Original Article The Eurasian Journal of Medicine EAJM 2011; 43: 39-44

The Effects of Atypical Antipsychotic Usage Duration on Serum Adiponectin Levels and Other Metabolic Parameters

Atipik Antipsikotik Kullanım Süresinin Serum Adiponektin Düzeyleri ve Diğer Metabolik Parametreler Üzerine Etkisi

Elif Oral[1], Mustafa Gulec[1], Nezahat Kurt[2], Sumeyra Yilmaz[1], Nazan Aydin[1], Ismet Kirpinar[1]

[1]Department of Psychiatry, Medical Faculty, Atatürk University, Erzurum, Turkey
[2]Department of Biochemistry, Medical Faculty, Atatürk University, Erzurum, Turkey

Abstract

Objective: Although atypical antipsychotics are well-tolerated and effective treatment options for schizophrenia, they have metabolic side effects, including weight gain and increased risk of Type II Diabetes Mellitus (DM). Adiponectin, produced exclusively in adipocytes, is the most abundant serum adipokine. Low levels of adiponectin are correlated with DM, insulin resistance and coronary heart disease. Usage of atypical antipsychotics may create a risk of metabolic syndrome. The aim of this study was to evaluate the effects of antipsychotic usage on parameters related to development of metabolic syndrome.

Materials and Methods: A total of 27 patients (n=27) (13 women and 14 men) were recruited from our out-patient psychiatry clinic. All patients had been treated with atypical antipsychotics for at least 3 months and were in remission. Patients were evaluated for levels of HDL (High Density Lipoprotein), LDL (Low Density Lipoprotein), TG (Triglyceride) total cholesterol and fasting blood glucose, body weight, BMI (Body Mass Index), waist circumference and serum adiponectin levels.

Results: Serum adiponectin levels were significantly lower (p:0.000) and body weights were significantly higher (p:0.003) in the patients who had been using atypical antipsychotics for longer than a year in comparison to patients who had been using atypical antipsychotics for one year or less.

Conclusion: Our findings supported the hypothesis that the length of administration of atypical antipsychotics has an effect on metabolic changes. They also highlight the fact that when investigating metabolic changes generated by atypical antipsychotic effects, the length of time that the patient has been on the atypical antipsychotics should also be considered.

Key Words: Atypical antipsychotics, Metabolic syndrome, Serum adiponectin levels, Usage duration

Özet

Amaç: Atipik antipsikotikler şizofreni tedavisi için iyi tolere edilebilen ve etkili tedavi seçenekleri olmakla birlikte bu ajanların kilo alımı ve TipII Diabetes Mellitus'a (DM) yatkınlık gibi metabolik yan etkileri olduğu da bilinmektedir. Adiponektin, sadece adipositler tarafından üretilen ve kanda en fazla miktarda bulunan serum adipokinidir. Düşük Adiponektin düzeyleri DM, insülin direnci ve koroner arter hastalıklarıyla ilişkilidir. Atipik antipsikotik kullanımı metabolik sendroma yatkınlık yaratabilmektedir. Bu çalışmada atipik antipsikotik kullanım süresinin metabolik sendroma yatkınlıkla ilişkili parametreler üzerine olan etkisini incelenmeyi amaçladık.

Gereç ve Yöntem: En az 3 aydır atipik antipsikotik tedavisi görmekte ve halen remisyonda olan toplam 27 (13 kadın ve 14 erkek) hastanın HDL, LDL, TG, total kolesterol ve açlık kan şekeri düzeyleri, kiloları, bel çevresi ölçümleri, VKİ (Vücut Kitle İndeksi) ve serum adiponektin düzeyleri değerlendirildi.

Bulgular: Bir yıl ya da daha kısa süredir antipsikotik kullananlara oranla, 1 yıldan daha uzun süredir antipsikotik kullanmakta olan hastaların adiponektin düzeyleri anlamlı olarak daha düşük bulundu (p:0.000) ve kiloları da anlamlı olarak daha fazlaydı (p:0.003).

Sonuç: Bulgularımız, atipik antipsikotik kullanımının neden olduğu metabolik değişikliklerin kullanım süresiyle ilişkili olduğunu desteklemektedir. Atipik antipsikotik kullanımında ortaya çıkan metabolik değişiklikler araştırılırken kullanım süresinin de önemli bir faktör olarak göz önüne alınması gerektiği düşünülmektedir.

Anahtar Kelimeler: Atipik antipsikotik, Kullanım süresi, Metabolik sendrom, Serum adiponektin düzeyleri

Received: December 01, 2010 / **Accepted:** December 14, 2010

Correspondence to: Elif Oral, Department of Psychiatry, Faculty of Medicine, Atatürk University, 25240 Erzurum, Turkey
Phone: +90 442 231 69 54 e-mail: oralelif@yahoo.com

doi:10.5152/eajm.2011.08

Introduction

Although the emergence of atypical antipsychotics has presented us with a group of well-tolerated and effective agents as treatment alternatives for schizophrenia, the metabolic side effects of these agents, such as weight gain and a tendency toward Type II DM (Diabetes Mellitus), cannot be denied [1-4]. Weight gain due to the use of the new generation of antipsychotics causes a general increase in adipose tissue, which in turn may cause insulin resistance, glucose intolerance and diabetes [5]. The use of atypical antipsychotics is often associated with weight gain, insulin resistance and metabolic syndrome. Metabolic syndrome is a disorder characterized by disrupted glucose metabolism and/or disrupted insulin metabolism (glucose intolerance, Type II DM, insulin resistance or hyperinsulinemia) and obesity (increased adipose tissue, especially in the abdominal area), and it affects many systems [6, 7]. Low levels of serum adiponectin are also associated with insulin resistance and Type II DM. Although the physiological role of adiponectin has not been determined fully, it is thought to have anti-atherogenic and anti-inflammatory properties [8]. Adiponectin is a plasma protein produced by mature adipocytes, and it has anti-inflammatory effects and increases insulin sensitivity. Its level in circulation decreases with increasing body mass index [9-12]. The effects of atypical antipsychotics, as well as other symptoms of metabolic syndrome, on serum adiponectin levels are increasingly becoming the subject of research. Previous studies investigating the relationship between serum adiponectin levels and the usage of atypical antipsychotics have focused more on short-term effects [9, 13-17]. In this study, our purpose was to investigate the effects of atypical antipsychotic usage on serum adiponectin levels and metabolic parameters based on their association with long- and short-term atypical antipsychotic usage.

Materials and Methods

Patient selection and evaluation: Approval for the investigation was obtained from the Medical Ethics Committee of the Atatürk University Department of Medicine.

A total of 27 patients were informed of the study outline and objectives, and after their informed consent was obtained, they were included in this study. These patients were 18 -60 years old and were consecutive outpatients with schizophrenia and schizoaffective disorders who were being tracked by Atatürk University Medical Faculty Psychiatry Department Outpatient Clinic. All patients were in remission, had stable drug usage, and were receiving atypical antipsychotic monotherapy for at least 3 months (with usage durations between 3 months and 10 years). Only patients being treated for diagnoses of schizophrenia or schizoaffective disorder according to DSM-IV criteria were accepted for the study. The diagnoses of the patients were confirmed by SCID-I. Exclusion criteria in the selection of patients were tobacco use, alcohol use, drug addiction, eating disorder diagnosis, long-term use of non-psychotropic drugs, mental retardation, neurological disorders and history of head injury. Some of our patients, in addition to atypical antipsychotics, were using anticholinergics (1-3 mg Biperiden) and/or benzodiazepine (1-4 mg Lorazepam) when necessary. The dosage ranges of the atypical antipsychotics were Olanzapine (5-20 mg), Risperidone (2-6 mg), Quetiapine (600-1200 mg), Amisulpride (400-800 mg), Clozapine (600 mg/g), Aripiprazole (30 mg/g), Sulpiride (200- 800 mg), and Paliperidone (9 mg/g). The demographic characteristics of the patients along with their weight, waist measurement and body mass index were recorded on a patient information form.

Biochemical analysis

The serum HDL (High Density Lipoprotein), LDL (Low Density Lipoprotein), total cholesterol, TG (Triglyceride) and fasting blood glucose levels of the patients were recorded. Serum adiponectin levels were measured by enzyme-linked immunosorbent assay (ELISA) using a ready commercial kit (RayBio® Human adiponektin /Acrp30 ELISA kit) (Cat#: ELH-ADIPNECTIN-001). The detection limit was 10 pg/ml (intra-assay CV<10%, interassay CV<12%). The kit used showed no cross-reaction with any cytokines, for example, human Angiogenin, BDNF, BLC, ENA-78, FGF-4, IL-1α, IL-1β, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-11, IL-12 p70, IL-12 p40, IL-13, IL-15, IL-309, IP-10, G-CSF, GM-CSF, IFN-γ, Leptin (OB), MCP-1, MCP-2, MCP-3, MDC, MIP-1α, MIP-1 β, MIP-1δ, PARC, PDGF, RANTES, SCF, TARC, TGF-β, TIMP-1, TIMP-2, TNF-α, TNF-β, TPO and VEGF.

Statistical evaluation

The SPSS 11.0 program was used for statistical analysis. The correlations between serum adiponectin levels and usage duration of atypical antipsychotics, gender, weight, body mass index, waist measurement and TG, HDL, LDL, total cholesterol and fasting blood sugar levels were evaluated using correlation analysis. The Mann-Whitney U test was used to make a comparison of weight, body mass index, serum adiponectin levels, HDL levels and fasting blood sugar levels and atypical antipsychotic usage among our patients, who were separated into two groups: Schizophrenia patients and Schizoaffective Disorder patients. The Mann-Whitney U test was used to compare serum adiponectin, fasting blood sugar and HDL levels and waist measurements between genders. The Mann-Whitney U test was used once more to compare the HDL, LDL, TG, fasting blood sugar, total cholesterol, and serum adiponectin levels and weight and waist measurements of patients who had been using atypical antipsychot-

ics less than one year to those of patients using atypical antipsychotics longer than one year.

Findings

A total of 27 patients (13 women and 14 men) were included in this study. The average age of our patients was 35.0±9.4 sd years. All of our patients had been receiving atypical antipsychotic treatment for at least 3 months; 17 patients (63.0%) had been using atypical antipsychotics for less than one year, and 10 patients (37.0%) had been using the treatment for over one year. Of the 27 patients, 55.6% (n=15) had been diagnosed with schizophrenia and 44.4% (n=12) with schizoaffective disorder. No significant correlation was found between the diagnoses of the patients and their serum adiponectin levels, BMI (body mass index), waist measurements, weights and biochemical parameters. The atypical antipsychotics used were Olanzapine (n=9), Quetiapine (n=6), Risperidone (n=5), Amisulpride (n=2), Sulpiride (n=2), Aripiprazole (n=1), Clozapine (n=1) and Paliperidone (n=1). The average values of various parameters of our patients are given in Table 1.

TG levels, waist measurements and patient weight were negatively correlated with serum adiponectin levels (Table 2).

The HDL levels of the patients were negatively correlated with the length of drug use (r=-0.508, p=0.008), TG levels (r=-0.598, p=0.001), weight (r=-0.437, p=0.029), and waist measurements (r=-0.495, p=0.014). LDL levels, on the other hand, showed a positive correlation with total cholesterol levels (r=0.944, p=0.000).

The average weight of the patients (72.0±8.7 kg) was positively correlated with waist measurements (r=0.577, p=0.003) and length of drug use (r=0.612, p=0.001), but it showed a negative correlation with HDL levels (r=-0.437, p=0.029). While the average weight of patients using atypical antipsychotics for less than one year was 67.8±7.08 kg, the average weight of patients who had been on atypical antipsychotics for more than one year was found to be 78.7±7.05 kg (p=0.003). The atypical antipsychotic use of the patients showed a correlation with their weights, HDL levels and serum adiponectin levels (Table 3).

In our study, there was a significant correlation between the length of atypical antipsychotic usage and adiponectin levels (Figure 1). These results show that the adiponectin levels of patients who had been using antipsychotics for more than one year were significantly lower than those who had been using antipsychotics for one year or less (p=0.000). Furthermore, there was a significant correlation between the weight of the patients and their atypical antipsychotic usage duration (p=0.003).

There were no significant gender-related differences with regards to the length of atypical antipsychotic usage; however, a number of other parameters did display a gender-related difference and are shown in Table 4.

Table 1. Average values of various parameters of our patients

Variables	average±SD
Age	35.0±9.4 year
Drug usage duration	25.6±30.3 month
BMI	26.56±2.8 kg/ml
Waist measurement	95.04±9.6 cm
Fasting blood sugar	101.5±34.5 mg/dL
HDL	44.2±13.2 mg/dL
LDL	117.4±33.7 mg/dL
Total cholesterol	185.3±40.6 mg/dL
TG	189.8±114.7 mg/dL
Adiponectin levels	1848.5±1021.8 pg/ml

SD: standard deviation

Table 2. The correlation of serum adiponectin levels and various variables

Variables	r	p
Weight	-0.270	0.182
Body mass index	0.028	0.890
Waist measurement	-0.097	0.645
Triglyceride	-0.059	0.775
HDL	0.254	0.210
LDL	0.134	0.514
Total cholesterol	0.264	0.193
Fasting blood sugar	-0.317	0.123
Gender	-0.382	0.049
Length of atypical antipsychotic use	-0.621	0.001

Table 3. Variables showing significant correlation with length of atypical antipsychotic use

Variables	r	p
Weight	.612	.001
HDL	-.508	.008
Adiponectin levels	-.621	.001

In our study, there were no significant differences between patients taking Olanzapine (n=9) and those taking other atypical antipsychotics in terms of length of drug use, average weight, waist measurement, and HDL, LDL, TG and serum adiponectin levels. Upon further evaluation of patients taking Olanzapine, a positive correlation was found between the length of drug use and waist measurements (r=0.761 and p=0.017). Although the number of patients using Olanzapine was not sufficient for a comparison based on their usage

duration, the differences in the averages within this group are shown in Table 5.

Discussion

The rate of death from cardiovascular disorders is higher in patients diagnosed with schizophrenia in comparison to the normal population [18]. Additionally, a group of clinical findings and symptoms, collectively known as "metabolic syndrome", has also been reported to create a significant risk for cardiovascular system disorders [19-22]. Low adiponectin levels show a correlation with almost all clinical components of metabolic syndrome, and this correlation is considered a significant indication of increased risk for cardiovascular disorders and is indicative of the severity of the illness [23-28]. In a literature review carried out by Gentile, when short-term studies were examined, Clozapine was found to carry the highest risk for weight gain, with the risk ratio diminishing in the order of Olanzapine, Quetiapine, Risperidone, Amisulpride, Aripiprazole and Ziprasidone. In the same analysis, when data pertaining to long-term studies (generally more than one year of drug use) were examined, Clozapine was again ranked first, and Ziprasidone was last; however, it was noted that the data on the other atypical antipsychotics did not reflect the correlation as well [16]. Hosojıma et al. observed that, although there was weight gain after 4 weeks of Olanzapine use, there was no significant increase in serum leptin, ghrelin and adiponectin levels [17]. Bai et al. found a higher rate of metabolic syndrome among Clozapine users than Olanzapine users (28.7% and 24.2%, respectively) in their study of 567 patients, whose average term of drug use was 45.8±27.8 months, and they also reported that the serum adiponectin levels of the Olanzapine using group were higher than those of the Clozapine group [29]. Murashita et al. reported that although there was weight gain by the 6th month of antipsychotic treatment, there was no significant difference in the serum adiponectin levels [13]. Perez-Iglesias et al. reported a non-significant drop in serum adiponectin levels, although they did find a significant increase in the serum insulin and leptin levels and patient weight after one year of treatment with atypical antipsychotics [30]. Studies focused on the correlation of atypical antipsychotics with weight gain and insulin resistance have shown that occasionally there is no significant difference among the atypical antipsychotics and that Olanzapine and Clozapine have more involvement with weight gain and the disruption of glucose regulation [31-34] than other drugs. Crespo-Facorro et al. determined that, although there is no difference in efficacy and tolerability, Olanzapine causes more weight gain compared to Risperidone [35], and Van Winkel et al. have drawn attention to the fact that Clozapine carried the highest risk of changing plasma glucose levels among schizophrenia and schizoaffective disorder patients using Risperidone, Aripiprazole or Clozapine [36]. Newcomer et al. found clinically significant weight loss, a marked drop in TG and total cholesterol levels and a marked increase in HDL levels in obese patients who had been using Olanzapine, after 16th week of switching to Aripipirazole [37]. In conclusion, current litera-

Table 4. Comparison of serum adiponectin levels, fasting blood sugar, HDL and waist measurements according to gender

Variables	Gender		p
	Female	Male	
Serum adiponectin levels pg/ml	2246.4±1240.0	1457.76±603.1	p=0.069
Fasting blood sugar mg/dL	88.27±22.0	112.92±39.5	p=0.026
HDL mg/dL	48.61±13.4	39.92±12.0	p=0.039
Waist measurement cm	93.46±10.3	96.75±9.0	

Table 5. Comparison of weight, waist measurement and serum adiponectin levels according to the usage duration of Olanzapine

Variables	Olanzapine usage duration	
	Less than one year (n=5)	More than one year (n=4)
Waist measurement	94.2±3.7 cm	105.0±6.6 cm
Average weight	66.4±5.4 kg	79.7±6.8 kg
Adiponectin	2301.23±494.61 pg/ml	1010.5±335 pg/ml

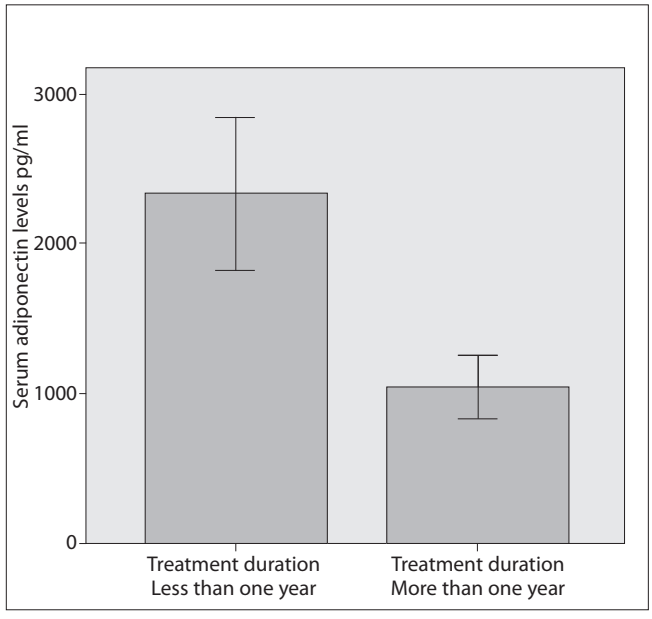

Figure 1. *Graph showing the correlation between the usage duration of atypical antipsychotics and adiponectin levels.*

ture on the use of antipsychotics and metabolic parameters calls for particular attention to Clozapine and Olanzapine and shows that the use of atypical antipsychotics affects many clinical factors that make up metabolic syndrome.

In our study, we found a significant correlation between the length of atypical antipsychotic use and adiponectin levels and patient weight. Our data are consistent with literature supporting the correlation of the length of atypical antipsychotics use with many variables positively affecting metabolic syndrome. In our study, we were unable to find a significant difference in length of drug administration and average weight, waist measurements and HDL, LDL, TG and serum adiponectin levels between the Olanzapine group and the rest of the sample. Patients using Olanzapine showed a positive correlation between length of drug use and waist measurements. The finding of lower adiponectin levels, larger waist measurements and higher weight ratios among patients who had been on Olanzapine for longer than one year are inconsistent with literature stating that the highest risk period for weight gain during Olanzapine usage is the first 6 weeks [38, 39].

Our study showed no significant differences in the duration of atypical antipsychotic usage between genders. Over half (57.7%) of our patients had HDL levels that would be considered unhealthy, and the female patients had relatively higher HDL levels; however, those higher levels could also be related to a generally higher risk among females. Furthermore, the female patients in our study had a higher risk of central obesity.

Low HDL levels have been associated with cardiovascular mortality, especially in women, and HDL levels below 50 mg/dl in women and 40 mg/dl in men are considered hazardous to health [40, 41]. Waist measurements greater than 88 cm for women and 102 cm for men are considered unhealthy. Fezeu et al. working within a large sample, determined a higher incidence of hyperglycemia, one of the components of metabolic syndrome, in men (6% in women, 12% in men) and a higher incidence of central obesity in women (81% in women, 52% in men) [42]. The prevalence of diabetes is lower in premenopausal women, which can be associated with the efficacy of 17-B estradiol in protecting insulin production [43, 44]. Nevertheless, some publications claim that estradiol levels above or below physiologic limits can speed the development of insulin resistance and Type II DM [45].

Our hypothesis focused on the possibility of changes in metabolic parameters as a result of prolonged usage of atypical antipsychotics, and the data support this hypothesis. However, our sampling was not large enough to investigate the effects of each drug separately. Again, although our study was focused solely on comparing short- and long-term drug use and each patient's process was observed separately, not having the starting values was restrictive.

Our finding that low serum adiponectin levels were associated with the duration of atypical antipsychotic use coupled with the accompanying high weight values supports the suggestion that the length of atypical antipsychotic use is positively correlated with metabolic syndrome. Our data also support the theory that lower adiponectin levels are an indication of disrupted glucose regulation and insulin resistance. This study, while investigating the parameters that could be used in the prevision and tracking of metabolic syndrome, focuses especially on the effects of the duration of atypical antipsychotic usage, and it draws attention to adiponectin, the subject of a relatively limited number of studies. Further studies that consider drug usage terms in addition to other biochemical parameters that can predict metabolic syndrome are needed.

Conflict of interest statement: The authors declare that they have no conflict of interest to the publication of this article.

References

1. Farwell WR, Stump TE, Wang J, Tafesse E, L'Italien G, Tierney WM. Weight gain and new onset diabetes associated with Olanzapine and risperidone.J Gen Intern Med 2004; 19: 1200-5.
2. Allison DB, Mentore JL, Heo M Chandler LP, Cappelleri JC, Infante MC et al. Antipsychotic-induced weight gain: a comprehensive research synthesis. Am J Psychiatry 1999; 156:1686-96.
3. Liebzeit KA, Markowitz JS, Caley CF. New onset diabetes and atypical antipsychotics. Eur Neuropsychopharmacol 2001; 11: 25-32.
4. Spoelstra JA, Stolk RP, Cohen D, Klungel OH, Erkens JA, Leufkens HG et al. Antipsychotic drugs may worsen metabolic control in type 2 diabetes mellitus. J Clin Psychiatry 2004; 65: 674-78.
5. Wirshing DA, Spellberg BJ, Erhart SM, Marder SR, Wirshing WC. Novel antipsychotics and new onset diabetes. Biol Psychiatry 1998; 44: 778-83.
6. Heiskanen T, Niskanen L, Lyytikainen R, Saarinen PI, Hintikka J. Metabolic syndrome in patients with schizophrenia. J Clin Psychiatry 2003; 64: 575-9.
7. Yumru M, Savas HA, Kurt E, Kaya MC, Selek S, Savas E et al. Atypical antipsychotics related metabolic syndrome in bipolar patients. Journal of Affective Disorders 2007; 98: 247-52.
8. Pischon T, Girman CJ, Hotamisligil GS et al. Plasma adiponectin levels and risk of myocardial infarction in men. JAMA 2004; 291: 1730-7.
9. Richards AA, Hickman IJ, Wang AY, Jones AL, Newell F, Mowry BJ et al. Olanzapine treatment is associated with reduced high molecular weight adiponectin in serum. A potential mechanism for Olanzapine-induced ınsulin resistance in patients with schizophrenia. Journal of Clinical Psychopharmacology 2006; 26: 232-7.
10. Arita Y, Kihara S, Ouchi N, Takahashi M, Maeda K, Miyagawa J et al. Paradoxical decrease of an adipose specific protein, adiponectin in obesity. Biochem Biophys Res Commun 1999; 257: 79-83.
11. Ouchi N, Kihara S, Arita Y, Okamoto Y, Maeda K, Kuriyama H et al. Adiponectin, adipocyte-derived plasma protein, Inhibits endothelial NFKB signaling through cAMP-dependent pathway. Circulation 2000; 102 1296-301.
12. Yokota T, Oritani K, Takahashi I, Ishikawa J, Matsuyama A, Ouchi N et al. Adiponectin, a new member of the family of soluble defense collagens, negatively regulates the growth of myelomonocytic progenitors and the functions of macrophages. Blood 2000; 96: 1723-32.

13. Murashita M, Kusumi I, Inoue T, Takahashi Y, Hosoda H, Kangawa K et al. Olanzapine increases plasma ghrelin level in patients with schizophrenia. Psychoneuroendocrinology 2005; 30: 106-10.
14. Murashita M, Inoue T, Kusumi I, Nakagawa S, Itoh K, Tanaka T et al. Glucose and lipid metabolism of long-term risperidone monotherapy in patients with schizophrenia. Psychiatry Clin Neurosci 2007; 61: 54-8.
15. Sporn AL, Bobb AJ, Gogtay N, Stevens H, Greenstein DK, Clasen LS et al. Hormonal correlates of clozapine-induced weight gain in psychotic children: an exploratory study. J Am Acad Child Adolesc Psychiatry 2005; 44: 925-33.
16. Gentile, S. Long-term treatment with atypical antipsychotics and the risk of weight gain: a literature analysis. Drug Saf 2006; 29: 303-19.
17. Hosojima H, Togo T, Odawara T, Hasegawa K, Miura S, Kato Y et al. Early effects of Olanzapine on serum levels of ghrelin, adiponectin and leptin in patients with schizophrenia Journal of Psychopharmocol 2006; 20: 75-9.
18. Brown S, Kim M, Mitchell C, Inskip H. Br J Psychiatry.Twenty-five year mortality of a community cohort with schizophrenia 2010; 196: 116-21.
19. Ninomiya JK, L'Italien G, Criqui MH, Whyte JL, Gamst A, Chen RS. Association of the metabolic syndrome with history of myocardial infarction and stroke in the Third National Health and Nutrition Examination Survey. Circulation 2004; 109: 42-6.
20. Alexander CM, Landsman PB, Teutsch SM. NCEP-defined metabolic syndrome, diabetes, and prevalence of coronary heart disease among NHANES III participants age 50 years and older. Diabetes 2003; 52: 1210-4.
21. Ninomiya T, Kubo M, Doi Y, Yonemoto K, Tanizaki Y, Rahman M et al. Impact of metabolic syndrome on the development of cardiovascular disease in a general Japa nese population: the Hisayama study. Stroke 2007; 38: 2063-9.
22. ik S, Wong ND, Franklin SS, Kamath TV, L'Italien GJ, Pio JR et al. Impact of the metabolic syndrome on mortality from coronary heart disease, cardiovascular disease, and all causes in United States adults. Circulation 2004; 110: 1245-50.
23. Matsuda M, Shimomura I, Sata M, Arita Y, Nishida M, Maeda N, et al. Role of adiponectin in preventing vascular stenosis. The missing link of adipo-vascular axis. J Biol Chem 2002; 277: 37487-91.
24. Okamoto Y, Kihara S, Ouchi N, Nishida M, Arita Y, Kumada M, et al. Adiponectin reduces atherosclerosis in apolipoprotein E-deficient mice. Circulation 2002; 106: 2767-70.
25. Ryo M, Nakamura T, Kihara S, Kumada M, Shibazaki S, Takahashi M, et al. Adiponectin as a biomarker of the metabolic syndrome. Circ J 2004; 68: 975-81.
26. Kondo H, Shimomura I, Matsukawa Y, Kumada M, Takahashi M, Matsuda M et al. Association of adiponectin mutation with type 2 diabetes: a candidate gene for the insulin resistance syndrome. Diabetes 2002; 51: 2325-8.
27. Lindsay RS, Funahashi T, Hanson RL, Matsuzawa Y, Tanaka S, Tataranni PA et al. Adiponectin and development of type 2 diabetes in the Pima Indian population. Lancet 2002; 360: 57-8.
28. Yamashita T, Matsuda M, Nishimoto O, Nakamoto K, Nishiyama H, Matsumoto K et al. Combination of Serum Adiponectin Level and Metabolic Syndrome is Closely Associated with Coronary Artery Disease in Japanese Subjects with Good Glycemic Control Inter Med 2010; 49: 721-7.
29. Bai YM, Chen TT, Yang WS, Chi YC, Lin CC, Liou YJ et al. Association of adiponektin and metabolic syndrome among patients taking atypical antipsychotics for schizophrenia: A cohort study. Schizophrenia Research 2009; 111: 1-8.
30. Perez-Iglesias R, Vazquez-Barquero JL, Amado JA, Berja A, Garcia-Unzueta MT, Pelayo-Terán JM et al. Effect of Antipsychotics on Peptides Involved in Energy Balance in Drug-Naive Psychotic Patients After 1 Year of Treatment Journal of Clinical Psychopharmacology 2008; 28: 289.
31. Chiu CC, Chen CH, Chen BY, Yue SH, Lu ML. The time-dependent change of insulin secretion in schizophrenic patients treated with Olanzapinee. Progress in Neuro-Psychopharmacology & Biological Psychiatry 2010; 13.
32. Bergman R. N, Ader M. Atypical Antipsychotics and Glucose Homeostasis. J Clin Psychiatry 2005; 66: 504-14.
33. Gebhardt S, Haberhausen M, Heinzel-Gutenbrunner M, Gebhardt N, Remschmidt H, Krieg JC. Antipsychotic-induced body weight gain: Predictors and a systematic categorization of the long-term weight course. Journal of Psychiatric Research 2009; 43: 620-6.
34. Oriot P, Feys JL, Mertens de Wilmars S, Misson A, Ayache L, Fagnart O et al. Insulin sensitivity, adjusted beta-cell function and adiponectinaemia among lean drug-naive schizophrenic patients treated with atypical antipsychotic drugs: a nine-month prospective study. Diabetes Metab 2008; 34: 490-6.
35. Crespo-Facorro B, Pérez-Iglesias R, Ramirez-Bonilla M, Martínez-García O, Llorca J, Luis Vázquez-Barquero J. A practical clinical trial comparing haloperidol, risperidone, and Olanzapine for the acute treatment of first-episode nonaffective psychosis. J. Clin. Psychiatry 2006; 67: 1511-21.
36. van Winkel R, De Hert M, Wampers M, Van Eyck D, Hanssens L, Scheen A et al. Major changes in glucose metabolism, including new-onset diabetes, within 3 months after initiation of or switch to atypical antipsychotic medication in patients with schizophrenia and schizoaffective disorder. J Clin Psychiatry 2008; 69: 472-9.
37. Newcomer JW, Campos JA, Marcus RN, Breder C, Berman RM, Kerselaers W, et al. A multicenter, randomized, double-blind study of the effects of aripiprazole in overweight subjects with schizophrenia or schizoaffective disorder switched from Olanzapine. J Clin Psychiatry 2008; 69: 1046-56.
38. Kinon BJ, Kaiser CJ, Ahmed S, Rotelli MD, Kollack-Walker S. Association Between Early and Rapid Weight Gain and Change in Weight Over One Year of Olanzapine Therapy in Patients with Schizophrenia and Related Disorders. J Clin Psychopharmacol 2005; 25: 255-8
39. Andersen SW, Clemow DB, Corya SA. Long-term weight gain in patients treated with open-label Olanzapinee in combination with fluoxetine for major depressive disorder. J Clin Psychiatry 2005; 66: 1468-76.
40. Bass KM, Newshaffer CJ, Klag MJ, Bush TL. Plasma lipoprotein levels as predictors of cardiovascular death in women. Arch Intern Med 1993; 153: 2209-16.
41. Gordon DJ, Probstfield JL, Garrison RJ, Neaton JD, Castelli WP, Knoke JD et al. High density lipoprotein cholesterol and cardiovascular disease: Four prospective American studies. Circulation 1989; 79: 8-15.
42. Fezeu L, Balkau B, Kengne AP, Sobngwi E, Mbanya JC. Metabolic syndrome in a sub-Saharan African setting: central obesity may be the key determinant. Atherosclerosis 2007; 193: 70-6.
43. Le May C, Chu K, Hu M, Ortega CS, Simpson ER, Korach KS et al. Estrogens protect pancreatic -cells from apoptosis and prevent insulin-deficient diabetes mellitus in mice. Proc Natl Acad Sci 2006; 103: 9232-7.
44. Liu S, Mauvais-Jarvis F. Minireview: Estrogenic Protection of {beta}-Cell Failure in Metabolic Diseases. Endocrinology 2010; 151: 859-64.
45. Ding EL, Song Y, Manson JE, Rifai N, Buring JE, Liu S. Plasma sex steroid hormones and risk of developing type 2 diabetes in women: a prospective study. Diabetologia 2007; 50: 2076-84.