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Research article

Efficacy of metformin on the body mass index of patients under treatment with SSRI drugs referred to psychiatry clinics of Rasht

Somayeh Shokrgozar [a], Fatemeh Momeni [a], Homa Zarabi [a], Elahe Abdollahi [a,*], Mohammadrasoul Khalkhali [a], Kiomars Najafi [a], Robabeh Soleimani [a], Sabra Pazhooman [a], Roghayeh Zare [b]

[a] Kavosh Cognitive Behavior Sciences and Addiction Research Center, Department of Psychiatry, School of Medicine, Guilan University of Medical Sciences, Rasht, Iran
[b] Biostatistics Neuroscience Research Center, Guilan University of Medical Science, Rasht, Iran

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ABSTRACT

Objective: Serotonin reuptake inhibitors cause weight gain, leading to drug discontinuation, relapse, and worsening of symptoms. This study aims to investigates the effect of metformin on weight loss, anthropometric indicators and laboratory assessments in patients of Rasht city.
Methods: This clinical trial study with parallel-group design was organized based on 60 patients in treatment group (undergoing metformin) and 60 patients in control group (undergoing routine treatment) in Shafa hospital during July 2019 to January 2020. First, we determined the overweight patients. After that, a psychiatric assistant randomly divides them into two groups, intervention and control. Both groups of patients will be explained in terms of how they were studied and whether or not they received metformin. In order to statistical analysis of collected data, we applied the Mann-Whitney *U* test and repeated measures ANOVA. For conducting all analysis, the IBM SPSS Statistics 28 software was used.
Results: The mean BMI and abdominal circumference decreased significantly in the intervention group. The wrist circumference in the intervention group decreased over time, but this difference was not statistically significant. There was no statistically significant difference between the average changes of the mean values of the laboratory assessment among the group.
Conclusion: Weight gain can cause problems related to compliance with treatment and anxiety and depression. On the other hand, in our study, metformin was not superior to lifestyle improvements and practicing preventive methods for weight control. Further research on SSRIs and monitoring of anthropometric indices is recommended.

1. Introduction

In the field of psychopharmacology, the development of selective serotonin reuptake inhibitors (SSRIs) represents a significant therapeutic breakthrough. This class of agents heralds a new era of rational drug design and neuropsychopharmacology, bolstering the creation of psychotropic drugs [1]. Despite their benefits, it is worth noting that SSRIs are not without potential side effects.

The majority of side effects caused by SSRIs in short-term treatment are transient and disappear after a few days or weeks. Such

* Corresponding author.
E-mail address: eabdollahi@rocketmail.com (E. Abdollahi).

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effects dissipate after a short period of initial medication use. Despite this, potential adverse outcomes may result from the extended use of SSRIs. However, diagnosing such adverse events may be difficult, given their resemblance to residual depressive symptoms. These outcomes can be severe, threatening the patient's life, and severely compromising their quality of life. Non-compliance with medication regimens due to these outcomes is frequent and may augment the risks of depressive episode relapse. The most prevalent adverse effects attributed to SSRIs, including nausea, headaches, nervousness, insomnia, and sexual dysfunction, are connected with the simulation of 5-HT2 and 5-HT3 receptors [2].

Both selective serotonin reuptake inhibitors (SSRIs) as well as other pharmacological agents such as dexfenfluramine (DFF) have highlighted the definitive role of serotonin (5HT) in carbohydrate (CHO) intake suppression. Given this, one might surmise that all SSRIs would have comparable anorectic effects; however, recent indications suggest the contrary. Despite their purported specificity, SSRIs still interact either directly or indirectly with diverse critical neurotransmitter systems. While the anorectic efficacy of fluoxetine (FLX) is recognized, extended investigations of long-term follow-up studies in depressed patients and in obese nondepressed patients have revealed that its weight-reducing effects are transient and can even subsequently culminate in weight gain. Paroxetine (PRX) and citalopram (CTP), despite their high potency and specificity as SSRIs, have similarly resulted in weight gain [3]. Weight gain is one of the important causes of drug discontinuation, relapse, and exacerbation of symptoms. Therefore, it is necessary to adopt a new approach to dealing with side effects caused by SSRIs.

Metformin is an oral pharmaceutics agent primarily utilized in the therapeutic management of type 2 diabetes, and it elicits modest reductions in body weight that are persistent. The mechanisms underlying metformin's improvement of glycemic control are attributed to the diminishing hepatic glucose production, the augmenting of peripheral insulin sensitivity, and an inhibitory effect on gastrointestinal glucose absorption. Metformin is known to help people with diabetes manage or maintain weight. Also, several studies have shown the effect of metformin on weight loss in non-diabetic people [4]. Metformin is now commonly recommended for individuals who suffer from polycystic ovary syndrome (PCOS), and it has been found to cause weight loss in those patients as well [5,6].

The weight loss effects of Metformin are attributed to its capacity to lower food intake. It operates primarily on the central nervous system, where it reduces appetite by reducing the activity of hypothalamic AMPK. This, in turn, decreases the expression of NPY (orexigenic) while stimulating POMC (anorectic). Moreover, Metformin has additional abilities when it comes to decreasing food consumption, including enhancing leptin and insulin sensitivity, increasing GLP-1 concentrations, and affecting gut flora by increasing production of short-chain fatty acids, modulation of glucose metabolism, and increasing abundance of beneficial bacteria [7–9]. It also lowers ectopic lipid depots, such as those found in the liver and skeletal muscles, by boosting fat oxidation while decreasing lipid synthesis, which may be regulated to some extent by circadian clock genes [10–12]. Therefore, the present study investigated the effect of metformin on body mass index in patients treated with selective serotonin reuptake inhibitors.

2. Methods

2.1. Study design and participants

This clinical trial study was approved by the Ethics committee of Guilan University of Medical Sciences (IR.GUMS.REC.1398.097) and registered on Iranian Registry of Clinical Trials (IRCT20140102016035N3). This study was a prospective randomized efficacy conducted at Shafa hospital. The study used a parallel-group design: treatment group (undergoing metformin) with sample size ($n = 60$) and control group (undergoing routine treatment) with sample size ($n = 60$). The inclusion criteria were patients with informed consent form, no history of side effects with metformin and SSRI drugs, the absence of elderly people (over 65 years of age), the absence of pregnancy, the absence of accompanying physical diseases such as diabetes and autoimmune disorders, body mass index of more than 25 kg/m2, the absence of kidney and liver disorders, no taking corticosteroids, not taking any type of drug and stimulant and the absence of psychotic features. Exclusion Criteria were having metabolic disorders (without taking metformin) and addiction. Also, patients with an incomplete data were excluded from the study. The patients were enrolled between July 2019 to January 2020.

After determining overweight patients, a psychiatric assistant will randomly divide them into two groups of intervention and control. Patients with the ability to enter this clinical trial are categorized as 1 to 1 in two groups of intervention and control. In this study the block randomization approach applied to random allocation. To do this, we used the block of size four. Both groups of patients will be described in terms of how to study and receive or not receive metformin. Metformin was administered according to previous studies, starting with 250 mg daily before lunch and after 4 days, it was increased to 250 mg twice a day before lunch and dinner. And according to the patient's tolerance (absence of gastrointestinal complications and fasting blood sugar monitoring), it was finally increased to a maximum of 2250 mg daily in three divided doses before breakfast, lunch and dinner. The total duration of metformin use was six months. Weight, body mass index, abdominal circumference, waist-hip ratio (indicate to fat distribution around the waist compared to the hips), wrist circumference (indicate to bone mineral density estimation and nutritional assessment), fasting blood sugar, cholesterol, and triglycerides were measured in both case and control groups at the beginning, 3 months, and 6 months intervals, and then was compared [13,14].

2.2. Statistical methods

The group statistics standards were recorded as mean ± standard deviation. In addition, categorical variables were outlined as percentages and frequency. Fisher's exact test was conducted for dichotomous variations; the Chi-squared test was applied for organized categorical variables. Mann-Whitney *U* test and repeated measures ANOVA were employed in order to analyze continuous measures. All data were analyzed two-tailed, and a p-value <0.05 was assumed statistically considerable for the aims of this paper. IBM

SPSS Statistics 28 was used for conducting all analysis.

3. Results

A total of 120 patients (60 in each group) were recruited and followed up for the study duration.

There were 27 females (90 %) in metformin group and 26 females (86.7 %) in control group ($P = 0.688$). Data on baseline characteristics of patients in each group is available on Table 1. The presented results shown that there is no statistically significant difference between the values of BMI (Body mass index), WHR (waist-hip ratio) and Wrist of patients in the intervention and control groups at the beginning of the study ($P > 0.05$). In the case of laboratory features, according to obtained results we can concluded that there are significant differences between mean of Cholesterol and Triglyceride in the initial measurements in underlying groups ($P < 0.05$). Moreover, there is no significant difference between mean of Fast Blood Sugar of patients in the intervention and control groups.

A repeated measure ANOVA with a Greenhouse-Geisser correction determined the mean value of BMI has been statistically significant between assessment stages in intervention and control groups ($P < 0.05$). Post hoc test using the Bonferroni correction revealed a slight decrease in the value of BMI at all assessment stages especially in patients treated by metformin (for more details see Table 2 and Fig. 1). In the case of mean value of WHR, obtained results show that there is a significant difference between assessment stages in intervention group ($P < 0.05$). However, there is no significant difference between assessment stages in control group ($P > 0.05$). Similar results were obtained for waist index. Based on reported results in Table 2, the mean value of waist has been statistically significant between assessment stages in intervention group ($P < 0.05$) and no significant in control group ($P > 0.05$). In other hand, a repeated measure ANOVA with a Greenhouse-Geisser correction determined the mean values of clinical features: Fast Blood Sugar, Cholesterol and Triglyceride has not been statistically significant between assessment stages in intervention and control groups ($P > 0.05$).

The mean value of daily metformin used in patients in the group receiving metformin (intervention) was 1233.30 ± 340.00 mg. Also, among the 30 patients in the intervention group, 19 patients (63.3 %) received less than 1000 mg of metformin and 11 patients (36.7 %) received more than 1000 mg of metformin. Moreover, 26.7 % of the patients had gastrointestinal complications.

The obtained results determined the mean value of BMI has been statistically significant between assessment stages in treated group with metformin<1000 mg and treated group with metformin>1000 mg ($P < 0.05$). Post hoc test using the Bonferroni correction revealed a slight decrease in the value of BMI at all assessment stages especially in patients treated by metformin>1000 mg (for more details see Table 3 and Fig. 2). In the case of mean value of WHR, obtained results show that there is just a significant difference between assessment stages in patients treated by metformin>1000 mg ($P < 0.05$). In the case of waist index, based on reported results in Table 3, there is no significant differences between assessment stages in both groups ($P > 0.05$).

4. Discussion

In our study, the average values of the BMI during the periods (beginning, third month, and sixth months) decreased significantly in the intervention group ($P < 0.001$). The average values of WHR during the periods (beginning, third month, and sixth month) decreased significantly in the intervention group ($P < 0.001$). Among the other results, it can be pointed out that there is a significant difference between the average values of wrist circumference during the periods (beginning, third month, and sixth month) decreased significantly in the intervention group over time ($P = 0.02$). However, there was no significant difference between the average values of wrist circumference during the periods (beginning, third month, and sixth month) in the control group ($P = 0.10$). Also, no

Table 1
Comparison of demographic characteristics, anthropometric features, and laboratory features among patients.

	Total (n = 60)	Metformin (n = 30)	Control (n = 30)	P-value
Demographic characteristics				
Age	34.16 ± 9.32	33.95 ± 8.12	35.11 ± 7.96	0.12**
Gender				
Male	7 (11.7)	3 (10.0)	4 (13.3)	0.69*
Female	53 (88.3)	27 (90.0)	26 (86.7)	
Anthropometric features				
Height	163.88 ± 7.60	163.40 ± 5.81	164.36 ± 9.12	0.63**
Weight	72.50 ± 13.03	74.24 ± 11.91	70.77 ± 14.05	0.31**
BMI	26.91 ± 4.08	27.81 ± 4.75	25.97 ± 3.07	0.07**
Waist	92.76 ± 11.71	95.00 ± 11.36	90.53 ± 11.83	0.14**
Hip circumference	105.65 ± 8.86	107.66 ± 8.57	103.63 ± 8.82	0.078**
Waist to hip ratio	0.87 ± 0.07	0.88 ± 0.06	0.87 ± 0.07	0.66**
Wrist	16.83 ± 1.38	17.06 ± 1.16	16.60 ± 1.56	0.20**
Laboratory features				
Fast Blood Sugar (FBS)	92.05 ± 8.74	93.73 ± 9.66	90.36 ± 7.50	0.14**
Cholesterol	172.03 ± 14.55	177.10 ± 14.32	166.96 ± 13.13	0.006**
Triglyceride	179.71 ± 12.73	184.13 ± 13.98	175.30 ± 9.69	0.006**

Data are presented as number (percentage) and mean (standard deviation).
*Chi square test.
**Mann-Withney test.

Table 2
Descriptive statistics and test of within subject effects of underlying variables.

Variable	Group	Assessment Stage	Mean	Std. deviation	*P* value	Partial Eta squared
		0 day	27.86	4.75	<0.001	
	Metformin	90th day	26.77	5.75		0.35*
		180th day	26.00	4.68		
BMI		0 day	25.97	3.07	<0.001	
	Control	90th day	25.38	3.08		0.90*
		180th day	24.41	3.11		
		0 day	0.881	0.06		
	Metformin	90th day	0.877	0.06	0.001	0.21*
		180th day	0.868	0.07		
WHR		0 day	0.872	0.07		
	Control	90th day	0.870	0.08	0.26	0.04*
		180th day	0.865	0.08		
		0 day	17.06	1.16		
	Metformin	90th day	17.06	1.16	0.02	0.18*
Wrist		180th day	16.93	1.16		
		0 day	16.60	1.56		
	Control	90th day	16.60	1.56	0.10	0.09*
		180th day	16.50	1.51		
		0 day	93.73	9.66		
	Metformin	90th day	91.46	6.06	0.14	0.07*
FBS		180th day	90.06	5.39		
		0 day	90.36	7.50		
	Control	90th day	90.90	5.64	0.66	0.01*
		180th day	89.56	5.84		
		0 day	177.10	14.32		
	Metformin	90th day	170.93	13.73	0.05	0.09*
		180th day	172.10	12.30		
CHL		0 day	166.96	13.13		
	Control	90th day	168.33	12.34	0.13	0.07*
		180th day	163.80	0.74		
		0 day	184.13	13.98		
	Metformin	90th day	177.23	17.81	0.53	0.09*
		180th day	179.33	14.67		
TRG		0 day	175.30	9.69		
	Control	90th day	175.90	11.91	0.55	0.02*
		180th day	173.53	13.35		

*Repeted measure ANOVA.

significant difference has been observed between the control and intervention groups concerning wrist circumference.

An open-label study led by Dr. John A. Morrison and colleagues in 2002 investigated the effectiveness of metformin as a treatment for weight gain in children who were taking olanzapine, risperidone, quetiapine, or valproate. The study involved 19 participants, aged between 10 and 18 years, consisting of 12 boys and 7 girls, with 15 participants being white and 4 being black. Over a period of 12 weeks, each participant received 500 mg of metformin three times a day. The researchers evaluated the changes in weight and body mass index using a repeated measures analysis of variance. The results showed that 15 out of the 19 participants lost weight, 3 gained 1.6 kg or less, and 1 participant had no change in weight. The mean changes in weight and body mass index were statistically significant after 12 weeks of treatment [15]. The results of this study are consistent with our study.

In 2006, Klein et al. conducted a study with the aim of investigating the effect of metformin treatment on weight gain related to the initiation of atypical antipsychotic treatment in children and adolescents. A 16-week, double-blind, placebo-controlled trial was designed to evaluate the efficacy of metformin in controlling weight gain in 39 individuals, aged 10–17 years, whose weight had increased more than 10 % while taking olanzapine, risperidone, and quetiapine for less than 1 year. In this study body weight, body mass index (kg/m2 of height), waist circumference, fasting insulin, and glucose levels were measured regularly. The results showed that the weight was stabilized in people receiving metformin, while those receiving placebo continued gaining weight (0.31 kg per week) [16].

It is worth mentioning that, in 2021, a study involving 52 patients meeting specific inclusion criteria utilized a pre-post study design to assess the impact of metformin treatment over a 12-month period. The research outcomes demonstrated noteworthy reductions in weight, body mass index (BMI), and waist circumference among female patients following 12 months of metformin therapy. Additionally, the use of metformin resulted in decreased fasting blood glucose and HbA1c levels in females. For male patients, a significant decrease in total cholesterol was observed, while serum HDL-C levels notably increased in females. Changes in serum LDL-C and triglycerides were not statistically significant in both genders. which is consistent with the results of our research [17]. Moreover, the study identified alterations in hormone levels post-metformin treatment. Males exhibited a significant increase in luteinizing hormone (LH) and progesterone levels, whereas females experienced elevated prolactin, follicular stimulating hormone (FSH), and dehydroepiandrosterone-sulphate (DHEA-S) levels, alongside a decrease in total testosterone levels. These results can be the subject of future research [17].

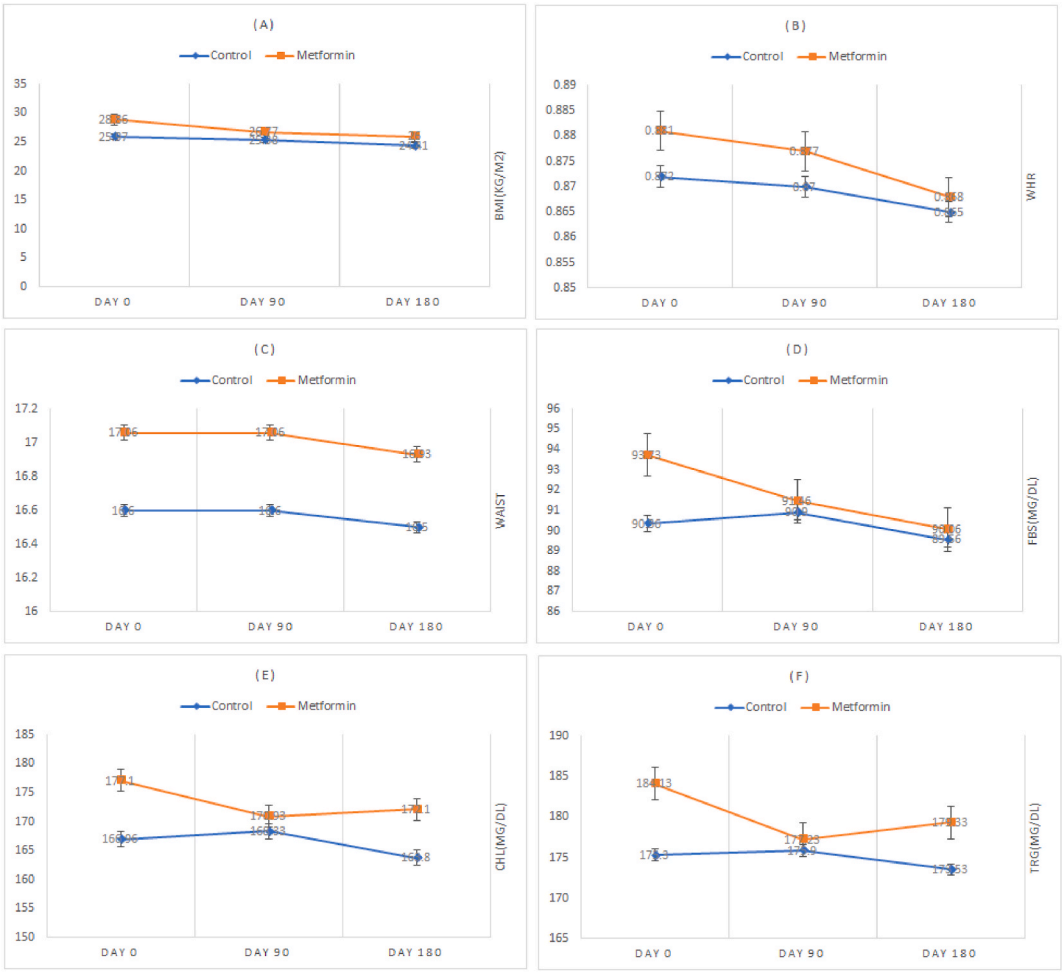

Fig. 1. The trend of changes of the variables: (A) BMI (B) WHR (C) Waist (D) FBS (E) CHL (F) TRG at assessment stages in two control and intervention groups.

Table 3
Descriptive statistics and test of within subject effects of underlying variables based on amount of received metformin.

Variable	Group	Assessment Stage	Mean	Std. deviation	*P* value	Partial Eta squared
		0 day	26.32	3.07	<0.001	
	Metformin<1000 mg	90th day	25.09	4.95		0.24*
		180th day	24.66	3.15		
BMI		0 day	30.52	6.02	0.02	
	Metformin>1000 mg	90th day	29.67	6.11		0.89*
		180th day	28.33	6.02		
		0 day	0.870	0.07		
	Metformin<1000 mg	90th day	0.870	0.07	0.001	0.12*
		180th day	0.860	0.08		
WHR		0 day	0.890	0.05		
	Metformin>1000 mg	90th day	0.880	0.05	0.09	0.60*
		180th day	0.870	0.05		
		0 day	16.71	1.13		
	Metformin<1000 mg	90th day	16.71	1.13	0.10	0.05*
Wrist		180th day	16.68	1.16		
		0 day	17.68	0.98		
	Metformin>1000 mg	90th day	17.68	0.98	0.33	0.40*
		180th day	17.36	1.07		

*Repeted measure ANOVA.

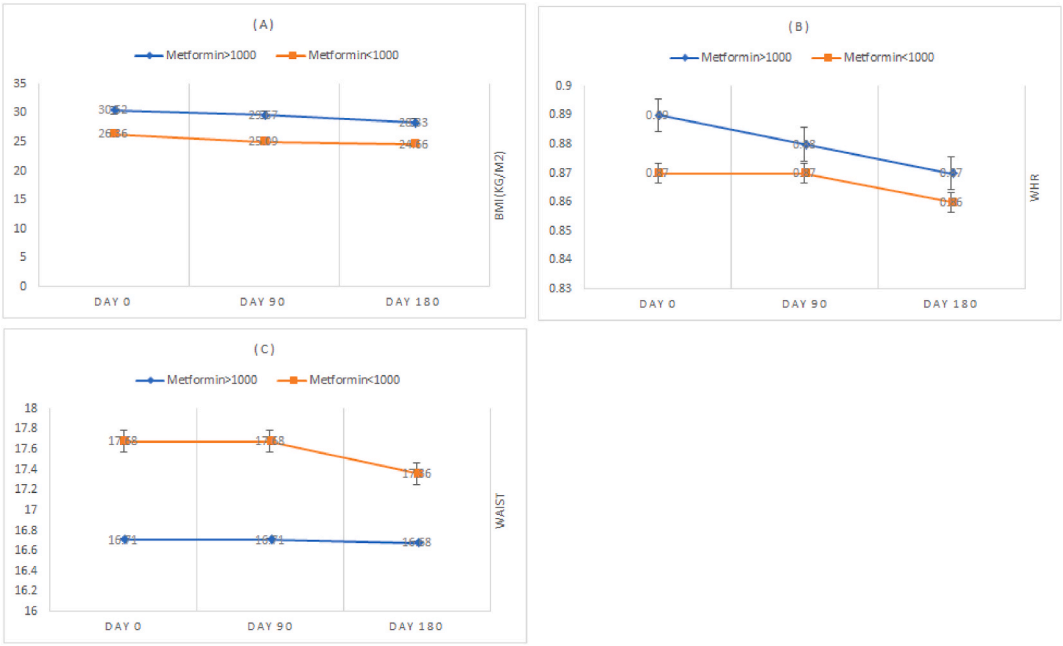

Fig. 2. The trend of changes of the variables: (A) BMI (B) WHR (C) Waist at assessment stages based on amount of received metformin.

A study conducted by Sedigheh Ghandi et al., in 2011 to investigate the effects of metformin or orlistat on obese women with polycystic ovary syndrome. In this prospective randomized open-label study, eighty women were selected in advance to receive either metformin or orlistat, with 40 women receiving each drug. The researchers measured weight, BMI, waist size, serum LH, total serum testosterone, and lipid profile at the beginning and after three months. Both treatments resulted in a significant reduction in body weight, BMI, and waist size, with no significant difference between the two groups [18].

A significant difference can be seen between the average blood cholesterol values at the beginning of the study and six months after the intervention in the two groups of patients (intervention and control) ($P = 0.006$ and $P = 0.007$). However, it was found that there is no significant difference between the average blood cholesterol levels three months after the intervention between the two groups of patients (intervention and control) ($P = 0.44$). It was also found that there is a significant difference between the average blood triglyceride values at the beginning of the study between the two groups of patients (intervention and control) ($P = 0.006$). However, it was found that there is no significant difference between the average values of blood triglycerides three months after the intervention and also six months after the intervention between the two groups of patients (intervention and control) ($P = 0.73$ and $P = 0.11$).

Taking SSRIs can result in weight gain, which may lead to insulin resistance and increase the risk of hyperglycemia. Some antidepressants have a strong affinity for adrenergic receptors, which causes side effects such as the dry mouth and leads to drinking large amounts of soft drinks (with high calories). Therefore, weight gain in these patients increases sometime after taking the drugs [19]. In explaining this problem, it can be said that metformin (diabetes control drug) can lead to blood sugar control and weight control, and the results of this study are consistent with our results.

In 2017, Shi et al. conducted a study on the effects of selective serotonin reuptake inhibitor drugs on weight gain and concluded that in multivariable regression models, the use of antidepressants was positively related to weight gain: anti-depressant users Depression causes weight gain of 0.22 (95 % CI 0.00 to 0.44) kg per year. They found that antidepressants lead to weight gain, and among antidepressants, selective serotonin reuptake inhibitors (SSRIs) had a stronger relationship with weight gain (0.48 kg) [20].

Another study was shown that long-term use of antidepressants (tricyclic antidepressants and SSRIs) (more than 24 months) with medium and high doses are associated with an increased risk of diabetes. Treatment with a low dose and in short periods did not lead to such a risk [21]. This risk, which is caused by non-selective serotonin reuptake inhibitor drugs (SSRI), is consistent with our study.

A significant difference between the average BMI values during the periods (the first and second trimester) is seen in patients receiving various selective serotonin reuptake inhibitor drugs and metformin less than 1000 mg ($P = 0.0001$). Also, there is a significant difference between the average BMI values during the periods (first and second trimester) in patients receiving various selective serotonin reuptake inhibitor drugs and those receiving metformin more than 1000 mg. ($P = 0.02$). However, there is no significant difference between the changes in the average BMI values between the two groups of patients (metformin recipients less than 1000 mg and more than 1000 mg daily) and those receiving selective serotonin reuptake inhibitor drugs ($P = 0.37$). There is a significant difference between the average values of BMI in all the researched periods between the two groups of patients (metformin recipients less than 1000 mg and more than 1000 mg daily) ($P = 0.01$ and $P = 0.03$ and $P = 0.03$). A significant difference between the average values of WHR during the researched periods can be seen in patients receiving various selective serotonin reuptake inhibitor drugs and those receiving metformin more than 1000 mg ($P < 0.001$). It was also found that there was a significant difference between

the average values of the wrist circumference at the beginning of the intervention and three months after the intervention among the two groups of patients (receivers of metformin less than 1000 mg and more than 1000 mg daily). The study's results prompt further investigation into the specific mechanisms underlying these variations and the clinical implications for patients undergoing combined treatment with metformin and SSRIs. Understanding how metformin dosage influences anthropometric parameters in conjunction with other medications can provide valuable insights for optimizing treatment strategies and tailoring interventions to individual patient needs. Further research in this area could elucidate the potential synergistic effects on weight-related outcomes and metabolic health, offering valuable insights for personalized patient care and treatment optimization.

5. Conclusion

Weight gain causes problems such as treatment compliance and aggravation of anxiety and depression. On the other hand, in our study, metformin was not superior to improving lifestyle and training preventive methods for weight control. Therefore, it is recommended to do more research on SSRI drugs with a larger sample size. Hence, we can speak with more confidence about the use of metformin. Likewise, while taking SSRI drugs, monitoring of anthropometric indicators and laboratory evaluations should be considered.

CRediT authorship contribution statement

Somayeh Shokrgozar: Data curation. **Fatemeh Momeni:** Formal analysis. **Homa Zarabi:** Investigation. **Elahe Abdollahi:** Data curation, Conceptualization. **Mohammadrasoul Khalkhali:** Writing – original draft. **Kiomars Najafi:** Formal analysis. **Robabeh Soleimani:** Methodology. **Sabra Pazhooman:** Formal analysis. **Roghayeh Zare:** Methodology.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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