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Effects of a nutritional intervention in obese postmenopausal women on atypical antipsychotics

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ABSTRACT

Objectives: To investigate the effects of a nutritional intervention on the body weight, body composition, blood glucose and lipid levels of obese postmenopausal women taking atypical antipsychotics in Greece.
Study design: In a case–control design, 25 obese postmenopausal women treated with antipsychotic medications and 28 obese healthy comparisons were followed for 3 months. A nutritional program was individually designed for each participant.
Main outcome measures: At baseline and at 3 months of the study, anthropometric, body composition, blood glucose and lipid measurements were performed.
Results: Significant reductions in body weight, body mass index (BMI), fat and waist circumference were found both in the patients and their healthy comparisons from baseline to 3 months ($P < 0.05$). Patients reduced significantly less their BMI ($P = 0.044$) and body fat percentage compared to the healthy women ($P = 0.023$). Waist circumference was significantly reduced in both subject groups, with no significant difference found between them ($P = 0.07$). Glucose and lipid levels were not altered during the intervention in the patients' group, while significant changes were observed in the healthy women in total cholesterol ($P = 0.016$), low density lipoprotein cholesterol ($P = 0.022$) and triglycerides ($P = 0.042$).
Conclusions: Obese postmenopausal women on atypical antipsychotic medication appear to respond favorably to a nutritional program. The improvements seen in BMI and body fat are attenuated in the patients compared to their healthy counterparts; moreover no change in lipid levels was found in the patients' group. These findings suggest that atypical antipsychotics may play an adverse role in fat loss and lipid metabolism in this population.

1. Introduction

The prevalence of severe mental illnesses such as schizophrenia is high and it is globally rising [1]. Despite the central role of atypical antipsychotics in the medical treatment of schizophrenia, these medications have also been shown to induce several severe side effects, the most important being their association with weight gain and obesity [2]. Furthermore, these medications have been shown to be related to metabolic disturbances such as glucose intolerance, insulin resistance, and dyslipidemia and thus increasing the risk for type 2 diabetes and cardiovascular disease [3].

The hormonal changes that take place since the initiation of the menopausal years expose women with schizophrenia to a greater risk of recurrence or instability [4,5]. Therefore, a large percentage of postmenopausal women may experience worsening of symptoms in cases where schizophrenia preexists or appearance of the disease not previously diagnosed [5,6,7]. Thus, the majority of these women will be treated with atypical antipsychotics. On the other hand, postmenopausal women are a high-risk population for obesity, cardiovascular and metabolic disorders [8]. The combination of these medications with menopause may increase this risk. The exact effect of atypical antipsychotics on body weight and cardiovascular and metabolic health of postmenopausal women is not known.

Diet and exercise are essential parts of the obesity treatment associated with schizophrenia and can induce significant weight loss and improvements in the metabolic and cardiovascular disease risk related to the antipsychotic medication treatment [9,10]. Furthermore, the reduction in body weight and body fat can lead to an improved quality of life, resulting to an improvement to the physical but also the psychological and mental state of the patients [11]. In healthy postmenopausal women, diet and exercise are the

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two cornerstones in the obesity treatment. A number of studies have shown that caloric restriction and average physical activity in healthy postmenopausal overweight or obese women improves their body composition and lipid profile [12,13]. However, no studies have investigated the effects of caloric restriction on the body composition and glucose and lipid levels of postmenopausal women with schizophrenia treated with atypical antipsychotic medication.

The present study aimed to investigate the effects of a nutritional intervention on the body weight, body composition, blood glucose and lipid levels of schizophrenic obese postmenopausal women taking atypical antipsychotic medication and to compare it with the improvements observed in obese healthy postmenopausal women. We hypothesized that the nutritional intervention will produce significant improvements in the body weight and body composition of both groups of postmenopausal women, but that the women taking antipsychotic medication will experience smaller changes in body weight, body fat and biochemical values due to the effect of the antipsychotic medications.

2. Methods

2.1. Subjects

Thirty-five obese postmenopausal women treated with atypical antipsychotic medications were recruited for the study (1/2009–6/2009). Subjects were recommended to participate in the study from the clinical psychologists in the Iaso Hospital in Athens, Greece and from private psychiatry offices located in Athens. Prior to participation in the study, all women were diagnosed with schizophrenia according to the Diagnostic and Statistical Manual of Mental Disorders IV (DSM-IV) by a certified psychiatrist [14]. Other inclusion criteria were BMI $\geq$ 30 kg/m^2, postmenopausal status (at least 4 years since the last menstrual cycle, without using hormonal replacement therapy), absence of any type of chronic disease (diabetes, cardiovascular disease, etc.), absence of smoking and alcohol use, and stable antipsychotic medication type and dosage during the last year. Ten patients dropped out from the study (drop out rate 28.5%) and 25 patients completed the intervention. Twelve patients were treated with olanzapine, 9 patients were treated with clozapine and 4 were treated with combination therapy consisted of both atypical antipsychotics. Twenty-eight healthy obese postmenopausal women were used as a control group. They were addressed by their physicians to the dietetic department of Iaso Hospital in Athens, Greece, for weight loss and dietary counseling. Inclusion criteria were BMI $\geq$ 30 kg/m^2, postmenopausal status (at least 4 years since the last menstrual cycle, without using hormonal replacement therapy), absence of any type of chronic disease (diabetes, cardiovascular disease, etc.), absence of smoking and alcohol use, and absence of any severe mental illness or use of antipsychotic medications. Prior to participation in the study, all healthy participants underwent an interview with a certified clinical psychologist in order to certify that they had not experience any mental health problems during the last year. Institutional review board approval for the study was obtained by the ethical committee of the Iaso Hospital. Prior to enrolment in the study, all subjects signed an informed consent form for participation in the study.

2.2. Experimental design and measurements

All women participated in an intensive 3-month dietary intervention program taking place at the Iaso Hospital, Athens, Greece. Prior to the beginning of the intervention as well as at the end of the intervention at 3 months, anthropometric measurements of body weight, height, and waist circumferences were performed. Body height was measured without shoes on a wall-mounted stadiometer (SEGA, England). Waist circumference was measured at the narrowest part of the subjects' waist using a non-stretch tape. In addition, measurement of body weight and body composition (body fat and fat free mass) was performed using the BodPod (Life Measurement Inc, CA, USA) following the manufacturers' instructions.

A subgroup of subjects (patients $n = 11$, control $n = 10$) had venous blood drawn (0.005 m^3) between 7:00 am and 8:00 am after overnight fasting. The samples were immediately analyzed for glucose, total cholesterol, HDL-cholesterol, LDL-cholesterol, and triglycerides in the central laboratory of the hospital using clinical routine methods. The rest of the subjects did not accept to have blood drawn from them due to psychological reasons. However, there were no statistically significant differences between basic characteristics (body weight, BMI, waist circumference, fat mass, percentage of body fat, fat free mass and percentage of fat free mass) of the participants which accepted or denied a blood drawn before the intervention (data not shown).

During the 3-month period, subjects were asked to visit the hospital every 15 days. During these visits, measurements of body weight, waist circumferences, body fat and fat free mass were performed by the same trained dietician. Individual counseling was also performed with the scope of improving the participants' eating behavior (lifestyle modifications) and increasing compliance to the nutritional intervention and exercise plan.

2.3. Nutritional intervention

The intervention period lasted 3 months and it was implemented in two phases: (a) an evaluation phase and (b) an intensive 3-month dietary intervention period with sessions taking place every 15 days. During the evaluation phase (before the intervention) all subjects participated in a complete screening session in order to gather data and to assess the subject's health profile, lifestyle and eating habits, physical activity, food preferences, food likes and dislikes. Based on the screening session, an individualized food plan was designed and was prescribed by a registered dietician. The individualized food plan was a reduced-energy diet that followed the Mediterranean diet. In particular, the prescribed food plan was based on the consumption of large amounts of fruits, vegetables, cereals, fish (particularly fish with a high content of ω-3 fatty acids), nuts and seeds with a high content of a-linolenic acid. The intake of meat, cured meat, sausage, etc., was replaced by poultry, fish or vegetarian dishes. Olive oil was the main source of dietary fat. The prescribed diet was characterized by a moderate consumption of carbohydrates (55% of total energy per day) and high-fiber content, approximately 15% protein, while the intake of fat was ~28–30% of total energy per day, designed to promote weight loss at a rate of 0.5–1 kg/week. The estimation of energy requirements were based on the Harris–Benedict equation multiplied by an activity factor of 1.3–1.5 according to the activity level of the patient [15]. The compliance to the dietary plan was assessed by weekly food diaries that were filled out by the participants and collected at each session by the dieticians. Apart from the dietary plan, the intervention program included dietary counseling and behavioral interventions with the scope of assisting the patient's adherence to a healthy life plan during the intervention period. Sessions consisted of one-to-one counseling, primarily on nutrition issues and teaching of basic nutritional principles. The topics of these sessions included healthy eating menus and recipes, weight management techniques, cooking techniques and grocery shopping.

2.4. Statistical analysis

An independent *t*-test was used to compare the demographic characteristics of the two subject groups at baseline (healthy vs

Table 2
Subjects' anthropometric and body composition characteristics pre- and post-intervention (means ± standard error).

Variable	Patients group		Control group	
	Pre	Post	Pre	Post
Body weight (kg)	86.40 ± 3.28	83.26 ± 3.08[a]	83.92 ± 16.57	79.69 ± 16.49[a]
Body mass index (kg/m^2)	35.00 ± 1.22	33.73 ± 1.13[a]	33.25 ± 7.39	31.51 ± 7.38[a,b]
Waist circumference (m)	1.05 ± 0.03	1.02 ± 0.02[a]	1.01 ± 0.14	0.96 ± 0.14[a]
Fat mass (kg)	43.11 ± 2.37	40.23 ± 2.28[a]	41.56 ± 13.73	37.51 ± 14.33[a,b]
Body fat (%)	49.01 ± 1.22	47.44 ± 1.29[a]	48.57 ± 7.28	45.55 ± 9.40[a,b]
Fat free mass (kg)	43.28 ± 1.07	43.03 ± 1.06	42.36 ± 5.66	42.18 ± 5.53
Fat free mass (%)	50.98 ± 1.22	52.55 ± 1.29[a]	51.42 ± 7.28	54.44 ± 9.40[a]

[a] $P < 0.05$ from pre to post.
[b] $P < 0.05$ in the relative (%) change from pre to post between groups.

Table 1
Baseline demographic and anthropometric characteristics of patients and control groups (means ± standard error).

Variable	Patients group	Control group	*P*-Value
Age (years)	58.28 ± 1.05	59.10 ± 1.87	0.711
Height (m)	1.57 ± 0.01	1.59 ± 0.01	0.250
Weight (kg)	86.40 ± 3.28	83.92 ± 3.05	0.582
Body mass index (kg/m^2)	35.00 ± 1.22	33.25 ± 1.45	0.362
Waist circumference (m)	1.05 ± 0.03	1.01 ± 0.02	0.308
Body fat (%)	49.01 ± 1.22	48.57 ± 1.37	0.811

patients). A repeated measures analysis of variance (RMANOVA) was used to assess differences from pre to post in the two subject groups. An independent *t*-test was used to compare the mean absolute and percent changes in body weight, fat mass, fat free mass and waist circumference between the two groups from pre- to post-intervention, in order to control for differences in the aforementioned parameters between groups at baseline. The threshold for significance in all tests was set at $P = 0.05$. Statistical analysis was performed with SPSS for Windows, version 16 (SPSS Inc, IL, USA). All values are presented as mean ± standard error.

3. Results

The baseline characteristics of both patient and control groups are presented in Table 1. At baseline no statistically significant differences were observed between the two groups in any of the assessed variables. Subjects in both groups were obese (BMI = 35.00 ± 1.22 kg/m^2 and BMI = 33.25 ± 1.45 kg/m^2 for patients and control group, respectively, $P > 0.05$) and had a high body fat percentage (49.01 ± 1.22% and 48.57 ± 1.37% for patients and control group, respectively, $P > 0.05$). Mean waist circumference was also above normal and classified at the level of abdominal obesity (1.05 ± 0.03 m and 1.01 ± 0.02 m for patients and control group, respectively, $P > 0.05$). Blood glucose levels were within the normal range in both groups with no statistically significant difference between the two groups ($P > 0.05$). Total cholesterol (TC), LDL-cholesterol, and triglyceride levels were higher than normal in both groups with no significant difference between the two groups ($P > 0.05$). No significant differences were found in any of the dependent variables at baseline between the subgroup of subjects (patients $n = 11$, control $n = 10$) that had their venous blood drawn and the subject group that did not accept to give blood for the study. Mean dose for olanzapine in patient group was 10.31 ± 5.90 mg/day and for clozapine mean dose was 200 ± 73.85 mg/day. For both medication doses were within normal therapeutic range. Also, duration of treatment was 86.57 ± 87.83 months. None of the participants was using hormonal replacement therapy.

The nutritional intervention resulted in significant changes in the anthropometric and body composition parameters in both groups (Table 2). In particular, the nutritional intervention produced significant reductions in body weight, BMI, fat mass, body fat percentage, and waist circumference in both groups from pre- to post-intervention period ($P < 0.05$). Also, fat free mass percentage was significantly increased in both groups after the intervention ($P < 0.05$).

When we compared the relative (%) changes observed during the intervention from pre to post, we found significant differences in the body composition changes between the two groups. More specifically, the percent reduction in BMI was found to be significant less in the patients compared to the healthy women (patients change: −3.62 ± 0.77%; healthy change: −5.23 ± 0.78%, $P < 0.05$). Furthermore, the percent reduction in fat mass was also significantly lower in the patients compared to the healthy women (patients change: −6.68 ± 0.51%; healthy change: −9.74 ± 0.59%, $P < 0.05$). Finally, a statistically significant difference in the relative reduction in body fat percentage was also found to be significantly different between the two groups, with the healthy women exhibiting greater changes in body fat percentage compared to the patients (patients change: −3.20 ± 1.04%; healthy change: −6.21 ± 1.41%, $P < 0.05$). No significant differences were found in the relative or absolute change of the dependent variables between the subgroup of subjects (patients $n = 11$, control $n = 10$) that had their venous blood drawn and the subject group that did not accept to give blood for the study.

The dietary intervention resulted in significant improvements in TC, LDL-cholesterol and triglycerides levels but only in the control group ($P < 0.05$) (Table 3). Since the lipids levels at baseline were higher in the control group (although not statistically significant) compared to the patients' group, we tested

Table 3
Subjects' blood glucose and lipid levels pre- and post-intervention (means ± standard error).

	Normal range	Patients group ($n = 11$)		Control group ($n = 10$)	
		Pre	Post	Pre	Post
Glucose (mmol/L)	3.5–6.5	6.30 ± 0.53	5.61 ± 0.38	5.20 ± 0.67	5.43 ± 0.48
Total cholesterol (mmol/L)	<5.18	6.29 ± 0.52	5.82 ± 0.42	7.49 ± 0.58	5.40 ± 0.46[a,b]
LDL-cholesterol (mmol/L)	<3.4	3.90 ± 0.56	3.49 ± 0.36	5.16 ± 0.56	3.22 ± 0.36[a,b]
HDL-cholesterol (mmol/L)	1.03–2.19	1.46 ± 0.12	1.45 ± 0.25	1.17 ± 0.13	1.51 ± 0.27
Triglycerides (mmol/L)	<1.7	1.83 ± 0.28	1.73 ± 0.24	2.24 ± 0.33	1.65 ± 0.29[a]

[a] $P < 0.05$ from pre to post.
[b] $P < 0.05$ in the absolute change in the biochemical level between groups.

the absolute and relative changes in all lipid levels in order to control for this factor. The absolute reduction of cholesterol concentration (patients change: -0.47 ± 0.33 mmol/L; healthy change: -2.08 ± 0.66 mmol/L, $P < 0.05$) and LDL-cholesterol concentration (patients change: -0.41 ± 0.17 mmol/L; healthy change: -1.93 ± 0.63 mmol/L, $P < 0.05$) was significantly greater in the healthy women compared to the patients' group.

4. Discussion

Menopause is associated with significant increments in body weight and an unfavorable alteration in body composition leading to an increased risk for obesity, metabolic and cardiovascular diseases [16]. Therefore, strategies for reducing body weight, metabolic and cardiovascular risk in postmenopausal women are of utmost importance. Additionally, a large number of postmenopausal women are using atypical antipsychotic medications treatment, a parameter that can independently lead to obesity and its co-morbidities [10,17–19]. The way that a dietary intervention can affect the body weight, body composition and lipid levels of postmenopausal women taking atypical antipsychotic medications is not known. This is the first study, to our knowledge, that has investigated the effects of a nutritional intervention on the aforementioned parameters in this high-risk population and has compared it to obese healthy postmenopausal women. Our study demonstrated that a dietary intervention can effectively improve the body weight, BMI, body composition and waist circumference of obese postmenopausal women taking atypical antipsychotic medication; however, we found smaller improvements in the BMI and body fat as well as no change in the blood lipid levels in our patients compared to our healthy women.

The present study demonstrates for the first time the effectiveness of a 3-month nutritional intervention on changes in body weight, BMI and also in body fat in obese postmenopausal women taking atypical antipsychotic medications. Our results are in agreement with previous weight loss studies in male and female patients on antipsychotic medications [10,12,20,21]. However, the present study cannot be directly compared with these studies since their populations consist of both male and female patients (not necessarily postmenopausal); hence there is a need for more research in this specific population. In regards to our group of healthy postmenopausal women, we found significant improvements in body weight, body fat and waist circumference, similar to those reported in previous studies in obese postmenopausal women [12,22].

A novel finding of this study is the attenuated response to the dietary intervention in terms of BMI and body fat reduction in the patients compared to their healthy controls. More specifically, we found that the healthy women reduced significantly greater their BMI and percentage of body fat compared to the women on antipsychotic medication. Our results are in accordance to our previous study in both males and females taking atypical antipsychotic medications, where the patients were found not to respond as effectively to a weight loss program and lost significantly less body fat compared to their healthy counterparts [23]. In vitro studies in animals have shown a direct cellular effect of atypical antipsychotic medications on adipocytes, demonstrated by increases in the rate of lipogenesis and a reduction in the rate of lipolysis [24]. Furthermore, recent studies in humans taking atypical antipsychotic medications indicate that leptin and nitric oxide might be associated with the medication-induced weight gain and resistance to weight loss [25]. Hence, a possible explanation for the attenuated fat loss in our women could be the cellular effect of atypical antipsychotic medications on lipogenesis and lipolysis. However, as there is a significant lack of human studies on the effects of atypical antipsychotic on lipolysis, no conclusive statements can be made at this point. More research is needed to investigate the effects of these medications on weight loss and possible alterations in the physiology of adipocytes.

Waist circumference was found to be significantly reduced in both groups of postmenopausal women as a result of the 3-month intervention. However, in terms of clinical importance, the patients exhibited almost half of the reduction in waist circumference compared to our healthy women, a finding that almost reached statistical significance ($P = 0.07$). Waist circumference is an index of abdominal visceral fat deposition and hence an important risk factor and contributor to the development of dyslipidemia, cardiovascular and other metabolic disorders [26]. Hence, this clinically important difference in the change in waist circumference between the two groups could imply that the antipsychotic medications may play an adverse role not only in the overall fat lipogenesis and lipolysis, but more importantly could potentially affect abdominal fat deposition and lipolysis. However, as no research has been reported to our knowledge in this area, only hypotheses can be stated at this point.

An important finding of the present study is the lack of change in lipid levels in the group of postmenopausal women taking atypical antipsychotics compared to the significant change in total cholesterol and LDL-cholesterol found in their healthy counterparts. The lack of change in lipid levels could be attributed to the smaller reduction in body fat observed in our women on antipsychotic medications compared to the healthy women. Even more importantly, the clinically important attenuated change in waist circumference, could possibly play a key role to the lack of change in lipid levels in our patients, as waist circumference is a known index of abdominal obesity and is associated to dyslipidemia. Finally, the atypical antipsychotic medications could possibly have an independent adverse effect on the blood lipid levels in spite of fat loss. Studies in patients taking atypical antipsychotic medication support this finding as it has been shown that they can induce dyslipidemia and other metabolic disorders [18,19]. Certainly, more clinical research studies are needed to investigate the effects of dietary interventions on the blood lipid levels of this population.

One of the limitations of the study is the small study sample and the short period of nutritional intervention (3 months). However, due to the special characteristics of the study population (postmenopausal women with mental illness) the recruitment of a large number of patients and the extension of the nutritional intervention are extremely difficult. Also, our patients were treated with two different antipsychotics (olanzapine and clozapine). Nevertheless, these two medications belong in the same category of atypical antipsychotics and they have been associated with similar metabolic side effects and weight gain, hence they should not have affected the results of the study [27]. Finally, as only a subgroup of the patients accepted to give blood for the study, while almost 50% of the patients did not accept due to psychological reasons (anxiety and fear of giving blood), there is the possibility that the patients that refused to give blood might have responded differently to the intervention. We tested for this possibility and we found no differences in the baseline characteristics as well as in the changes from pre to post in all outcomes measures between the two patient subgroups, hence excluding the possibility of different finding in this subgroup of patients.

In conclusion, our study demonstrates for the first time that obese postmenopausal women on atypical antipsychotic medication can respond favorably to a nutritional program by significantly improving their body weight, BMI, body fat and waist circumference. However, the improvements observed in BMI and body fat in this clinical population were attenuated compared to obese healthy postmenopausal women, suggesting that the medications may play an adverse role in fat loss in this population. Furthermore, the attenuated reduction in body fat particularly in the waist area in

the women on antipsychotics could have attributed to the lack of change in lipid levels in this population. Future clinical studies are needed to further investigate this finding before we establish such a phenomenon.

Contributors

Maria Skouroliakou participated in the conception and design of the study, the analysis and interpretation of data, the revision of the manuscript and saw and approved the final version. Ifigenia Giannopoulou participated in the design of the study, the analysis and interpretation of data, the drafting of the manuscript and saw and approved the final version. Christina Kostara participated in the collection, analysis and interpretation of data, the revision of the manuscript and saw and approved the final version. Katerina Koutri participated in the collection of data, the revision of the manuscript and saw and approved the final version. Maria G. Stathopoulou participated in the design of the study, the analysis and interpretation of data, the drafting of the manuscript and saw and approved the final version. Christina Kakavelaki participated in the collection of data, the revision of the manuscript and saw and approved the final version.

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Ethical approval

Institutional review board approval for the study was obtained by the ethical committee of the Iaso Hospital. Prior to enrolment in the study, all subjects signed an informed consent form for participation in the study .

Conflict of interest statement

Authors declare that there are no conflicts of interest.

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