The risk of significant body weight gain and abdominal obesity during short-term treatment with olanzapine

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Abstract

Introduction: The prevalence of obesity has been increasing both in the United States and Europe. Epidemiological data have indicated an explicit increase in morbidity and mortality in a group of patients with BMI higher than 25. Important is also the problem of obesity in people with mental disorders (especially in psychotic patients) due to the introduction of atypical antipsychotics, e.g. olanzapine, after which significant body weight gains are often observed during short-term therapy.

Material and methods: Sixty two patients who suffered from paranoid schizophrenia, aged from 18 to 45, were examined. Total change in body weight, height, waist and hip circumferences, BMI and WHR at both time points was evaluated. The type of obesity (considering the patients' gender) and the correlation between initial BMI values and body weight gain during olanzapine treatment were also examined.

Results: Higher gains have been observed in the group of patients who did not meet the obesity criteria at $t = 0$. A significant negative correlation between BMI ($t = 0$) and body weight gain during the 8-week olanzapine treatment was observed. A significant correlation between the patients' gender and abdominal obesity was also observed at $t = 1$.

Conclusions: Over 1/3 of examined patients exhibited a significant body weight gain during olanzapine treatment. Patients with normal weight or underweight before olanzapine treatment increased their body weight significantly more as compared to the patients with overweight or obesity found at $t = 0$. Abdominal obesity was diagnosed in the examined group at $t = 1$ more frequently in women than in men.

Key words: body weight gain, abdominal obesity, schizophrenia, atypical antipsychotics.

Introduction

Obesity is a body composition disorder defined as a relative or a total excess of fat reserve in the organism. The adipose tissue excess usually induces a body weight gain. A classification criterion submitted by the National Heart, Lung and Blood Institute, used in most studies, is the body mass index (BMI) [1]. It is presently recommended that BMI constitute a basis for overweight and obesity classification (Table I) [2].

These definitions comply with the suggestions presented by the World Health Organisation (WHO) [3].

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Table I. Classification of overweight and obesity based on the body mass index (BMI), 1997

Category	BMI
Underweight	< 18.5
Normal	18.5-24.9 (kg/m^2)
Overweight	25-29.9
Obesity	> 30
– I degree	30-34.9
– II degree	35-39.9
– III degree (in. extreme, utmost, pathological)	> 40

Evaluation of BMI is the most convenient method for measuring obesity, which quite well correlates with the adipose tissue content [4]. Admittedly, the adipose tissue is not distributed evenly. In overweight women the adipose tissue distribution is different than in men.

Recent research has demonstrated that "new" adipocytes could be differentiated from fibroblast-like pre-adipocytes in every period of life. Therefore, late obesity occurring in adults could be associated not only with increased size of adipocytes, but also with their increased number. People with extreme obesity can have even four times more adipocytes as compared to healthy subjects, and every obese person may have even double the amount of fat in adipocytes as compared to a slim person [5].

In 1947 Jean Vague identified two types of obesity:
1) central type obesity (visceral, "apple-shaped", android), where excessive adipose tissue accumulates in the region of abdominal cavity organs in the portal vein catchment area and is characterized by much more intense triglyceride (TG) metabolism;
2) gluteo-femoral obesity ("pear-shaped", gynoid) occurs mostly in women and is particularly important for maintenance of the species; the adipose tissue in this area is a complete opposition to the visceral tissue in metabolic respect; it serves as a reservoir of fat and is characterized by slow metabolism [6-8].

Central obesity is connected with a completely different metabolic profile and different factors of the risk of development of many diseases as compared to gynoid obesity. For this reason overweight patients should be commonly classified in respect of obesity type. Such division can be done by determining the waist to hip ratio (WHR). Abdominal obesity bearing a high risk is diagnosed when WHR in women equals or exceeds 0.8, and in men when it equals or exceeds 1.0.

An even simpler measurement allowing one to determine the type of obesity is determination of the waist size itself. Pursuant to the latest consensus reached by the International Diabetes Federation (IDF), central obesity is recognised when the waist size equals or exceeds 80 cm for European women, or equals or exceeds 94 cm in European men (in other ethnic groups these values vary) [9, 10].

Differences have been indicated in the correlation between measurements of the waist size and WHR ratio between women and men as well as the patients' age, and the occurrence of circulatory system diseases. The results of the measurement of waist size and WHR have been found to be significantly higher in younger men as compared to those of advanced age. At the same time it was found that in women of advanced age the WHR ratio was higher than in younger women, which may suggest that accumulation of abdominal adipose tissue in older age concerns mainly women. This type of obesity in women is largely enhanced after menopause. Studies evaluating the distribution and amount of adipose tissue within the abdominal cavity, carried out using magnetic resonance, revealed that it correlated well with a simple measurement of waist size. The measurement of waist size was shown to supply information about the extent and size of obesity, which is not observed in the case of WHR measurement [11].

In the latter half of the 20th century, significant epidemiological changes were found in human body composition. For over 100 years the obesity prevalence has been increasing both in the United States and Europe. The incidence of obesity in West European countries has reached "epidemic" magnitude. The incidence of overweight has increased even more: in 1998 this problem affected over 60% of men and over 55% of women. Other studies indicate that approx. Thirty-three percent of adult Americans suffer from obesity.

Obesity is presently known to result from the impact of environmental and lifestyle factors (physical activity, availability and type of food, mental response and medicinal drugs) as well as the effects of hereditary/genetic factors [10].

There are genetically conditioned differences in metabolic rate, but evidence confirming the contribution of decreased metabolism to the development or maintenance of obesity is scarce, which means that overweight people often consume more calories than those with correct body weight. Noteworthy is also the presence of potentially strong genetic conditions of behavioural factors such as dietetic preferences for fats, choice of breaks between meals, degree of caloric compensation in response to nutritional restrictions, and practising physical activity [12]. Much evidence points to the importance of environmental factors contributing to the occurrence of obesity. No doubt

the dramatic increase in the prevalence of overweight and obesity in many populations within the past 30 years results from "toxic" environmental effects [13]. Recently certain populations have experienced a significant change, with increased availability of high-caloric foodstuffs containing a lot of fats, with a simultaneous evident decrease in physical activity.

Also gender and race are important factors connected with the body mass index. The findings of the National Health and Nutrition Evaluation Status (NHANES III) in the USA indicate that the joint prevalence of overweight and obesity in the general population is much higher in men (age > 20). In white men the results are very similar to those of the general population, whereas among the black race a much higher prevalence of overweight and obesity is observed among women [10].

For a long time epidemiological data have indicated an explicit increase in morbidity and mortality in a group of patients with BMI higher than 25. In 1991 it was estimated that in the USA the incidence of deaths due to obesity (BMI > 30) and diseases related to obesity was 280 000-325 000 people annually [10, 14].

The results of numerous epidemiological studies demonstrate that obesity is a status predisposing to the development of diabetes, arterial hypertension, dyslipidaemia, coronary athero-sclerosis, degenerative heart diseases, cerebral stroke, cholelithiasis, certain diseases of the liver, kidneys, lungs, skin, osseo-articular system (including osteoporosis), uric acid diathesis, sleep apnoea, as well as some types of cancer (of breast, intestines – mainly colon, uterus, bladder), menstruation disorders, pathological pregnancy, and infertility [15, 16]. Obesity also constitutes a significant factor which hampers operative treatment, and deteriorates prognosis after injuries or acute infections. Furthermore, obesity decreases the affected people's chances for proper education and work, generating high economic costs connected with the care for them.

Obesity is quite common in psychotic patients. The few controlled studies often differ in the obtained results. Among patients with the first episode of schizophrenia before pharmacotherapy is launched, obesity was three times higher and glucose metabolism disorders were significantly more frequent as compared to healthy subjects of the same age and similar body weight [17].

Thakore et al. noted in schizophrenic patients an increased content of fat in the visceral tissue as compared to the control group, occurring before antipsychotic treatment was included [18].

Some studies revealed no differences in BMI in schizophrenic patients, and increased BMI values

in affected women as compared to healthy ones. Many factors increase mortality in schizophrenic patients, including twice as prevalent as compared to the general population, complications of somatic diseases (mainly within the circulatory system), the occurrence of which is predisposed by: obesity, fat metabolism disorders, diabetes, arterial hypertension and unhealthy lifestyle (lack of physical activity, nicotinism) [17].

The studies carried out in the USA during 1987-1996 on a representative group of schizophrenic adults demonstrated that the average BMI value in those subjects was significantly higher than in healthy controls. Over the years covering the study a general trend of increasing BMI value was noticed in a population of healthy subjects (in both genders and all examined age groups). The observed obesity was usually of visceral type [19]. The results of other studies confirm that in the group of patients with mental disorders the BMI is higher as compared to healthy subjects, usually by approx. 30% [20-22]. Thus, as results from the above studies show, mental disease should be considered as a significant factor of the risk of the occurrence of obesity and other metabolic disorders [23].

Body weight gains have often been described as a side effect of typical antipsychotics (TAPs). During the 1990s interest in this problem was enhanced due to the introduction of atypical antipsychotics (AAPs), after which significant body weight gains are often observed during short-term therapy. The body weight gain concerns approx. 26-80% of antipsychotic patients, treated both with TAPs and AAPs [2, 3, 15, 24-27] (Figure 1).

The studies indicate that 58-73% of chronic antipsychotic patients are affected by abdominal obesity [22, 28, 29]. The observation carried out by Newcomer et al. indicates that antipsychotic treatment may to a variable extent induce body weight gains: from mild (< 2 kg) during the use of amisulpride, ziprasidone and aripiprazole, to severe (4-10 kg) during treatment with olanzapine and clozapine.
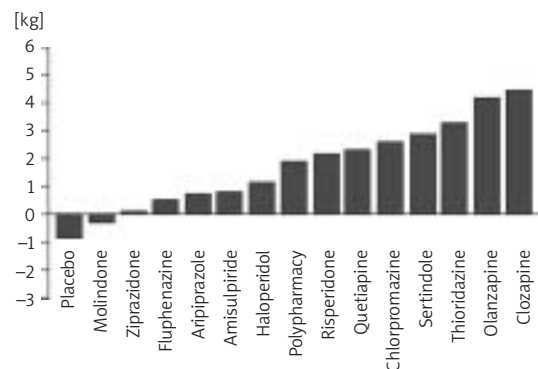

Figure 1. Average body weight gains after 10-week treatment with antipsychotics in "standard" doses [28]

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In body weight gain mechanisms connected with antipsychotic treatment the following symptoms are assumed: increased appetite, basal metabolism disorders, lowered physical activity, and changes in concentrations of neurotransmitters and neuro-peptides. Reduced body weight in certain patients before treatment may also contribute to obesity. The contribution of particular factors may differ among patients [30].

The results of certain studies point to a correlation between the body weight gain and clinical effects of treatment (e.g. in case of use of clozapine and olanzapine) [31]. The body weight gain is thought to be correlated with the intensity of pharmacological and behavioural treatments [32].

The results of short-term studies on body weight gain indicate that all AAPs (olanzapine, quetiapine, risperidone, ziprasidone, aripiprazole) induced, unlike the placebo, a variable level of clinically significant body weight gain (at least double), defined by the U.S. Food and Drug Administration (FDA) as a gain above 7% as compared to the initial value [33, 34]. It seems that the percentage of patients with a body weight gain over 7% of the initial BMI is the most proper index of evaluation of the clinical risk of body weight gain and it should be the standard information apart from the average change in body weight expressed in kilograms. Researchers from the Institute of Medicine (Washington DC) opine that a body weight gain by just above 5% increases morbidity and premature death risk (coronary disease, cancer, diabetes), especially when the treatment is accompanied by nicotinism as an additional risk factor.

Material and methods

Included in the study were 62 patients aged from 18 to 45. The lower limit of the age criterion was established according to olanzapine preparations registration from the age of 18, whereas the upper limit was established based on the occurrence of menstruation (the patients included in the study had to menstruate correctly).

All the examined patients suffered from paranoid schizophrenia F20 (ICD-10). A substantial majority of patients included in the study had not been treated antipsychotically (it was their first episode of the disease).

The study period comprised the first 8 weeks from inclusion of olanzapine. The study involved both inpatients and outpatients. Excluded from the study were 23 patients. This was usually due to the need for a change of treatment because of its inefficacy, adding medicinal drugs from other groups such as normothymics or antidepressants, a change of neuroleptic or occurrence of severe adverse (mainly extrapyramidal) symptoms (15 persons). Another reason for exclusion from the study was withdrawal of consent (8 persons).

Among the patients included in the study 14 were overweight and 1 was obese. Abdominal obesity defined according to IDF criteria was diagnosed in 14 women and 1 man, whereas abdominal obesity calculated according to WHR was diagnosed in 16 women and 3 men included in the study. Variables characterizing selected quantitative anthropometric traits of the examined population are presented in Table II. Groups with and without a significant body weight gain did not differ statistically significantly in respect of age.

In the examined group of patients a total change in body weight was evaluated by double weighing, i.e. before olanzapine administration ($t = 0$) and after 8 weeks of treatment ($t = 1$). Measurements were made each time using the same scales. In addition, height, waist and hip circumference measurements were carried out and BMI and WHR were calculated at both time points. The measurements were made between strictly defined body points, located mainly in the bones. Body height was measured in the morning in upright posture from the body base (base) to the top of the head

Table II. Variables characterising selected quantitative anthropometric traits of the examined population

Variable		Mean value	Median (Me)	Minimum (Min.)	Maximum (Max.)	Standard deviation (S.D.)	CV%
Increase [cm]		168.87	169.0	147.0	181.0	9.1	5.3
Body weight [kg]		69.53	68.5	42.5	93.5	10.9	15.6
BMI [kg/m^2]		24.43	23.6	17.2	38.9	3.8	15.5
Waist circum. [cm]	W	82.18	82.5	65.0	111.0	10.9	13.3
	M	84.94	88.0	68.0	97.0	7.6	8.9
Hips circum. [cm]		95.66	96.0	73.0	126.0	8.6	8.9
WHR	W	0.84	0.8	0.7	1.0	6×10^{-2}	7.1
	M	0.91	0.9	0.8	1.0	7×10^{-2}	7.7

W – women, M – men

(vertex). Circumferences were measured using a non-stretchable tape, at characteristic points: hips – waist – through the navel, whereas the circumference of the hips was measured in the widest place.

To verify the hypothesis about body weight gains occurring during olanzapine treatment, first the incidence of body weight gain was evaluated in the entire examined group and then in groups selected because of the occurrence of obesity/overweight at $t = 0$. The results of analyses are presented in Tables III and IV, whereas the distribution of total [kg] and relative body weight gain [%] is presented in Figures 2, 3.

In view of many authors' observations relating to a correlation between initial BMI values and body weight gain during olanzapine treatment, a decision was taken to check whether or not the examined group exhibited a correlation between body weight gain and BMI value determined at the beginning of the treatment, i.e. at $t = 0$. Two types of analyses were carried out for this purpose: using the Mann-Whitney test, average values of body weight gain were compared in groups selected due to obesity or overweight at $t = 0$ (Table V) and a correlation between the mentioned traits was estimated using the Tau Kendall correlation nonparametric coefficient. The dispersion for the tested variables (body weight gain and BMI at $t = 0$) with an equation and regression line is presented in Figure 4.

As from the clinical point of view it is not enough to diagnose obesity but more important is specifying the type of obesity [35, 36], such an analysis was carried out, using Fisher's test, considering the patients' gender.

The groups with and without a significant body weight gain (group A vs B) did not differ statistically significantly in age.
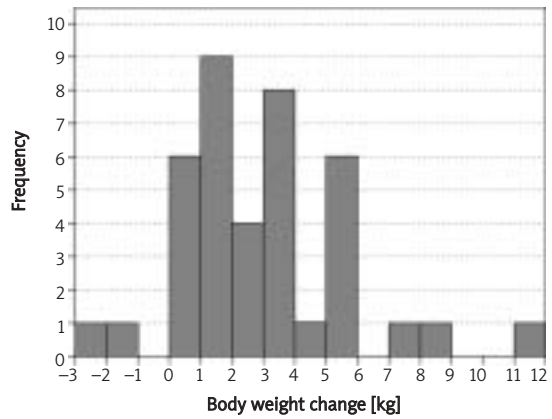

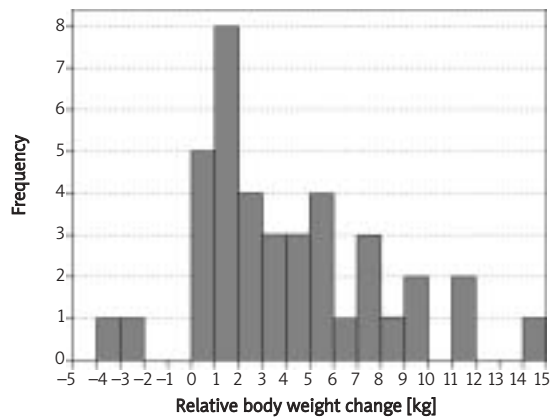**Figure 2.** Histogram of the body weight change distribution

Figure 3. Histogram of the relative body weight change distribution

Table III. Number of patients with a significant body weight gain (group A) and without a body weight gain (group B)

Variable	Level	Number	Fraction
Body weight gain ≥ 5%	No	25	0.64
	Yes	14	0.36

Table IV. Descriptive statistics related to the body weight gain observed in the examined group during the study

Variable	Mean value	Median (Me)	Minimum (Min.)	Maximum (Max.)	Standard deviation (S.D.)	CV%
Change in body weight [kg]	2.72	2.3	−2.9	11.0	2.71	99.6
Relative change in body weight [%]	4.04	3.1	−3.3	14.0	3.90	96.5

Table V. Descriptive statistics related to the body weight gain observed in the examined group during the study

Variable	Obesity or overweight at $t = 0$	Average	Me.	Min.	Max.	S.D.	CV%	U	Z	p
Body weight gain [%] $t = 1$	Yes	2.18	1.7	−3.3	7.3	3.20	146.8	103.5	2.2	0.05
	No	5.21	4.5	0.0	14.5	3.94	75.6			

U – U statistics value in Mann-Whitney test, Z – standardised value of normal distribution for Mann-Whitney test statistics, p – exact value of bilateral test probability
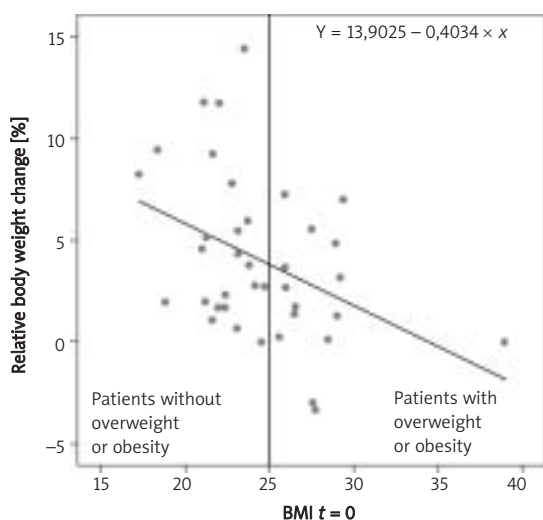
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Figure 4. Body weight gain (in %) during 8-week treatment with olanzapine depending on BMI before the onset of treatment

Analyses and graphic presentations of the results were carried out using SPSS 12.0 PL for Windows (Statistical Package for Social Science, SPSS, Chicago Il. 1989-2003) and STATISTICA 7.1 PL for Windows (StatSoft, Inc. 2005). Evaluation of the significance of differences in distributions of quantitative variables in two independent groups was carried out using the Mann-Whitney U test. For characteristics expressed on the nominal scale the structure was examined and incidence of individual classes in contingency tables was evaluated. The correlations between quantitative variables were tested using the chi^2 (χ^2) independence test and precise Fisher's test for four-field tables. The significance of changes in correlated dichotomous variables was evaluated by McNemar's test. For all analyses $\alpha = 0.05$ was assumed as the maximum allowable value of the probability of type I error (i.e. rejection of the real zero hypothesis).

Results

At $t = 1$ a significant body weight gain was found in 14 patients (9 women and 5 men) – "group A". Patients without a significant body weight gain (< 5%) constituted "group B". The most representative in the entire group was the body weight gain from the lowest range contained within 0-2 kg and concerning 15 patients. The highest body weight gains within the range 7-12 kg concerned 3 patients. In 9 patients the body weight gain exceeded 7%. Interestingly, 2 patients reduced their body weight during the study by 1-3 kg. In total, obesity (according to BMI) was diagnosed at $t = 1$ in 4, and overweight in 15 patients.

Groups of patients singled out due to obesity or overweight at $t = 0$ differed significantly in the value of the body weight gain observed during the study, higher gains having been observed in the group of patients who did not meet the obesity criteria at $t = 0$.

Evaluation of co-variability of the body weight gain during the 8-week olanzapine treatment and initial value of BMI ($t = 0$) demonstrated a significant negative correlation between these variables (Tau Kendall correlation coefficient = –0.277, $p = 0.013$, $N = 39$).

Abdominal obesity at $t = 1$ was diagnosed in 20 patients – 17 women and 3 men (according to WHR) and in 16 women and 3 men (according to IDF criteria).

A significant correlation at $t = 1$ was observed between the patients' gender and abdominal obesity evaluated according to IDF and WHR criteria (Fisher precise test respectively: $p = 0.0011$ and $p = 0.0003$).

Discussion

Pursuant to numerous publications, during short- and long-term olanzapine therapy some significant body weight gains are observed ($\geq 7\%$) [37-42], which concern 15 to 50% of patients [32, 42-44]. In our study a significant body weight gain (perceived as an increase by $\geq 7\%$) was found in 9 of 39 patients included in the study, which constitutes approximately. 23.1%. On the other hand, the body weight gain which in this study was considered as significant and was subjected to analysis (i.e. $\geq 5\%$) was shown by 14 patients, which constitutes approximately 35.9%. Patients with such gains were characterised by lower BMI values at $t = 0$ as compared to those patients in whom no significant body weight gains were observed. Similar observations are presented by Kinon *et al.*, who in the examined group of 1191 patients with diagnosed schizophrenia or schizoaffective disorder found a significant correlation between lower initial BMI values and higher and faster body weight gains [42]. Other authors also agree that the highest body weight gains occur in underweight patients and occur as early as after 2-8 weeks of therapy [37-41, 45].

The growing adipose tissue has a tendency to central accumulation. Abdominal obesity was diagnosed in this study in 19 patients (according to IDF) and in 20 patients (according to WHR). Such a tendency is consistent with the study carried out by Graham *et al.*, who in the examined (small) group of 9 patients with the first episode of psychosis, who had never been treated antipsychotically, found in the 12th week of olanzapine treatment a significant increase in the content of "central" adipose tissue [35]. These observations have also been confirmed by the tests carried out on dogs by Ader *et al.* [36].

Higher body weight gains have been observed in women. Pursuant to BMI criteria, obesity was

diagnosed at $t = 0$ in 1 female patient and in no male patients, whereas at $t = 1$ in 4 patients (including 3 women). Higher body weight gains in women were described in 2003 by Koga [46].

Furthermore, it was found that during 8-week olanzapine treatment women significantly more frequently than men met the criteria of abdominal obesity, according to both IDF ($p < 0.01$) and WHR ($p < 0.001$). Abdominal obesity at $t = 1$ was diagnosed in 16 women (fraction 0.84) and 3 men (according to IDF) and in 17 women (fraction 0.85) and 3 men (according to WHR). An explanation of this phenomenon may be sought in the hormonal differences between females and males. Usually young women (before menopause), both slim and obese, have a lower content of visceral adipose tissue as compared to men [11]. When oestradiol concentration is decreased in the organism, as is the case with women entering the menopause, the visceral adipose tissue accumulation is increased. Such a correlation has been indicated by Clegg *et al.* during testing of rats. Regular microinjections of specific doses of oestradiol into the brains of female rats subjected to ovariectomy induced a decrease in appetite, body weight, and LEP concentrations in blood serum, and an increase in brain's sensitivity to LEP as well as a change of the nature of the "pattern" of adipose tissue accumulation into a more "female" one [47]. Possibly, it is in this particular mechanism that olanzapine induces abdominal obesity more often in women than in men. Canuso *et al.* while examining 16 women during the pre-menopausal period, treated with typical antipsychotics (5 patients), risperidone (3 patients), olanzapine (7 patients) and clozapine (1 patient), found in the 9th week of the study – independently of PRL concentrations and applied treatment – reduced top concentration of oestradiol below the standard for the pre-ovulation phase of the menstrual cycle [48]. However, to answer reliably the question about the correlation between olanzapine treatment and decreased concentrations of oestrogens and consequently increased content of visceral adipose tissue, appropriate research should be planned and carried out.

During this study the initial body weight was reduced in 2 patients (1 woman and 1 man). These subjects had almost identical initial BMI, 27.6 and 27.5, and a very similar body weight loss, i.e. 2.9 and 2 kg. Sporadically, casuistic descriptions of body weight decrease during olanzapine treatment may be encountered, e.g. Cohen described a case of a patient who during 8-months olanzapine treatment exhibited a decreased BMI from 25 to 19.5 [49], which could also be caused by factors other than pharmacotherapy.

The limitations of the study were: the small sample size ($N = 39$), and not taking into consideration age at onset of schizophrenia or application of para-medicaments during the study.

In conclusion, over 1/3 of examined patients exhibited a significant body weight gain during olanzapine treatment. Patients with normal weight or underweight before olanzapine treatment increased their body weights significantly more as compared to the patients with overweight or obesity found at $t = 0$. Abdominal obesity was diagnosed in the examined group at $t = 1$ more frequently in women than in men according to WHR, and according to IDF.

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