HDL ratio of 2.0 or less is generally considered optimal. However, individual circumstances and other risk factors should be considered when interpreting your results. Significantly high ratios, especially those above 3, may be associated with an increased risk of heart attack and stroke.

BMI was calculated by dividing patient's weight in kilograms by their height in meters squared.

Waist ratio was measured at the middle point between the lower border of the rib cage and the iliac crest by using a flexible centimeter tape

STATISTICAL ANALYSIS

Statistical analysis was performed with statistical program SPSS 26.0 for Windows. Testing of data distribution was performed with Kolmogorov Smirnov and Shapiro-Wilk' s W tests. Qualitative data are presented with absolute numbers and percentages, and quantitative data with average values, minimum and maximum values, standard deviation, median and interquartile ranks. For comparison of quantitative data, parametric and non-parametric tests for independent samples (Student t-test and Mann-Whitney U test) were used, depending on the distribution of the data. The relationship between two variables was analyzed with Spearman Rank Correlation. Statistical significance was defined at a level of $p<0.05$.

RESULTS

The study included 68 women, aged 18 to 36 years, with an average age of 24.2 ± 5.1 years.

The patients were divided into 2 groups depending on the type of therapy they received:

– 34 patients were placed on Metformin therapy,

– 34 patients received Myoinositol.

The difference in age of both groups of patients on Metformin and Myoinositol therapy was statistically insignificant (23.9 ± 5.8 vs 24.5 ± 4.4 years, p=0.66).

Before the start of therapy, the body mass index for this cohort of patients averaged 28.34 ± 7.3 kg/m2 and ranged from 17.5 to 47.3 kg/m2.

BMI – The mean BMI before the start of therapy was 29.76 ± 7.2 kg/m2 in the Metformin group, 26.92 ± 7.3 kg/m2 in the Myoinositol group.

At the end of treatment, the mean BMI was 28.21 ± 6.4kg/m2 in the Metformin group, 25.40 ± 6.3 kg/m2 in the Myoinositol group.

A significant decrease in BMI was registered in both groups after therapy (p=0.000001 and p=0.000013, respectively in the Metformin and Myoinositol groups).

The body mass index did not differ significantly between the two groups before and after the completion of the 6-month therapy (p=0.11 and p=0.07, respectively).

That is, the difference in the avarage decrease in BMI by 1.547±1.45kg/m2 in the Metformin group and by 1.523±1.73kg/m2 in the Myoinositol group was not statistically significant (p = 0.95).

An analysis of the influence of BMI on the studied variables was performed:

Before the start of therapy, patients with BMI lower and higher than 25 kg/m2 did not differ significantly in terms of cholesterol (p=0.96), LDL (p=0.252), FPG (p=0.96), insulin (p=0.49) and HOMA-IR (p=0.31) values .The body mass index had a significant effect on HDL (p=0.0036), triglycerides (p=0.046), TG/HDL (p=0.046) and LAP (p<0.0001) values before therapy. Patients with a BMI lower than 24,9 kg/m2 had significantly higher mean HDL values (1.47 ± 0.3 vs 1.27 ± 0.2mmol/L), and significantly lower triglyceride values (1.09 ± 0.5 vs 1.38 ± 0.72mmol/L). In the group of patients with a BMI lower than 24,9 kg/

Table 1 . *Age of patients / BMI before and after treatment*

Statistical parameters		Type of therapy		p-level
		Metformin n=34	**Myoinositol n=34**	
Age/years	mean ± SD	23.9 ± 5.8	24.5 ± 4.4	t=0.45 p=0.66
	min- max	18 – 36	20 – 35	
BMI (kg/m^2) Start	mean ± SD	29.76 ± 7.2	26.92 ± 7.3	t=1.6 p=0.11
	min- max	17.5 – 40.7	17.6 – 47.3	
BMI (kg/m^2) End	mean ± SD	28.21 ± 6.4	25.40 ± 6.3	t=1.8 p=0.07

BMI-Body Mass Index

m2, significantly lower values of the TG/HDL ratio (mean=0.80 ± 0.45 vs 0.80 ± 0.45; median=0.88 vs 1.04) and of the LAP parameter (mean=15.85 ± 14.3 vs 55.46 ± 35.9; median=11.16 vs 36.86) were registered.

Before starting treatment:

In the group of patients with a BMI less than 24.9kg/m2, patients treated with metformin and myoinositol before treatment had similar values of cholesterol (p=0.14), HDL (p=0.41), triglycerides (p=0.23), FPG (p=0.96), insulin (p=0.21), HOMA-IR (p=0.56), TG/HDL ratio (p=0.41) and LAP (p=0.41). A significant difference between the metformin and myoinositol groups before therapy was confirmed for LDL (p=0.043), which was due to significantly higher mean LDL values in patients in the metformin group (3.04 ± 0.7 vs 2.59 ± 0.5 mmol/L). In the group with a BMI of 25kg/m2 and higher, patients treated with metformin , before treatment, had significantly lower cholesterol values (4.41 ± 0.99 vs 5.06 ± 0.9, p=0.042), had significantly higher insulin values (20.53 ± 5.9

Table 2. *Influence of BMI on the studied variables*

Whole group			
variable	Statistical parameters	BMI (kg/m^2) before therapy	
		< 24.9	≥ 25
cholesterol	mean ± SD	4.7 ± 0.7	4.7 ± 0.98
	min - max	3.4 – 5.5	3.4 – 7.1
	p-level	t=0.05 p=0.96	
LDL (mmol/L)	mean ± SD	2.8 ± 0.6	2.99 ± 0.9
	min - max	1.8 – 4.04	1.9 – 5.5
	p-level	t=1.16 p=0.25	
HDL (mmol/L)	mean ± SD	1.5 ± 0.3	1.3 ± 0.2
	min - max	1.0 – 2.2	0.89 – 1.7
	p-level	t=3.01 **p=0.0036	
triglycerides (mmol/L)	mean ± SD	1.1 ± 0.5	1.4 ± 0.7
	min - max	0.4 – 1.98	0.4 – 2.7
	p-level	t=2.04 *p=0.046	
FPG (mmol/l)	mean ± SD	4.97 ± 0.4	4.96 ± 0.5
	min - max	4.4 – 5.9	4.1 – 6.0
	p-level	t=0.05 p=0.96	
Insulin (μIU/ml)	mean ± SD	17.3 ± 6.1	18.3 ± 5.7
	min - max	10.3 – 37.5	9.9 – 27.9
	p-level	t=0.69 p=0.49	
HOMA IR	mean ± SD	3.97 ± 1.3	4.3 ± 1.5
	min - max	2.4 – 8.0	2.3 – 7.4
	p-level	t=1.03 p=0.31	
TG/HDL	mean ± SD	0.8 ± 0.5	1.2 ± 0.7
	median (IQR)	0.9(0.29-1.19)	1.04(0.75-1.73)
	p-level	Z=1.99 *p=0.046	
LAP	mean ± SD	15.9 ± 14.3	55.5 ± 35.9
	median (IQR)	11.2(4.9-24.6)	36.9(25.52-81.6)
	p-level	Z=-5.36 ***p=0.00000	

t(Student t-test); Z(Mann-Whitney test)
*sig p<0.05, ***sig p<0.0001

LDL- low-density lipoprotein; HDL- high-density lipoprotein; FPG-fasting glycemia; HOMA IR-Homeostasis Model Assessment for Insulin Resistance; TG- triglycerides; LAP- lipid accumulation product; BMI-Body Mass Index;

Table 3. *Comparison of studied variables between groups, before treatment, depending on BMI*

variable	Statistical parameters	BMI <24.9 (kg/m^2) before therapy		BMI ≥25(kg/m^2) before therapy	
		Metformin n=34	Myoinositol n=34	Metformin n=34	Myoinositol n=34
Cholesterol (mmol/L)	mean ± SD	4.9 ± 0.7	4.5 ± 0.6	4.4 ± 0.99	5.06 ± 0.9
	min - max	3.4 – 5.5	3.5 – 5.5	3.4 – 7.1	3.7 – 6.6
	p-level	t=1.52 p=0.14		t=2.11 *p=0.042	
LDL (mmol/L)	mean ± SD	3.04 ± 0.7	2.6 ± 0.5	2.8 ± 1.0	3.2 ± 0.7
	min - max	1.8 – 4.04	2.02 – 3.2	1.9 – 5.5	1.97 – 4.3
	p-level	t=2.11 *p=0.043		t=1.31 p=0.2	
HDL (mmol/L)	mean ± SD	1.4 ± 0.2	1.5 ± 0.3	1.2 ± 0.2	1.4 ± 0.3
	min - max	1.1 – 1.7	1.0 – 2.2	0.9 – 1.7	1.0 – 1.7
	p-level	t=0.83 p=0.41		t=1.83 p=0.076	
Triglycerides (mmol/L)	mean ± SD	1.2 ± 0.5	0.99 ± 0.5	1.4 ± 0.7	1.3 ± 0.6
	min - max	0.4 – 1.98	0.2 – 1.5	0.4 – 2.7	0.5 – 2.4
	p-level	t=1.22 p=0.23		t=0.37 p=0.71	
FPG (mmol/l)	mean ± SD	4.97 ± 0.3	4.97 ± 0.5	4.85 ± 0.6	5.11 ± 0.3
	min - max	4.6 – 5.4	4.4 – 5.9	4.1 – 6.0	4.5 – 5.5
	p-level	t=0.047 p=0.96		t=1.8 p=0.076	
Insulin (μIU/ml)	mean ± SD	15.6 ± 2.8	18.5 ± 7.5	20.5 ± 5.9	15.2 ± 3.4
	min - max	11.5 – 20.3	10.3 – 37.5	12.3 – 27.9	9.9 – 20
	p-level	t=1.27 p=0.21		t=3.18 **p=0.003	
HOMA IR	mean ± SD	3.8 ± 0.6	4.08 ± 1.6	4.9 ± 1.6	3.5 ± 0.9
	min - max	3.2 – 4.6	2.4 – 8.0	2.3 – 7.4	2.4 – 5.4
	p-level	t=0.56 p=0.56		t=3.19 **p=0.0029	
TG/HDL	mean ± SD	0.9 ± 0.5	0.7 ± 0.4	1.3 ± 0.7	1.03 ± 0.5
	median (IQR)	0.8(0.64-1.23)	0.9(0.29 -1.10)	1.05(0.75-1.93)	0.9(0.69-1.33)
	p-level	Z=0.8 p=0.41		Z=0.7 p=0.49	
LAP	mean ± SD	22.3 ± 19.6	11.6 ± 7.1	56.4 ± 37.3	54.2 ± 35.2
	median (IQR)	15.7(6.6-45.54)	11.2(4.9-15.95)	40.3(33.3-79.2)	35.9(25.2-89.5)
	p-level	Z=0.8 p=0.41		Z=0.46 p=0.66	

t(Student t-test); Z(Mann-Whitney test)
*sig p<0.05, **sig p<0.01

LDL- low-density lipoprotein; HDL- high-density lipoprotein; FPG-fasting glycemia; HOMA IR- Homeostasis Model Assessment for Insulin Resistance;TG- triglycerides; LAP- lipid accumulation product; BMI-Body Mass Index;

Table 4. *Comparison of studied variables between groups, after completion of treatment, depending on BMI*

variable	Statistical parameters	BMI <24.9 (kg/m^2) after therapy		BMI >25(kg/m$^{2)}$ after therapy	
		Metformin n=34	Myoinositol n=34	Metformin n=34	Myoinositol n=34
Cholesterol (mmol/L)	mean ± SD	5.1 ± 0.6	4.5 ± 0.7	5.2 ± 1.01	4.5 ± 0.9
	min - max	4 – 5.95	2.9 – 5.5	3.9 – 6.9	3.3 – 6.9
	p-level	t=2.41 *p=0.022		t=2.15 *p=0.039	
LDL (mmol/L)	mean ± SD	3.1 ± 0.8	2.6 ± 0.6	2.9 ± 0.8	3.3 ± 1
	min - max	1.8 – 4.5	1.3 – 3.4	1.9 – 5.1	1.97 – 4.98
	p-level	t=1.96 p=0.06		t=1.4 p=0.16	
HDL (mmol/L)	mean ± SD	1.5 ± 0.4	1.43 ± 0.3	1.1 ± 0.3	1.2 ± 0.3
	min - max	1.02 – 2.2	0.9 – 1.9	0.6 – 1.5	0.6 – 1.5
	p-level	t=0.84 p=0.41		t=0.63 p=0.53	
Triglycerides (mmol/L)	mean ± SD	0.9 ± 0.4	0.9 ± 0.4	1.35 ± 0.5	1.37 ± 0.8
	min - max	0.4 – 1.4	0.5 – 1.7	0.6 – 2.5	0.6 – 2.9
	p-level	t=0.33 p=0.74		t=0.067 p=0.95	
FPG (mmol/L)	mean ± SD	4.9 ± 0.5	4.9 ± 0.3	4.7 ± 0.5	5.01 ± 0.3
	min - max	4.2– 5.8	4.4– 5.4	3.9 – 5.7	4.7 – 5.6
	p-level	t=0.15 p=0.88		t=2.05 *p=0.049	
Insulin (µIU/ml)	mean ± SD	11.8 ± 6.8	10.98 ± 4.2	18.8 ± 5.96	14.8 ± 5.0
	median (IQR) min - max	10.1(6.6-17.9)	9.9(7.3-13.0)	9.03 – 31.4	6.4 – 22.6
	p-level	Z=0.85 p=0.39		t=1.97 p=0.058	
HOMA IR	mean ± SD	1.97 ± 1.1	2.4 ± 0.9	2.9 ± 1.1	2.3 ± 0.6
	median (IQR) min - max	1.9(1.2-2.2)	2.2(1.6-2.8)	1.1 – 4.3	1.6 – 3.4
	p-level	Z=0.119 p=0.84		t=2.07 *p=0.046	
TG/HDL	mean ± SD	0.7 ± 0.4	0.7± 0.4	1.33 ± 0.7	1.31 ± 0.8
	median (IQR)	0.7(0.34-1.02)	0.6(0.32-0.93)	1.1(0.79-2.09)	1.01(0.63-2.27)
	p-level	Z=0.85 p=0.39		Z=0.56 p=0.58	
LAP	mean ± SD	10.5 ± 7.7	10.1 ± 6.9	46.6 ± 29.9	47.9 ± 24.3
	median (IQR)	9.5(3.12-16.38)	9.1(4.1-18.7)	45.1(25.6-50.9)	45.9(41.5-51.7)
	p-level	Z=0.56 p=0.58		Z=0.487 p=0.63	

t(Student t-test); Z(Mann-Whitney test)
*sig p<0.05

LDL- low-density lipoprotein; HDL- high-density lipoprotein; FPG-fasting glycemia; HOMA IR- Homeostasis Model Assessment for Insulin Resistance;TG- triglycerides; LAP- lipid accumulation product; BMI- Body Mass Index ;

vs 15.21 ± 3.4, p=0.003), as well as significantly higher HOMA IR values (4.91 ± 1.6 vs 3.51 ± 0.9, p=0.0029).

LDL, HDL, triglycerides, FPG, TG/HDL, and LAP values were not significantly different between the metformin and myoinositol groups (p=0.2, p=0.076, p=0.71, p=0.076, p=0.49, and p=0.66, respectively).

After completion of treatment:

The type of therapy had a significant impact on cholesterol values in the groups with a BMI less than 24,9kg/m2 and greater than 25kg/m2 (p=0.022 and p=0.039). After therapy, cholesterol had significantly lower average values in patients with BMI less than 25kg/m2 who were treated with myoinositol (5.06 ± 0.6 vs 4.45 ± 0.7 mmol/L),and significantly lower values in patients treated with myoinositol with BMI higher than 25kg/m2 (5.22 ± 1.01 vs 4.46 ± 0.9 mmol/L).

In the group with a BMI less than 25kg/m2, no statistically significant difference was found in the remaining analyzed parameters, depending on the type of therapy: LDL (p=0.059), HDL (p=0.41), triglycerides (p=0.74), FPG (p=0.88), insulin (p=0.39), HOMA-IR (p=0.84), TG/HDL (p=0.39) and LAP (p=0.58).

A significant difference between the metformin and myoinositol groups after therapy was confirmed in patients with a BMI greater than 25kg/m2 for FPG and HOMA-IR (p=0.049 and p=0.046, respectively); patients treated with metformin had significantly lower values of FPG (4.65 ± 0.5 vs 5.01 ± 0.3 mmol/L) and HOMA-IR (2.94 ± 1.1 vs 2.25 ± 0.6 mmol/L). The difference between patients treated with metformin and myoinositol was statistically insignificant in terms of LDL (p=0.16), HDL (p=0.53), triglycerides (p=0.95), insulin (p=0.058), TG/HDL (p=0.58) and LAP (p=0.63) values.

An analysis of the correlation of LAP and TG/HDL with HOMA IR was also performed. The results of the statistical analysis showed a non-significant correlation between HOMA IR and LAP (p=0.088), and a significant positive correlation between HOMA IR and the TG/HDL ratio (R=0.2086 p=0.016).

DISCUSSION

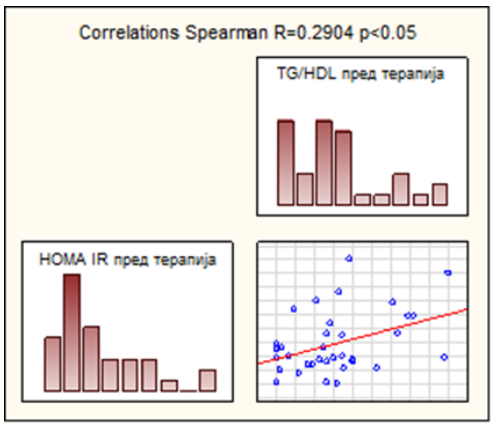
Our study showed that BMI significantly influenced HDL (p=0.0036) and triglyceride (p=0.046) values. Patients with BMI lower than 25 kg/m2 had higher mean HDL values (1.47 ± 0.3 vs 1.27 ± 0.2 mmol/L) and significantly lower triglyceride values (1.09 ± 0.5 vs 1.38 ± 0.72 mmol/L).

These results correlate with the findings of meta-analyses of previous studies, where it was

Table 5. *Correlation analysis of LAP and TG/HDL with HOMA IR before treatment*

CORELATIONS		
variable	Spearman R	p-value
HOMA IR before & TG/HDL	0.2904	*0.016
HOMA IR before & LAP	0.2086	0.088

HOMA IR- Homeostasis Model Assessment for Insulin Resistance ;TG- triglycerides; HDL- high-density lipoprotein LAP- lipid accumulation product



found that the most common lipid profile disorder in PCOS is elevated triglyceride levels and reduced HDL-C levels, i.e. a classic atherogenic lipid profile, which is associated with elevated BMI, but in PCOS is also monitored independently of BMI. [8]

Another study observed a difference in triglyceride, total cholesterol, and LDL-C levels, with no changes in HDL-C in relation to BMI. [9] Most likely, the interaction between different pathogenic mechanisms, such as obesity, hyperinsulinemia, oxidative stress, anovulation, and hyperandrogenism, are implicated in the occurrence of dyslipidemia in PCOS.Insulin is one of the main regulators of lipoprotein lipase activity, and hyperadrenergic activity has an independent function in lipoprotein and lipid metabolism. [10]

Lipoprotein indices, especially TG/HDL-C, have been shown to be directly related to insulin resistance and as such can be used as predictors of glucose intolerance in women with PCOS.

In recent years, indices that combine anthropometric parameters with lipid values, such as VAI and LAP, have been increasingly used, which have shown high accuracy in identifying visceral obesity and as such are effective predictors of insulin resistance and metabolic syndrome and are positively associated with cardiometabolic risk in PCOS. [11]

In our study, an analysis of the values of these indices was performed before the start of treatment, whereby in the group of patients with a BMI lower than 25 kg/m2, significantly lower values of the TG/HDL ratio (mean=0.80 ± 0.45 vs 0.80 ± 0.45; median=0.88 vs 1.04) and of the LAP parameter (mean=15.85 ± 14.3 vs 55.46 ± 35.9; median=11.16 vs 36.86) were registered.

The TG/HDL ratio in most studies was found to be elevated in patients with PCOS, correlating with BMI and waist circumference, with higher values observed in obese patients with PCOS. Our research showed a clear significant positive correlation between HOMA IR and the TG/HDL ratio (R=0.2086 p=0.016), indicating that this index could be an effective predictor of insulin resistance in PCOS, i.e. for early recognition of patients with increased risk of metabolic disorders and increased cardiovascular risk.

In a study conducted in patients with PCOS, a cut-off value of 2.5 was obtained as a predictor of insulin resistance in these patients, i.e. it was suggested that at values higher than the mentioned above, OGTT be performed for early detection of glucose intolerance. [12]

In our study, no significant correlation was shown between HOMA IR and LAP (p=0.088).

After completing the 6-month treatment, the sub-analysis of the two therapeutic modalities depending on BMI showed that the type of therapy had a significant impact on cholesterol values in the groups with BMI less than and greater than 25kg/m2 (p=0.022 and p=0.039).

That is, in patients with a BMI of less than 25kg/m2, Myoinositol showed greater efficacy in reducing total cholesterol compared to metformin (4.45 ± 0.7 vs 5.06 ± 0.6 mmol/L) and in the group with a BMI higher than 25kg/m2, significantly lower values were observed in patients treated with Myoinositol (4.46 ± 0.9 vs 5.22 ± 1.01 mmol/L). This result is confirmed in some of the studies where a comparison of these two therapeutic modalities was performed. [12, 14] While in the meta-analysis of randomized clinical trials comparing these insulin sensitizers, greater efficacy of Myoinositol was observed in reducing triglycerides in patients with PCOS.

In our study, in the group with a BMI less than 25kg/m2, despite an observed decrease in the values of parameters such as TG, FPG, insulin, HOMA IR, TG/HDL, LAP in both groups, there was still no statistically significant difference in the analyzed parameters between the two therapeutic modalities: LDL (p=0.059), HDL (p=0.41), triglycerides (p=0.74), FPG (p=0.88), insulin (p=0.39), HOMA-IR (p=0.84), TG/HDL (p=0.39) and LAP (p=0.58).

In the group of patients with a BMI greater than 25kg/m2, a significant difference was observed between the Metformin and Myoinositol groups in terms of FPG and HOMA-IR (p=0.049 and p=0.046, respectively); i.e. Metformin showed higher efficacy in reducing FPG values (4.65 ± 0.5 vs 5.01 ± 0.3 mmol/L) and HOMA-IR (2.94 ± 1.1 vs 2.25 ± 0.6 mmol/L). Regarding the other parameters in this group, no significant difference was observed between the two therapeutic modalities.

CONCLUSION

In our study, in terms of glycemic profile, we observed the greater efficacy of Metformin in overweight patients, in terms of FPG and HO-

MA-IR values. The fact that we observed this effect only in the group with a BMI above 25kg/m2 may be related to the higher body weight and higher degree of hyperinsulinemia in the patients included in this group in our study, but further research in this direction is needed.

The more pronounced reduction in fasting glycemia is most likely due to the reduction in insulin resistance with this treatment, which is shown by a decrease in HOMA IR. Regarding the lipid profile, apart from the effect of Myoinositol on total cholesterol, therapy with insulin sensitizers Metformin and Myoinositol in both groups of subjects did not show a significant effect on the lipid profile in patients with PCOS, regardless of their BMI.

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Резиме

ВЛИЈАНИЕТО НА ИНСУЛИНСКИТЕ СЕНЗИБИЛИЗАТОРИ ВРЗ ГЛИКЕМИСКИОТ И ВРЗ ЛИПИДНИОТ ПРОФИЛ КАЈ ПАЦИЕНТИТЕ СО СИНДРОМ НА ПОЛИЦИСТИЧНИ ЈАЈНИЦИ (PCOS)

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Вовед: Синдромот на полицистични јајници (PCOS) се поврзува со зголемен кардиоваскуларен ризик во подоцнежниот живот на пациентките. Инсулинската отпорност, која се среќава кај PCOS, го зголемува ризикот од дијабетес тип 2, дислипидемија, хипертензија и кардиоваскуларни болести. Оваа студија истражува дали инсулинските сензитајзери, преку намалување на инсулинската отпорност, би довеле до модификација на традиционалните кардиоваскуларни фактори на ризик.

Методи: Проспективна, рандомизирана клиничка студија спроведена на Клиниката за ендокринологија во Скопје (2022/2023). Беа вклучени жени од 18 до 40 години со дијагноза на ПЦОС според Ротердамските критериуми од 2003 г. Пациентките беа поделени во две групи: група А – метформин 1500 mg XR, и група Б – миоинозитол 2 g + фолна киселина 200 mg на 12 часа, во текот на 6 месеци. Следени параметри: BMI, FPG, HOMA-IR, вкупен холестерол, LDL-C, HDL-C, триглицериди, LAP, TG/HDL.

Резултати: Се покажа значително влијание на BMI врз HDL-C, триглицеридите, TG/HDL и LAP пред терапија. Кај пациентките со BMI ≤ 24,9 kg/m² се покажа повисок HDL-C, а пониски вредности на триглицеридите. Миоинозитолот покажа значаен ефект врз холестеролот независно од BMI, но не и врз другите параметри. Кај пациентките со BMI ≥25 kg/m², метформинот значајно ги намали вредностите на FPG и HOMA-IR. TG/HDL индексот покажа позитивна корелација со HOMA-IR.

Заклучок: Миоинозитолот покажа значаен ефект врз холестеролот во однос на липидниот профил кај ПЦОС, додека метформинот значително влијаеше врз гликемискиот профил кај пациентките со повисок BMI. TG/HDL може да послужи како ефикасен предиктор за инсулинска резистенција.

Клучни зборови: полицистичен оваријален синдром, метформин, миоинозитол, липиден статус, гликемиски статус, инсулинска резистенција