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CAN IRISIN BECOME A BIOMARKER OF PHYSICAL ACTIVITY, OR ANOTHER METABOLIC RISK ASSESSMENT PARAMETER, IN PSYCHIATRIC CARE PATIENTS?

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Abstract

Purpose: Physical activity (PA) is considered to be a major preventive factor in psychopharmacotherapy-induced metabolic adverse effects, such as metabolic syndrome induction. The recent discovery of irisin might bring a potential tool with which to supervise patient compliance or create an additional metabolic risk assessment parameter.

Methods: The sample consisted of 66 in- and out-patients of a Polish hospital. Irisin serum concentrations were measured using commercially available ELISA kits. Sociodemographic and clinical data were obtained from medical records. PA sufficiency was assessed with the use of the International Physical Activity Questionnaire. *t*-Student, χ^2, Fisher's exact test, Pearson correlation and ANCOVA were used for statistical analysis. The significance level was set at $\alpha = 0.05$.

Results: The difference in irisin concentrations between patients with sufficient and insufficient PA was not statistically significant. Patients given second generation antipsychotic drugs exhibited lower PA and irisin concentrations than patients on antidepressant drugs or first-generation antipsychotic drugs. Additionally, irisin concentrations were lower in patients with central obesity compared to patients without it.

Conlusions: Irisin does not appear to be a valid, objective tool for the evaluation of patients. However, significant associations between irisin concentrations, psychopharmacotherapy and metabolic parameters were found.

Key words: metabolic syndrome, antipsychotics, antidepressants, psychopharmacotherapy, irisin.

INTRODUCTION

Pharmacotherapy is a very important factor in modern psychiatric treatment, regardless of a diagnosis. Antidepressants (ADs) and antipsychotic drugs are widely used, often with adverse effects. One of the most important side effects of these lines of therapy is a possible development of metabolic syndrome (MetS) or its component conditions. MetS is defined as the co-occurrence of at least three out of five of the following [1]: 1 – increased waist circumference (≥ 80 cm in women and ≥ 94 cm in men), 2 – elevated blood pressure (systolic ≥ 130 mmHg and/or diastolic ≥ 85 mmHg), 3 – elevated triglycerides (TG) level (≥ 150 mg/dl) or treatment for hypertriglyceridemia, 4 – reduced high-density lipoprotein cholesterol (HDL-C) level (< 50 mg/dl in women and < 40 mg/dl in men) or treatment of this disorder, and 5 – elevated glucose level ≥ 100 mg/dl or treatment for hyperglycaemia. Each one of the aforementioned is a risk factor for developing cardiovascular disease (CVD). Considering that

some psychiatric illnesses alone (such as major depressive disorder and schizophrenia [2]) are also associated with increased CVD risk, the co-occurrence of MetS poses an even greater danger. Additionally, weight gain is one of the most common reasons for patient's non-adherence [3] to treatment, which in turn increases the risk of relapse. However, there are some preventive strategies that can be undertaken, both pharmacological and behavioural [4, 5]. The least dangerous of these, though often problematic for a patient, is physical exercise. Numerous studies show the positive impact of physical activity (PA) on both mental and physical health [6-9], which is why it is one of the first recommendations made by physicians, especially when prescribing psychotropic agents. Unfortunately, the means of controlling patient's compliance in ambulatory care are very limited, especially in terms of PA, as there is no direct biomarker that can indicate the amount of exercise an individual is taking or their overall fitness. Recent studies, however, might have brought a potential solution.

Irisin, a fragment of fibronectin type III domain containing protein 5 (FNDC5) extracellular domain, is an adipomyokine, as it is secreted both by striated muscle tissue cells and adipocytes. Since its discovery in 2012, irisin physiology and function have been intensely studied [10-12]. Currently, despite some ambiguity, it has been established that irisin has an influence on glucose metabolism and causes white adipose tissue 'browning', which in turn increases energy expenditure. An individual's serum irisin levels may depend on the intensity and/or pattern of the exercise they undertake [13-15]. Additionally, it has been observed that patients with several metabolic disorders (such as type 2 diabetes mellitus [DM2] or osteoporosis) also differ in irisin serum levels [16].

The aim of this study was to examine the possible association between serum irisin level, MetS components and physical activity among psychiatric care patients as potential biomarkers of patients' compliance or additional metabolic risk assessment parameters. An additional goal was to validate patients' compliance in terms of PA and determine whether compliant patients benefit more than non-compliant ones.

METHODS

This was a cross-sectional study with the following inclusion criteria: minimum 2 weeks of current mono- or poly-pharmacotherapy either with antipsychotic agent or antidepressant, age between 18 and 70, stable somatic condition. Exclusion criteria: simultaneous administration of second-generation antipsychotics (SGAs) with first generation antipsychotics (FGAs) or ADs, current acute psychotic or manic episode, expression of a desire to withdraw from the study (even after signing the informed consent form). All participants were informed about the aims and methods of the study prior to giving their informed written consent.

Blood samples used to measure irisin serum levels were collected after a minimum of 8-hour fasting period, between 6 and 9 AM, on the same day or a maximum of 2 weeks after the collection of blood samples used to measure other metabolic parameters. Samples were collected straight into tubes with gel-separator and clotting activator, then centrifuged at 4000 rotations per minute (RPM) for 20 minutes and stored in –80°C until the analysis was conducted. Irisin levels were measured using the commercially available ELISA kit (Fine Biotech, China), according to the producer's instructions. Information on patients' diagnoses, current pharmacotherapy, overall length of psychiatric treatment, age, height, weight, blood pressure, glucose, TGs, HDL, LDL and total cholesterol levels, was collected from current medical records. Waist and hip circumference were measured with the use of measuring tape.

Participant's PA was assessed during an interview with the use of the short version of the International Physical Activity Questionnaire (IPAQ-short) [17]. The questionnaire consists of 7 items, which divide PA (based on 7 days prior to the interview) into four categories: vigorous and moderate activity, walking and sitting or lying down (while performing other activities, i.e. watching TV, reading books etc). Each form of activity, apart from sitting, is graded in two dimensions – in days per week, and time per day spent performing these kinds of exercise. Sitting/lying is graded only by the approximate time spent in a day in those postures. After completing the interview, the results are calculated and can be reduced to a single number, given in MET-min/week (Metabolic Equivalent of Work multiplied by number of minutes performing the given activities per week). This number is an approximate, mean amount of PA performed a day by an individual. Then, based on the intensity and regularity of exercise, subjects can be divided into three groups: insufficient, sufficient or high level of PA. Sitting/lying time is not taken into consideration in this assessment, although it can be considered as information on a subject's behaviour.

In this study, we decided to divide patients into groups in terms of several criteria: by sex, by treatment settings (in- or out-patients), by sufficiency of physical activity and by administered medication. For the latter, we chose to divide our patients into two drug groups, each having a different influence on metabolic parameters – patients on SGAs and those not treated with SGAs (more precisely: FGAs and ADs).

The statistical analysis was performed with STATISTICA 13.1 (StatSoft, USA). Basic descriptive statistics were generated for continuous variables (mean ± standard deviation). Since the number of study subjects was > 50, the verification of normal distribution was omitted based

on the central limit theorem. Differences between groups were analysed using the *t*-Student test. For discreet variables, associations were analysed with the use of the χ^2 test or Fisher's exact test, depending on the expected values in contingency tables. Pearson correlation was used for the analysis of associations between continuous variables. The impact of additional variables on irisin concentration was analysed using the ANCOVA analysis. The significance level was set at $\alpha = 0.05$ (two-tailed).

The protocol for this research project was approved by The Ethics Committee of Medical University of Lodz (RNN/52/16/KE as amended) and it conforms to the provisions of the Declaration of Helsinki (1995).

RESULTS

A total of 66 subjects were included in this study, of which 42 (64%) were in-patients and 24 (36%) were out-patients of the same hospital. 34 (52%) participants were treated with SGAs and 32 (48%) with either ADs or FGAs. 25 patients (38%) were treated with more than one psychotropic drug: 18 patients in the SGAs group (53%) and 7 patients in the FGAs and ADs group (22%). Detailed demographic and clinical information is shown in Tables 1 and 2 (more precise data on patients' diagnosis, irisin concentrations and medication can be found in Appendix). Since there were very few patients meeting the criteria for high level of PA ($n = 3$), we decided to divide them into two groups: those with insufficient PA (iPA, $n = 44$, 67%) and those with at least sufficient PA (sPA, $n = 22$, 33%).

Irisin

In the studied population, the mean irisin concentration was 44.98 ± 25.08 ng/ml. The irisin concentration in the sPA group was higher in comparison with the iPA group; however, the difference was not statistically significant (51.5 ± 34.4 ng/ml vs. 41.7 ± 18.4 ng/ml respectively, $p = 0.14$) (Figure I).

It was significantly lower in the following: in men vs. Women (38.39 ± 17.3 ng/ml vs. 51.17 ± 29.6 ng/ml, respectively, $p = 0.04$), subjects on SGAs vs. subjects on ADs or FGAs (39.1 ± 17.9 ng/ml vs. 51.3 ± 30.0 ng/ml respectively, $p < 0.05$) (Figure II) and in patients with central obesity vs. without (40.6 ± 15.9 ng/ml vs. 55.5 ± 38.4 ng/ml, $p = 0.03$) (Figure III). There was no significant difference between in- and out-patients. Irisin concentration correlated significantly and negatively with BMI ($r = –0.27$, $p = 0.04$), waist circumference ($r = –0.35$, $p < 0.01$), WHR ($r = –0.30$, $p = 0.02$), total cholesterol level ($r = –0.31$, $p = 0.02$), LDL-C level ($r = –0.27$, $p = 0.04$) and TG level ($r = –0.30$, $p = 0.02$).

However, the analysis of the covariance models, including the effects of BMI, sex and age on irisin concentration, showed a statistically significant influence of BMI only ($F = 4.44$, $p = 0.04$), with sex being close to statistically significant ($F = 3.77$, $p = 0.06$).

Physical activity

Overall psychiatric treatment period in the sPA group was significantly shorter than in the iPA group: 4.5 ± 5.4 yrs vs. 13.1 ± 9.2 yrs, respectively ($p < 0.001$) (Figure IV), as well as sitting/lying time per day being sig-

Table 1. Detailed demographic and clinical information on study group

	Total			Men			Women			*t*	*p*
	N	M	SD	*n*	M	SD	*n*	M	SD		
Age (years)	66	39.20	13.18	32	37.56	12.01	34	40.74	14.19	–0.977	0.332
BMI (kg/m^2)	65	28.38	6.20	32	28.66	6.62	33	28.11	5.85	0.35	0.725
Irisin (ng/ml)	**66**	**44.98**	**25.08**	**32**	**38.39**	**17.30**	**34**	**51.17**	**29.60**	**–2.125**	**0.037**
sBP (mmHg)	66	126.88	15.16	32	129.25	15.45	34	124.65	14.75	1.238	0.220
dBP (mmHg)	66	80.65	9.71	32	81.34	10.71	34	80.00	8.79	0.559	0.578
Heart rate (n/min)	66	82.64	14.33	32	83.31	15.47	34	82.00	13.38	0.369	0.713
WHR	**64**	**0.94**	**0.09**	**32**	**0.98**	**0.07**	**32**	**0.90**	**0.09**	**4.121**	**< 0.001**
T-Chol (mg/dl)	64	199.06	41.49	30	193.60	42.67	34	203.88	40.44	–0.989	0.326
HDL (mg/dl)	**64**	**52.53**	**14.25**	**30**	**44.57**	**9.28**	**34**	**59.56**	**14.27**	**–4.910**	**< 0.001**
LDL (mg/dl)	63	118.00	31.72	29	113.72	28.39	34	121.65	34.31	–0.988	0.327
TG (mg/dl)	**64**	**143.33**	**86.90**	**30**	**172.63**	**103.88**	**34**	**117.47**	**58.86**	**2.653**	**0.010**
Glucose (mg/dl)	65	92.98	13.24	31	95.03	16.49	34	91.12	9.23	1.195	0.237
Treatment duration (years)	66	10.22	9.03	32	9.28	8.57	34	11.11	9.48	–0.821	0.415
Overall DDD	66	2.00	1.22	32	2.03	1.24	34	1.96	1.21	0.234	0.816

N – numer of patients, M – mean, SD – standard deviation, t – t-Student test result, p – significance level (men vs. women), BMI – body mass index, sBP – systolic blood pressure, dBP – diastolic blood pressure, WHR – waist to hip ratio, T-Chol – total cholesterol, HDL – high-density lipoproteins, LDL – low-density lipoproteins, TG – triglycerides, DDD – defined daily dose

Table 2. Medications taken by study's participants. Note that some patients were treated with more than one psychotropic drug

Medication		Number of subjects	Mean DDD
SGAs		34	1.33
	Amisulpride	6	1.83
	Aripiprazole	3	1.33
	Clozapine	13	1.04
	Quetiapine	15	1.22
	Olanzpaine	11	1.68
	Risperidone	5	1
FGAs or antidepressants		32	1.52
	SSRIs	26	1.73
	SNRIs	2	1.63
	TeCAs	4	0.75
	other (trazodone)	4	0.4
	FGAs	3	2.17

SGAs – second generation antipsychotics, FGAs – first generation antipsychotics, SSRIs – selective serotonin reuptake inhibitors, SNRIs – selective serotonin and norepinephrine reuptake inhibitors, TeCAs – tetracyclic antidepressants, DDD – defined daily dose

Table 3. Parameters with no statistical significance, but with a statistical trend

	sPA	iPA	*p*
Age (years)	34.7 ± 10.4	41.4 ± 13.9	> 0.05
BMI (kg/m^2)	26.4 ± 6.2	29.4 ± 6.0	0.07
Waist circumference (cm)	95.1 ± 19.7	103.6 ± 15.8	0.06
WHR	0.91 ± 0.1	0.96 ± 0.08	> 0.05

BMI – body mass index, WHR – waist to hip ratio, iPA – insufficient physical activity group, sPA – at least sufficient physical activity group

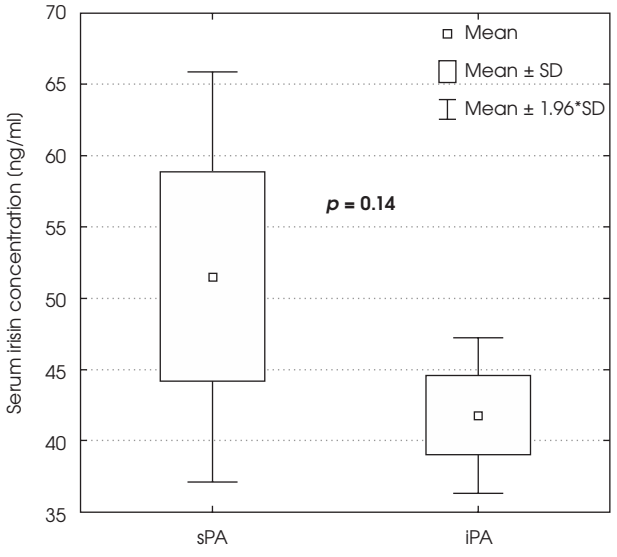

Figure I. Comparison of serum irisin concentrations by amount of physical activity (sPA – at least sufficient physical activity, iPA – insufficient physical activity)

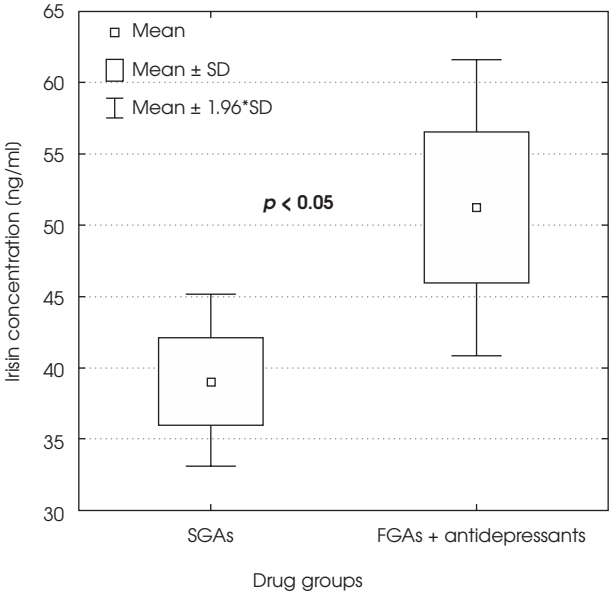

Figure II. Comparison of serum irisin concentrations in different drug groups (SGAs – second generation antipsychotics, FGAs – first generation antipsychotics)

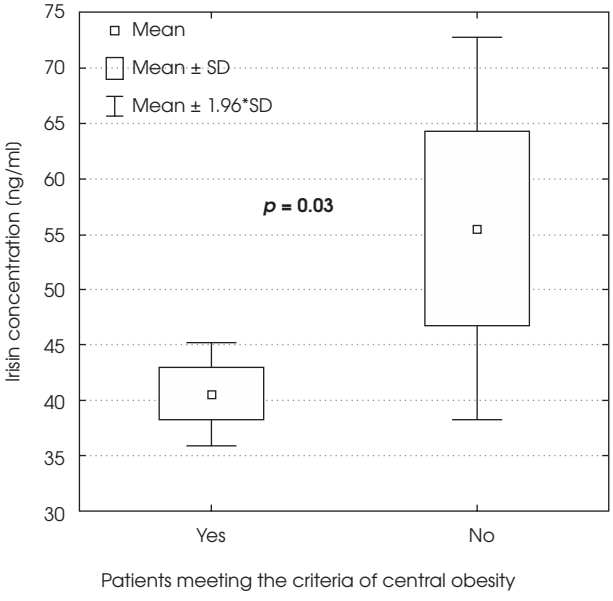

Figure III. Comparison of serum irisin concentrations in groups of patients divided according to the criteria for central obesity

nificantly shorter in the sPA group (349.5 ± 148.4 min/day) compared to 555.7 ± 182.8 min/day in the iPA group ($p < 0.001$) (Figure V). We also found several other interesting differences in the parameters studied. We decided to include them in this report (shown in Table 3), as they were on the verge of statistical significance. Additionally, we found a significant difference between patients treated with different drug groups in terms of PA sufficiency

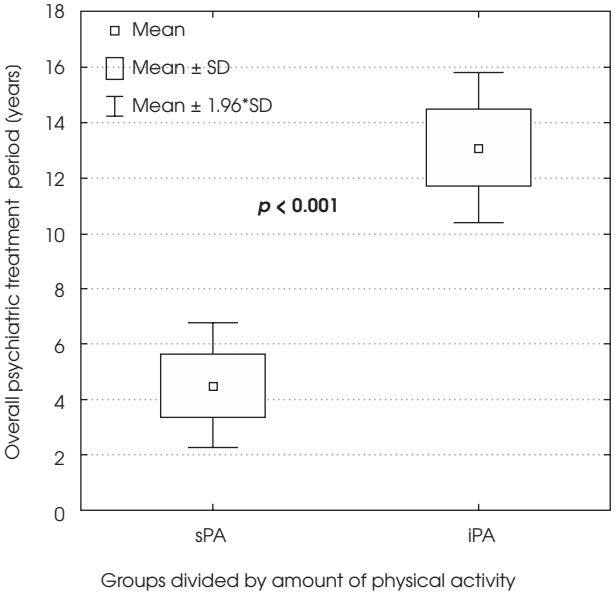

Figure IV. Comparison of overall psychiatric treatment period between groups divided by amount of physical activity (sPA – at least sufficient physical activity, iPA – insufficient physical activity)

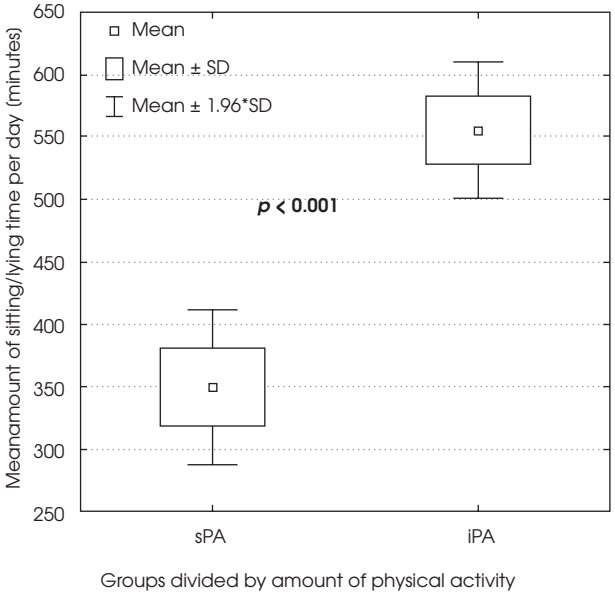

Figure V. Comparison of mean amount of sedentary time per day between groups divided by amount of physical activity (sPA – at least sufficient physical activity, iPA – insufficient physical activity)

(exact Fisher test, two-sided $p = 0.04$). Only 21% ($n = 7$) of patients treated with SGAs exhibited at least a sufficient amount of PA, compared to 47% ($n = 15$) of patients treated with ADs or FGAs.

The amount of physical activity (measured in MET-min/week) was lower in patients that met the criteria of MetS, though the difference was insignificant (436.2 ± 400.1 vs. 937.3 ± 1369.2, $p = 0.075$). We also found that there was no significant difference in MET-min/week nor sitting/lying time spent per week between genders, in- and out-patients, or participants taking different medication (SGAs vs. ADs or FGAs). However, the amount of MET-min/week correlated significantly and negatively with overall length of psychiatric treatment ($r = -0.31$, $p = 0.01$), fasting glucose levels ($r = -0.26$, $p = 0.04$) and sitting/lying time per day ($r = -0.41$, $p < 0.01$). In addition to the latter, sitting/lying time per day correlated significantly and positively with overall length of psychiatric treatment ($r = 0.33$, $p < 0.01$).

DISCUSSION

Irisin function has been thoroughly examined and discussed since its discovery, yet no final consensus has been reached to date. Our study focused on irisin's connection with physical activity and metabolic syndrome components in a very specific population. Thus, our findings may not be concurrent with the literature available.

Multiple studies have shown that irisin levels were elevated after physical activity; however, the effect lasted only for a limited period of time (1 to 24 hours [18, 19]). Safarimosavi *et al.* [14] pointed out that the type of exercise plays an important role in the raising of irisin serum concentration post-exercise. A meta-analysis recently conducted by Fox *et al.* [20] confirmed the post-exercise acute elevation of irisin concentration. The authors concluded that an individual's fitness level is the best predictor of PA-induced irisin concentration elevation. On the other hand, the role of the intensity of PA or fitness level on resting irisin concentration is still undetermined: some studies have shown that those factors had no influence [18, 21], while others (including a meta-analysis by Qiu *et al.* [13]) stated the opposite, reporting reductions in irisin concentration levels after training programmes lasting several weeks [14]. It is suggested that, as irisin is partially secreted by adipose tissue, the drop in its level is a consequence of lower body fat mass. Our results only add to the aforementioned ambiguity regarding resting irisin concentrations, as we showed that patients with sufficient PA had higher irisin levels than those with insufficient PA. However, the difference was not statistically significant, and thus further research is needed. In addition, we found that irisin concentration correlates negatively with BMI and WHR in accordance with the study by Moreno-Navarrete *et al.* [22], but also oppositely to a number of other reports [23, 24].

It is important to point out that none of the aforementioned studies included subjects that were undergoing psychiatric treatment. We cannot conclude, however, that therapy with psychotropic agents itself influences irisin secretion, as we did not include a non-treated control

group. However, we found that patients who had SGAs prescribed had lower irisin levels compared to patients treated with FGAs and/or ADs. The difference between irisin levels in distinct medication groups in our study suggests there may be an association between the class of drug in use and the regulation of irisin secretion. Psychopharmacotherapy may have a significant impact on several aspects of circadian rhythm [25]. Anastasilakis *et al.* [26] reported that irisin secretion varies depending on time of day, which may be an explanation for the difference discussed here. Another possible factor in the alteration of irisin secretion could be different potentials for drug-induced appetite increase, and, in turn, weight gain, as irisin is partially secreted by adipose tissue [10]. The mechanism of psychopharmacotherapy-induced weight gain is still not fully known and needs further research; however, several receptors are reported to be important factors. Type 2C serotonin receptor ($5HT_{2C}$) antagonists, i.e. the SGAs clozapine, olanzapine, and quetiapine, and the ADs mirtazapine, mianserin, and trazodone, are known for their potential to increase appetite [27, 28]. On the other hand, there are medications that also act as $5HT_{2C}$ antagonists, though their influence on weight gain is much less expressed, i.e. SGA, ziprasidone or the selective serotonin reuptake inhibitor (SSRI) fluoxetine [27, 28]. What is more, histamine type 1 (H_1) receptor antagonists are also well-documented as weight-gain-inducing agents, and the receptor affinity is associated with the potency of this effect [29]. The highest anti-H_1 affinity is reported for clozapine and olanzapine, but several ADs also have anti-H_1 properties, i.e. mirtazapine, mianserin and trazodone [28]. The fact that medications in both of our studied groups – SGAs, and FGAs with ADs – may cause weight gain but have different influence on irisin secretion proves that its regulation is still not fully investigated and should be researched further.

Many studies showed that irisin levels are lower in prediabetes or T2DM patients compared to healthy control groups [16, 23, 30]. Also, in our study patients with elevated fasting glucose levels or those treated for hyperglycaemia had lower irisin levels (compared to subjects with normal glucose levels), though the difference was not statistically significant. Several studies (including a meta-analysis by Du *et al.* [30]) reported that ethnicity is an important factor regarding irisin levels in T2DM, with a bigger impact in Asian populations. Since all our participants were Caucasian, the depletion of irisin level in T2DM patients might be less apparent. We also found that irisin levels were lower in patients that met the criteria of abdominal obesity and that irisin levels correlated negatively with waist circumference. It has been established that waist circumference is not only an independent factor for cardiovascular diseases but can also be a good predictor of developing or identifying insulin resistance [31-33]. Therefore, our results seem to further confirm the connection between irisin and T2DM pathogenesis.

In our study, we found that there are negative correlates of total cholesterol, LDL cholesterol, TGs and irisin levels. These results seem to be in line with most of the available literature. For instance, Xiong *et al.*'s study in mice [34] showed that increased expression of FNDC5, the irisin precursor, is associated with reduced total cholesterol and TGs levels. Human studies also prove that higher irisin levels are associated with better "metabolic profile" [35]. On the other hand, de la Iglesia *et al.* [36] reported depletion of lipid metabolism biomarkers independently of body weight in patients whose irisin levels dropped during a trial. However, in this study the intervention was dietary and participants were asked to maintain their "usual physical activity". As the main inclusion criterion was a MetS diagnosis, it raises questions about the amount and intensity of participants' PA (data regarding this matter were not shown), which seem to play an important role in irisin secretion.

The additional goal of this study was to validate patients' physical activity and determine its relationship with their metabolic parameters. We found that, in general, the longer the treatment the more sedentary a lifestyle our patients develop: the sPA group were treated for a shorter time and spent less time sitting/lying per week. What is more, treatment duration was correlated positively with amount of sitting/lying time per week and negatively with amount of PA measured in MET-min/week. This could be attributed to the possible progression of negative symptoms in patients with schizophrenia, possibly a worse response to treatment and/or lesser adherence over time in all patients resulting in psychomotor drive deterioration or persisting 'low mood', which has been identified as one of the biggest obstacles to exercising for patients by Firth *et al.* [3]. In their comparative meta-analysis Stubbs *et al.* [37] also reported that schizophrenic patients exercised less in older age and with more severe depressive symptoms, which further supports our results.

Apart from the aforementioned connections, we found that amount of PA in terms of MET-min/week is correlated negatively with fasting glucose levels. Many studies, as shown in Boniol *et al.*'s recent systematic review [38], state that even moderate exercise leads to a significant reduction of fasting glucose levels. We also observed that patients meeting the criteria for MetS exercised less that those not meeting them. The difference was not statistically significant, but this result is supported by other researchers, such as Balkau *et al.* [39] and their RISC study, in which subjects exercising more exhibited better insulin sensitivity. We also found other intuitive, yet not statistically significant, trends: patients in our sPA group had lower BMI, waist circumference and WHR

ratio. Despite these things not being statistically significant, we think they are still worth mentioning and investigating further, since they might form a strong case in encouraging patients to exercise more.

Interestingly, we found no significant difference in amount of exercise nor sitting/lying time between genders and in- and out-patients. Ehrbar *et al.* [40] reported that 50-60% of in-patients in Switzerland show sufficient physical activity. This percentage, however, is achieved largely due to structured exercise or sport therapy conducted daily. We must sadly admit that, in the hospital where our study was carried out, patients are only encouraged to participate in PA therapy, which makes it easier for them to avoid it when they "do not feel up to it", and its frequency is only up to three times a week. As a result, the percentage of patients exhibiting sufficient physical activity in our research reached only 33%. On the other hand, some of our out-patients declared that having to come to the hospital every day makes it easier to take up healthy habits (such as taking a walk instead of riding a bus) and keep a certain routine. These might be the factors that shift the pattern of adherence in terms of PA between the in- and out-patients in this study.

No significant difference was found between drug groups in the amount of MET-min/week and sitting/lying time/week; however, comparing the PA sufficiency in the drug groups did show a significant difference. This ambiguity could be attributed to the lack of homogeneousness in terms of diagnosis – SGAs were administered to patients diagnosed with schizophrenia, bipolar disorder and, in some cases, major depressive disorder. The aforementioned factors, accompanied by the self-reported PA intensity measurement means used rather than objective ones, are limitations of our study that we are aware of and will, if possible, try to improve in future research. Celis-Morales *et al.* [41] have proven that self-report methods can lead to inconsistencies in the measurement of PA intensity.

Another limitation of this study was small group size, which was possibly the most important factor in terms of statistical significance, especially in those analyses that were on the verge of being significant. What is more, the recruitment was non-randomised and limited to only one clinical facility, which could further compromise our results. In future research, more emphasis should be put on the method of patient recruitment, and more clinical facilities should be engaged. This should lead to an increase in the number of patients enrolled in the study and quality of the results. The one limitation that will be the hardest to overcome is the absence of a control group. However, gathering subjects that are drug-naïve, show signs of (possibly acute) mental disorder development for a significant amount of time, are able to provide valid information on their physical activity, and are able to give informed consent might constitute a task difficult to complete, especially in a project of a scale such as ours.

CONCLUSIONS

This was one of the first studies to examine the associations between the serum irisin level, metabolic syndrome components and physical activity among psychiatric patients. Despite some limitations, we can conclude that irisin concentration measurement does not appear to be a valid, objective tool for the evaluation of patients' physical activity. We did find, however, significant associations between irisin, several metabolic parameters and psychopharmacotherapy. Because of the continuing inconsistency or information – deficiency in the literature, more studies of these matters should follow. Additionally, our study further underlines the importance of physical activity on patients' overall state of health, as well as seems to point out the insufficiency of doctors' efforts in encouraging patients to perform more physical activities and exercise.

Conflict of interest

Absent.

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Appendix. Detailed information on patients' diagnosis, serum irisin concentration and psychopharmacotherapy (antidepressants and antipsychotics)

Sex	Diagnosis (ICD-10)	Irisin concetration (ng/ml)	DDD
M	F20	16.65	AMI 1.5 + QUE 1.25
M	F20	19.07	OLA 1
M	F20	15.85	CLO 1.83
M	F20	17.58	CLO 0.67 + AMI 2
F	F20	33.33	OLA 2 + QUE 2
M	F20	27.71	CLO 0.75
M	F31	32.45	QUE 0.75
M	F20	28.83	CLO 0.83 OLA 2
F	F31	31.28	CLO 1
M	F20	30.86	OLA 2
F	F20	64.28	QUE 0.75
F	F20	45.59	RIS 1.2 QUE 1.75
F	F20	33.91	CLO 0.75
F	F20	34.22	AMI 2 + QUE 1.5
M	F20	25.84	RIS 1 + QUE 1.5
M	F21	28.83	ARI 2 + AMI 2
M	F20	44.82	AMI 2 CLO 1.33
M	F20	35.54	OLA 2 + CLO 0.5 + QUE 2
F	F20	34.59	OLA 1.5 + ARI 1
M	F20	27.68	CLO 1.83 + OLA 2
F	F20	43.12	CLO 1.17 + OLA 2
F	F20	35.84	CLO 1.08 + OLA 0.5
M	F23	29.28	QUE 1.5
M	F20	59.62	CLO 0.42 + AMI 1.5
M	F31	97.69	QUE 0.75
M	F20	54.55	RIS 0.8
M	F31	20.51	QUE 1.5
F	F31	55.60	QUE 0.75
F	F34	47.35	QUE 0.25
F	F20	77.31	OLA 2 ARI 1
M	F20	35.02	QUE 1.75 + RIS 1.2
M	F20	46.65	OLA 1.5 + RIS 0.8
F	F20	63.43	CLO 1.33
M	F61	33.47	QUE 0.25
M	F32	38.25	SER 1
M	F43	69.96	SER 1.5
M	F40	53.92	FLUV 1.5
M	F43	41.11	FLU 1
F	F43	28.30	SER 1
F	F60	27.69	ESCIT 1
M	F42	40.36	FLUV 3 MIR 0.5
F	F33	44.81	PAR 1
F	F33	45.74	FLU 2

Appendix. Cont.

Sex	Diagnosis (ICD-10)	Irisin concetration (ng/ml)	DDD
F	F31	57.45	VEN 2.25 CTX 0.15
F	F33	28.11	MAPR 1.5
F	F41	34.80	PAR 1.5
M	F45	29.42	TRAZ 0.3 ESCIT 1
F	F44	28.70	PER 1
F	F41	19.08	SER 2
F	F33	38.84	FLU 1.5 MIAN 0.5
M	F32	49.76	MIR 0.5
F	F41	76.65	CIT 2
F	F43	54.27	ESCIT 1
F	F41	43.18	PAR 2
F	F33	45.11	CIT 2
F	F61	55.44	DULO 1 HALO 0.5
M	F43	35.54	SER 2
F	F41	174.05	FLU 1.5
F	F43	68.91	TRAZ 0.3 SER 4
M	F43	48.34	CIT 1
F	F41	100.96	SER 0.5
M	F71	33.59	SER 4 CTX 0.05
M	F31	59.76	SER 1
F	F33	61.28	TRA 0.5 SER 4
F	F61	95.35	TRA 0.5 SER 1
F	F41	11.39	PER 5

M – male, F – female, AMI – amisulpride, ARI – aripiprazole, CLO – clozapine, OLA – olanzapine, RIS – risperidone, QUE – quetiapine, SER – sertraline, FLUO – fluoxetine, FLUV – fluvoxamine, PAR – paroxetine, ESCIT – escitalopram, CIT – citalopram, TRAZ – trazodone, VEN – venlafaxine, DULO – duloxetine, MIR – mirtazapine, MIAN – mianserin, MAPR – maprotiline, PER – perazine, HALO – haloperidole, CTX – chlorprothixene, DDD – defined daily dose (normalised)