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METABOLIC AND ANTHROPOMETRIC IMPACT OF ANTIPSYCHOTIC TREATMENT IN FIRST-EPISODE PSYCHOSIS PATIENTS: A 12-WEEK PROSPECTIVE STUDY

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RESUMEN

Objetivo: Evaluar los cambios metabólicos, hormonales y antropométricos tras 12 semanas de antipsicóticos en 219 pacientes con primer episodio psicótico (PEP), e identificar diferencias según sexo y porcentaje de ganancia de IMC.

Métodos: Estudio longitudinal prospectivo con comparaciones pareadas basal vs. 3 meses. Se tomaron medidas antropométricas y analítico-metabólicas al inicio y a los 3 meses de iniciarse el tratamiento antipsicótico. Se aplicaron análisis McNemar y ANOVA-ANCOVA ajustados por valores basales, sexo, edad e IMC, para explorar diferencias en lípidos, glucemia, leptina y marcadores antropométricos.

Resultados: En el conjunto de la muestra, se observó un empeoramiento significativo del perfil lipídico y hormonal: el colesterol total aumentó una media de +17,14 mg/dL ($p < 0,001$), el LDL +13,38 mg/dL ($p < 0,001$), los triglicéridos +8,72 mg/dL ($p = 0,020$), la leptina +2,51 ng/mL ($p = 0,001$) y la HbA_1c +0,05 % ($p = 0,019$).

Al analizar por sexo, los hombres presentaron aumentos más marcados en triglicéridos (+17,65 frente a +2,01 mg/dL; $p = 0,036$) y glucemia (+2,84 frente a –0,12 mg/dL; $p = 0,038$), mientras que las mujeres mostraron incrementos más pronunciados en colesterol HDL (+13,98 frente a –3,45 mg/dL; $p = 0,007$) y leptina (+6,13 frente a –2,36 ng/mL; $p < 0,001$).

En relación con el porcentaje de ganancia de IMC, se evidenció una relación dosis-respuesta tanto en el colesterol total (+10,98, +22,29 y +29,40 mg/dL para aumentos < 7 %, 7–20 % y > 20 %, respectivamente; $p = 0,042$) como en la leptina (–1,04, +5,08 y +7,68 ng/mL; $p < 0,001$).

Desde el punto de vista antropométrico y hemodinámico, los participantes experimentaron una ganancia media de peso de +4,85 kg ($p < 0,001$), un incremento del IMC de +1,68 kg/m² ($p < 0,001$), un aumento del perímetro abdominal de +2,28 cm ($p < 0,001$) y una elevación de la tensión arterial sistólica de +4,57 mmHg ($p < 0,001$).

Conclusión: El tratamiento antipsicótico en PEP produce un deterioro metabólico precoz y heterogéneo, con perfiles de riesgo distintos según sexo y magnitud de aumento de IMC. Estos hallazgos apoyan la implementación de monitorización intensiva y protocolos preventivos personalizados desde el inicio del tratamiento.

ABSTRACT

Objective: To evaluate metabolic, hormonal, and anthropometric changes after 12 weeks of antipsychotic treatment in 219 first-episode psychosis (FEP) patients, and to identify differences by sex and percentage of BMI gain.

Methods: Prospective longitudinal study with paired baseline vs. 3-month comparisons. Anthropometric and metabolic-analytical measurements were taken at baseline and three months after the initiation of antipsychotic treatment. McNemar and ANOVA–ANCOVA analyses were applied, adjusted for baseline values, sex, age, and BMI, to explore differences in lipid levels, glucose, leptin, and anthropometric markers.

Results: Across the full sample, we observed a significant deterioration in the lipid and hormonal profile: total cholesterol increased by an average of +17.14 mg/dL ($p < 0.001$), LDL by +13.38 mg/dL ($p < 0.001$), triglycerides by +8.72 mg/dL ($p = 0.020$), leptin by +2.51 ng/mL ($p = 0.001$), and HbA_1c by +0.05% ($p = 0.019$).

When analyzed by sex, men exhibited greater increases in triglycerides (+17.65 vs. +2.01 mg/dL; $p = 0.036$) and glucose (+2.84 vs. –0.12 mg/dL; $p = 0.038$), whereas women showed more pronounced elevations in HDL cholesterol (+13.98 vs. –3.45 mg/dL; $p = 0.007$) and leptin (+6.13 vs. –2.36 ng/mL; $p < 0.001$).

A dose-response relationship was observed with respect to BMI gain: total cholesterol increased progressively with higher BMI categories (+10.98, +22.29, and +29.40 mg/dL for < 7%, 7–20%, and > 20% increase, respectively; $p = 0.042$), as did leptin (–1.04, +5.08, and +7.68 ng/mL; $p < 0.001$).

From an anthropometric and hemodynamic perspective, participants experienced a mean weight gain of +4.85 kg ($p < 0.001$), an increase in BMI of +1.68 kg/m² ($p < 0.001$), a waist circumference expansion of +2.28 cm ($p < 0.001$), and a systolic blood pressure rise of +4.57 mmHg ($p < 0.001$).

Conclusion: Antipsychotic treatment in FEP induces an early and heterogeneous metabolic deterioration, with risk profiles varying by sex and BMI gain magnitude. These findings support the implementation of intensive monitoring and personalized preventive protocols from treatment initiation.

PALABRAS CLAVE / KEYWORDS

Español: primer episodio psicótico; antipsicóticos; síndrome metabólico; ganancia ponderal; perfil lipídico

Inglés: first-episode psychosis; antipsychotics; metabolic syndrome; weight gain; lipid profile

INTRODUCTION

General Context: Psychosis and Metabolic Risk

Psychotic disorders, including schizophrenia, are associated with an increase in premature mortality of 13 to 15 years compared to the general population, with cardiovascular and metabolic diseases being the main contributors to this reduced life expectancy (Teasdale et al., 2025). In this context, metabolic syndrome (MS) - a cluster of factors including abdominal obesity, hyperglycemia, hypertension, and dyslipidemia - has been identified as one of the most prevalent conditions in patients with chronic schizophrenia, with an incidence reaching up to 49% of cases (Garrido-Torres et al., 2021) and is linked to a higher risk of cardiovascular disease, type 2 diabetes, and overall mortality.

The initiation of antipsychotic treatment in first-episode psychosis (FEP) patients has been directly associated with significant metabolic changes, which may include weight gain, alterations in glucose homeostasis, and dyslipidemia (Pillinger et al., 2023). Contrary to the notion that these effects develop gradually and late, it has been observed that the main changes - especially weight gain - occur rapidly and at very early stages. In this regard, a critical period has been described during the first three months of treatment (Pérez-Iglesias et al., 2007), during which up to 80% of the total long-term weight gain occurs, suggesting a key window of opportunity for early intervention (Pérez-Iglesias et al., 2014). This evidence highlights the need to focus prevention and metabolic monitoring efforts in the initial phase of treatment. The results of this study reinforce this hypothesis by showing that, after 12 weeks of treatment, antipsychotic-naïve FEP patients experienced significant weight increases with various antipsychotics. Specifically, the mean weight gain was 7.5 kg with olanzapine, 4.3 kg with risperidone, and 4.1 kg with haloperidol. In addition, significant elevations in total cholesterol and LDL were observed, regardless of the antipsychotic used.

Another relevant aspect is that these changes occur in a population that is initially young, without associated medical comorbidities, and in many cases with normal weight at baseline. This circumstance makes antipsychotic treatment the principal modifiable risk factor for the development of MS during early psychosis. While genetic factors or a family history of diabetes may contribute, the iatrogenic impact of these drugs is decisive in the development of short-term metabolic alterations.

Impact of Antipsychotics on Metabolic Health

Second-generation antipsychotics (SGAs) have been widely linked to the development of metabolic dysfunctions, including weight gain, dyslipidemia, and glucose intolerance. A recent study reported that hospitalized FEP patients gained an average of 3.46 ± 7.81 kg in the first 44.6 days of treatment, with this change dependent on antipsychotic exposure (Vochoskova et al., 2023).

However, there are differences in metabolic effects among antipsychotics. For example, olanzapine and clozapine have been identified as having the highest obesogenic potential, whereas others, such as aripiprazole, have a more favorable metabolic profile (Galiano Rus et al., 2022; Vázquez-Bourgon, Ortiz-García de la Foz, et al., 2022). A recent meta-analysis highlighted that weight gain associated with olanzapine in FEP patients can reach a mean of 7.53 kg, with more pronounced effects in treatments longer than 13 weeks (Correll et al., 2023).

Studies have shown that olanzapine has the greatest obesogenic potential, followed by risperidone and haloperidol. These differences are also reflected in the lipid profile, with olanzapine producing the most pronounced increases in LDL cholesterol (Pérez-Iglesias et al., 2007). Although some studies have suggested that using low doses or antipsychotics with a better metabolic profile, such as aripiprazole, could minimize these effects, the evidence remains limited.

Additionally, treatment duration and antipsychotic polypharmacy may also play a key role in the magnitude of metabolic changes. One recent study found that polypharmacy in early psychosis is associated with a higher risk of developing MS compared to treatment with a single antipsychotic (Vázquez-Bourgon, Ortiz-García de la Foz, et al., 2022). Conversely, the introduction of preventive measures such as structured exercise programs and specialized dietary plans has shown promising results in reducing the metabolic impact of antipsychotics (Coentre et al., 2022).

An innovative element of the present study lies in assessing patients' habitual weight prior to admission. It is known that a significant proportion of FEP patients experience weight loss during the prodromal phase or in the days preceding hospitalization, due to reduced food intake and diminished self-care. However, the literature has not systematically addressed how much of the weight gained after treatment initiation corresponds to physiological recovery of previously lost weight versus pathological excess attributable to pharmacological treatment. This distinction is crucial for understanding the true magnitude of the metabolic impact of antipsychotic treatment and for designing prevention strategies tailored to patients' real needs.

In summary, the available literature suggests that the adverse metabolic effects of antipsychotic treatment in FEP concentrate in the first months of therapy, with rapid and significant weight gain that conditions the future risk of developing metabolic syndrome. The choice of antipsychotic, its dose, treatment duration, and individual factors such as baseline weight and medical history directly influence the patient's metabolic trajectory. Therefore, it is imperative to study these phenomena in detail, with special attention to the period of greatest vulnerability, which coincides with the onset of pharmacological treatment.

HYPOTHESIS AND STUDY OBJECTIVES

Hypothesis

To evaluate metabolic changes following the introduction of antipsychotics in early phases of psychosis, especially during the first three months of treatment, a critical period in which the greatest alterations occur.

Primary Specific Objectives

1. To analyze the evolution of weight and other metabolic parameters in FEP patients after initiating antipsychotic treatment.
2. To determine whether these metabolic and anthropometric changes are pathologically significant.

Secondary Specific Objectives

1. To investigate whether there are differences between sexes.
2. To investigate whether there are differences between subjects older than 35 years and those younger than 35 years.

This study aims to provide a more detailed understanding of the metabolic effects of antipsychotic treatment in early phases, with the goal of optimizing therapeutic strategies that minimize metabolic impact and improve clinical care in FEP patients.

METHODOLOGY, MATERIALS, AND METHODS

1. Setting and Study Design

The study was conducted within the Early Psychosis Intervention Program of Cantabria (ITPCan), covering Health Areas I and II (University Hospital Marqués de Valdecilla and Laredo Hospital, respectively). ITPCan is a fourth-level program providing specialized, intensive care - both outpatient and/or inpatient - with a multidisciplinary, assertive approach during the most critical period of FEP, the first three years after psychosis onset. Its goal is to achieve early remission of psychotic symptoms and functional recovery.

For this study, we included patients treated in these settings between January 2020 and December 2024. We performed an observational, longitudinal, prospective study, following FEP patients from the start of antipsychotic treatment until 12 weeks thereafter. Measurements were obtained at two time points: baseline (before antipsychotic initiation) and week 12.

2. Study Population

Patients enrolled in ITPCan must meet the program's inclusion/exclusion criteria, which ensure that participants can benefit from the specialized intervention. Thus, our study subjects also fulfilled these criteria:

- Inclusion Criteria:
    - Age between 16 and 65 years.
    - First-episode psychosis, including non-affective (schizophrenia spectrum) and affective (e.g., bipolar disorder) psychoses.
    - Antipsychotic-naïve or with less than 6 weeks of prior exposure.

- Exclusion Criteria:
    - Substance dependence (except tobacco or cannabis).
    - Neurological disorder or severe brain injury.
    - Severe intellectual disability.
    - Toxic-induced psychosis.

3. Antipsychotic Treatment Allocation

Choice of antipsychotic (e.g., olanzapine, risperidone, aripiprazole) and initial dosing were at the discretion of the treating psychiatrist, following usual clinical practice, illness severity, and patient characteristics. Medication changes during follow-up - based on efficacy or tolerability - were recorded, including drug type, daily dose (mg/day), and any modifications over the 12 weeks.

4. Variables and Measures

Sociodemographic & Clinical Variables:

- Sex, age
- Family history of diabetes or dyslipidemia
- History of pre-admission weight loss (kg)

Anthropometric & Physical Health:

- Weight (kg), height (m), body mass index (BMI = weight/height^2), waist circumference (cm)
- Blood pressure (systolic/diastolic) measured at rest with an automatic cuff on the non-dominant arm, seated after 5 minutes of rest; three measurements taken, with the mean of the last two used.

Laboratory Analyses (fasting ≥ 8 h):

- Glucose, insulin, leptin, lipid profile (total cholesterol, HDL, LDL, triglycerides), HOMA index, and glycated hemoglobin (HbA_1c).

All assays were performed in our hospital laboratory after an overnight fast at baseline and 3-month follow-up. Fasting status and treatment adherence (good adherence defined as ≥ 90% of prescribed doses) were reported by patients and relatives. Glucose, total cholesterol, HDL, and triglycerides were measured on a TechniconDax analyzer (Technicon Instruments Corp., Tarrytown, NY) using Boehringer-Mannheim reagents. LDL cholesterol was calculated by the Friedewald formula. Insulin was assayed by immunoradiometric assay (Immunotech, Beckman Coulter, Prague, Czech Republic), with normal reference 2–17 µU/mL. Insulin resistance was calculated via HOMA and the triglyceride/HDL ratio, per McLaughlin et al., using a cutoff of 3.5.

5. Definition of Derived Altered Variables
    - Elevated waist circumference: >102 cm in men, >88 cm in women.
    - Elevated blood pressure: ≥130/85 mmHg.
    - High triglycerides: >150 mg/dL.
    - High total cholesterol: >200 mg/dL.
        - Low HDL cholesterol: <40 mg/dL in men, <50 mg/dL in women (or on specific lipid-lowering treatment).
        - High LDL cholesterol: >130 mg/dL.
    - Fasting hyperglycemia: ≥110 mg/dL.
    - High insulin: >17 µU/mL.
    - High leptin: >10 ng/mL in men, >25 ng/mL in women.
    - Altered HOMA index: >3 µU/mL.
    - High HbA_1c: >5.9%.

6. Statistical Analysis
    - Continuous variables are presented as mean ± standard deviation; categorical variables as frequencies and percentages.
    - Paired t-tests compared weight and metabolic parameters over time.
    - McNemar's test analyzed paired categorical clinical variables (baseline vs. 3 months).
    - ANOVA and ANCOVA examined effects by sex and percentage BMI increase.
    - Significance threshold set at $p < 0.05$.
    - Analyses were performed using SPSS v26.0 (IBM Corp., Armonk, NY).

7. Ethical Considerations

The study complied with the Declaration of Helsinki and Spanish data protection regulations (LOPD-GDD).

The study was approved by the Research Ethics Committee on Medicinal Products (CEIm) of Cantabria (ref.: 2023.046).

RESULTS

GENERAL DESCRIPTION OF THE SAMPLE

The sample comprised a total of 219 subjects. The main sociodemographic characteristics are shown in Table 1.

Table 1. Sociodemographic characteristics of the sample (N = 219)

Variable	Category	Frequency (n)	Percentage (%)
Place of birth	Spain	170	77.6
	Foreign (Regularized: 44)	49	22.4
Sex	Male	100	45.7
	Female	119	54.3
Estado civil	Single	137	62.6
	Married	54	24.7
	Separated	17	7.8
	Divorced	11	5.0
Living situation	Lives alone	43	19.6
	Lives with others	176	80.4
Ethnoracial group	Caucasian	171	78.1
	Other	48	21,9

The mean age of the participants was 36.5 years (SD = 13), with a median of 36 years and an age range from 17 to 64 years.

Regarding educational attainment, four participants had no formal education, 31 had completed primary school, 75 had secondary-level studies, 60 had finished high school (Bachillerato), 16 held a university diploma, and 33 had obtained a full university degree (Licenciatura).

At the time of study entry, 22 participants were employed, 54 were on medical leave, 74 were unemployed but had previous work experience, and nine were seeking their first job. Two were retired, two had a permanent disability, 39 were full-time students, 13 were homemakers, and four reported being in other circumstances.

CLINICAL DESCRIPTION OF THE SAMPLE

Baseline laboratory parameters are presented in Table 2.

Table 2. Baseline laboratory characteristics of participants

Clinical parameter		**Category**		**Frequency (n)**	**% of tota**	**% valid***	**Missing (n)**
Total cholesterol		Normal		161	73,5	78,9	15
		Hypercholesterolemia		43	19,6	21,1	
HDL	**Total**	Normal		128	58,4	64,3	20
		Low		71	32,4	35,7	
	By sex	Women	Normal	65	28,8	31,7	20
			Low	44	20,1	22,1	
		Men	Normal	65	29,7	32,7	
			Low	27	12,3	13,6	
LDL		Normal		170	77,6	85,4	20
		High		29	13,2	14,6	
Triglycerides		Normal		188	85,8	90,8	12
		Hypertriglyceridemia		19	8,7	9,2	
Glucose		Normoglycemia		206	94,1	95,8	4
		Hyperglycemia		9	4,1	4,2	
Insulin		Normal		180	82,2	95,2	30
		Hyperinsulinemia		9	4,1	4,8	
Leptin	**Total**	Normal		141	64,4	90,4	63
		High		15	6,8	9,6	
	By sex	Women	Normal	79	36,1	50,6	63
			High	9	4,1	5,8	
		Men	Normal	62	28,3	39,7	
			High	6	2,7	3,8	
HOMA index		Normal		168	76,7	89,8	32
		High		19	8,7	10,2	
HbA_1c		Normal		183	83,6	95,3	27
		High		9	4,1	4,7	

* Valid percentages exclude missing data.

Baseline physical parameters

At baseline, 140 participants were classified as normotensive, while 30 met criteria for hypertension (≥130/85 mmHg). An additional 34 individuals exhibited isolated systolic elevations without full hypertension, and 11 showed isolated diastolic elevation.

With respect to body mass index, 15 participants were underweight (BMI < 18.5 kg/m²), 131 fell within the normal range (18.5–24.9 kg/m²), 54 were overweight (25–29.9 kg/m²), and 15 met criteria for obesity (BMI ≥ 30 kg/m²).

ANALYSIS AT 3 MONTHS

Laboratory results at 3 months are shown in Table 3.

Table 3. Laboratory characteristics at 3 months

Clinical parameter		**Category**		**Frequency (n)**	**% of tota**	**% valid***	**Missing (n)**
Total cholesterol		Normal		120	54,8	63,2	29
		Hypercholesterolemia		70	32	36,8	
HDL	**Total**	Normal		146	66,7	76,8	29
		Low		44	20,1	23,2	
	By sex	Women	Normal	84	38,4	44,2	29
			Low	27	12,3	14,2	
		Men	Normal	62	28,3	32,6	
			Low	17	7,8	8,9	
LDL		Normal		133	60,7	70,4	30
		High		56	25,6	29,6	
Triglycerides		Normal		167	76,3	86,5	26
		Hypertriglyceridemia		26	11,9	13,5	
Glucose		Normoglycemia		183	83,6	94,8	26
		Hyperglycemia		10	4,6	5,2	
Insulin		Normal		38	17,4	92,7	178
		Hyperinsulinemia		3	1,4	7,3	
Leptina	**Total**	Normal		132	60,3	84,6	63
		High		24	11	15,4	
	By sex	Women	Normal	70	32	44,9	63
			High	15	6,8	9,6	
		Men	Normal	62	28,3	39,7	

			High	9	4,1	5,8	
HOMA index		Normal		32	14,6	84,2	181
		High		6	2,7	15,8	
HbA_1c		Normal		175	79,9	96,7	38
		High		6	2,7	3,3	

After three months of antipsychotic treatment, the majority of participants - 63.5% (n = 139) - remained normotensive, while only 6.8% (n = 15) met the criteria for hypertension. An additional 11.9% (n = 26) exhibited isolated systolic elevations (systolic blood pressure above 140 mmHg without a formal hypertension diagnosis), and 7.3% (n = 16) had isolated diastolic elevations (> 85 mmHg) in the absence of frank hypertension.

In terms of body mass index, only 1.8% of participants (n = 4) were underweight, whereas 38.4% (n = 84) fell within the normal weight range. Overweight status was observed in 36.5% (n = 80) and obesity in 12.8% (n = 28) of the sample.

When we compared baseline and three-month paired data, antipsychotic initiation was associated with a significant deterioration in both metabolic and physical profiles. Triglyceride levels rose by an average of 8.72 mg/dL (95% CI: 1.40–16.05; t(183) = –2.35; p = 0.020), total cholesterol increased by 17.14 mg/dL (95% CI: 12.24–22.04; t(176) = –6.90; p < 0.001), and LDL cholesterol by 13.38 mg/dL (95% CI: 9.17–17.58; t(171) = –6.28; p < 0.001). Although HDL rose by 6.62 mg/dL (95% CI: 0.47–12.78; t(172) = –2.13; p = 0.035), this increase did not offset the overall worsening of the lipid profile. Concurrently, leptin levels increased by 2.51 ng/mL (95% CI: 1.01–4.02; t(114) = –3.31; p = 0.001), and HbA_1c rose by 0.05% (95% CI: 0.009–0.096; t(160) = 2.38; p = 0.019), indicating early disruption of glucose metabolism.

Anthropometrically, participants gained a mean of 4.85 kg (95% CI: 4.07–5.63; t(195) = –12.26; p < 0.001), corresponding to a BMI increase of 1.68 kg/m² (95% CI: 1.40–1.96; t(195) = –11.80; p < 0.001) and a waist circumference increase of 2.28 cm (95% CI: 1.28–3.27; t(195) = –4.51; p < 0.001). Systolic blood pressure rose by 4.57 mmHg (95% CI: 2.23–6.90; t(195) = 3.86; p < 0.001), with no significant change in diastolic pressure (p = 0.150). Fasting glucose (p = 0.297), insulin (p = 0.960), and HOMA-IR (p = 0.510) remained statistically unchanged.

Regarding the distribution of weight and BMI gain, 49.5% of patients gained less than 7% of their baseline weight, 41.8% gained between 7% and 20%, and 8.7% gained more than 20% at three months - meaning that half of the sample exceeded the 7% clinical risk threshold. Similarly,

49.5% had a BMI increase of less than 7%, 41.3% had an increase between 7% and 20%, and 9.2% exceeded a 20% increase in BMI.

Overall, during the first three months of antipsychotic treatment in first-episode psychosis, there are harmful increases in plasma lipids, pro-inflammatory hormonal markers, adiposity indicators, and systolic blood pressure. While lipid and adiposity measures deteriorated significantly, changes in glycemic and hormonal markers were less consistent:

Table 4. Baseline vs. 3 months (McNemar's test)

VARIABLE	BASELINE	3MONTHS	CHANGE	MCNEMAR
	% altered	% altered	%	P value
Hypercholesterolemia (>200 mg/dL)	21,1	36,8	15,7	<0,001
Low HDL (<40 mg/dL men, <50 mg/dL women)	13,6 men 22,1 women 35,7 total	8,9 men 14,2 women 23,1 total	-4,7 men -7,9 women -12,6 total	<0,001
High LDL (>130 mg/dL)	14,6	29,6	15	0,001
Hypertriglyceridemia (>150 mg/dL)	9,2	13,5	4,3	0,327
Hyperglycemia (≥110 mg/dL)	4,2	5,2	1%	0,774
Altered HOMA (>3 µU/mL)	10,2	15,8	5,6	0,5
Altered insulin (>17 µU/mL)	4,8	7,3	2,5	1
Altered leptin (>10 ng/mL men; >25 ng/mL women)	3,8 men 5,8 women 9,6 total	5,8 men 9,6 women 15,4 total	2 men 3,8 women 5,8 total	0,189
Altered HbA_1c (>6 %)	4,7	3,3	-1,4	1
Obesity (BMI ≥30)	7	14,3	7,3	<0,001
Elevated waist circumference (>102 cm men y >88 cm women)	12,6 men 32,6 women 45,2 total	15,3 men 38,3 women 53,6 total	2,7 men 5,7 women 8,4 total	0,071

Thus, after three months of antipsychotic therapy, there is a clear deterioration of the lipid profile - particularly marked increases in total cholesterol and LDL - and a pronounced rise in obesity,

whereas glycemic and hormonal parameters change less markedly and without statistical significance. The reduction in the prevalence of low HDL may reflect lifestyle variations or specific drug effects, but the overall balance indicates an early increase in cardiovascular risk during the course of treatment.

When we analyze the results by sex, we obtain the following findings:

Table 5. ANOVA-ANCOVA analysis by sex. Covariates: baseline analytic value, BMI, and age

Variable	Sex	M ± SD (N)	ANOVA F (p)	ANCOVA EMM ± SE	F (p)
Δ cholesterol	Men	14,66 ± 36,24 (74)	0,715 (0,399)	14,624 ± 3,620	0,814 (0,368)
	Women	18,92 ± 30,60 (103)		18,950 ± 3,055	
Δ Triglycerides	Men	15,46 ± 61,31 (79)	2,494 (0,116)	17,645 ± 5,515	4,440 (0,036)
	Women	3,66 ± 39,80 (105)		2,010 ± 4,758	
Δ Glycemia	Men	3,04 ± 12,19 (83)	2,675 (0,104)	2,841 ± 1,050	4,384 (0,038)
	Women	–0,40 ± 15,86 (107)		–0,119 ± 0,922	
Δ HDL	Men	–0,08 ± 10,90 (73)	3,428 (0,066)	–3,450 ± 4,748	7,516 (0,007)
	Women	11,52 ± 52,69 (100)		13,979 ± 4,030	
Δ LDL	Men	13,68 ± 29,66 (72)	0,013 (0,909)	13,685 ± 3,182	0,016 (0,900)
	Women	13,16 ± 26,80 (100)		13,157 ± 2,689	
Δ Insulin	Men	0,48 ± 2,98 (11)		0,771 ± 1,038	

	Women	–0,24 ± 5,36 (17)	0,165 (0,688)	–0,428 ± 0,825	0,777 (0,387)
Δ Leptin	Men	0,76 ± 5,41 (49)	4,072 (0,046)	–2,364 ± 1,153	26,089 (0,000)
	Women	3,81 ± 9,52 (66)		6,129 ± 0,959	
Δ HbA1c	Men	–0,062 ± 0,232 (67)	0,163 (0,687)	–0,060 ± 0,028	0,121 (0,729)
	Women	–0,045 ± 0,309 (94)		–0,047 ± 0,023	
Δ HOMA-IR	Men	0,091 ± 0, 709 (11)	0,977 (0,333)	0,166 ± 0,199	3,911 (0,062)
	Women	-0,314 ± 1,202 (14)		-0,373 ± 0,176	

After adjusting for baseline values, BMI, and age, the ANCOVA analysis revealed significant sex-related differences in four metabolic variables:

- Triglycerides: Men showed a higher adjusted mean increase of 17.65 mg/dL (± 5.52), compared to 2.01 mg/dL (± 4.76) in women ($F = 4.44$; $p = 0.036$).
- Glucose: The adjusted mean increase in men was 2.84 mg/dL (± 1.05), while women showed a slight decrease of -0.12 mg/dL (± 0.92) ($F = 4.38$; $p = 0.038$).
- HDL cholesterol: Men experienced an adjusted mean reduction of -3.45 mg/dL (± 4.75), in contrast with a mean increase of 13.98 mg/dL (± 4.03) in women ($F = 7.52$; $p = 0.007$).
- Leptin: Women showed a substantial adjusted increase of 6.13 ng/mL (± 0.96), whereas men experienced a decrease of -2.36 ng/mL (± 1.15) ($F = 26.09$; $p < 0.001$).

No statistically significant differences were observed between men and women in changes in total cholesterol, LDL, insulin, HbA1c, or HOMA-IR ($p > 0.05$).

On the other hand, when these same analyses were carried out based on the percentage of BMI increase, we obtained the following data:

Table 6. ANOVA-ANCOVA analysis based on percentage of BMI increase. Covariates: baseline analytic value, BMI, age, and sex

Variable	BMI Group	M ± SD (N)	ANOVA F (p)	ANCOVA EMM ± SE	F (p)
Δ cholesterol	< 7 %	11,45 ± 36,43 (88)	3,560 (0,031)	10,979 ± 3,463	3,219 (0,042)
	7–20 %	21,26 ± 28,18 (70)		22,293 ± 3,743	
	> 20 %	31,11 ± 27,43 (18)		29,404 ± 7,614	
Δ Triglycerides	< 7 %	–2,44 ± 43,21 (89)	4,898 (0,008)	0, 421 ± 5,409	2,205 (0,113)
	7–20 %	17,54 ± 57,67 (76)		15,544 ± 5,649	
	> 20 %	28,33 ± 38,81 (18)		22,621 ± 11,872	
Δ Glycemia	< 7 %	–0,88 ± 13,60 (92)	1,732 (0,180)	-0,268 ± 1,041	2,347 (0,099)
	7–20 %	2,44 ± 13,98 (77)		1,478 ± 1,106	
	> 20 %	4,50 ± 18,84 (18)		5,450 ± 2,341	
Δ HDL	< 7 %	7,34 ± 51,84 (86)	0,072 (0,931)	5,797 ± 4,627	0,117 (0,889)
	7–20 %	5,22 ± 29,50 (68)		6,463 ± 4,997	
	> 20 %	8,56 ± 10,90 (18)		11,276 ± 10,067	
Δ LDL	< 7 %	11,12 ± 29,80 (86)	0,686 (0,505)	10,326 ± 3,078	1,011 (0,366)
	7–20 %	15,85 ± 26,93 (67)		16,953 ± 3,368	
	> 20 %	16,94 ± 21,50 (18)		16,617 ± 6,672	
Δ Insulin	< 7 %	-1,97 ± 4,64 (13)	2,821 (0,079)	-0,798 ± 1,186	0,539 (0,591)
	7–20 %	2,10 ± 4,17 (10)		1,047 ± 1,165	
	> 20 %	1,18 ± 2,99 (5)		0,223 ± 1,850	
Δ Leptin	< 7 %	-1,02 ± 7,45 (53)	11,000 (0,000)	-1,035 ± 0,934	12,282 (0,000)
	7–20 %	5,30 ± 6,90 (51)		5,079 ± 0,916	
	> 20 %	6,58 ± 10,27 (11)		7,683 ± 2,011	
Δ HbA_1c	< 7 %	-0,06 ± 0,33 (74)		–0,081 ± 0,028	

	7–20 %	-0,05 ± 0,24 (68)	0,120 (0,887)	–0,045 ± 0,028	1,556 (0,214)
	> 20 %	-0,03 ± 0,20 (18)		0,035 ± 0,056	
Δ HOMA-IR	< 7 %	-0,63 ± 0,98 (12)	3,179 (0,061)	-0,129 ± 0,253	0,175 (0,840)
	7–20 %	0,36 ± 0,99 (8)		-0,051 ± 0,266	
	> 20 %	0,24 ± 0,65 (5)		-0,288 ± 0,369	

We found statistically significant differences in two variables:

- Total cholesterol: There was a progressive increase corresponding to the magnitude of BMI gain, with adjusted means of 10.98 mg/dL for the group with <7% increase, 22.29 mg/dL for those with a 7–20% increase, and 29.40 mg/dL for increases >20% ($F = 3.22$; $p = 0.042$).
- Leptin: A significantly greater increase was observed in groups with higher BMI gains, with adjusted means of –1.04 ng/mL (<7%), 5.08 ng/mL (7–20%), and 7.68 ng/mL (>20%) ($F = 12.28$; $p < 0.001$).

The remaining variables - triglycerides, glucose, HDL, LDL, insulin, HbA1c, and HOMA-IR - did not reach statistical significance in the ANCOVA after adjusting for covariates ($p > 0.05$), although triglycerides had shown a significant result in the unadjusted ANOVA ($p = 0.008$), which diminished after controlling for baseline values and demographic factors.

DISCUSSION

The findings of this study support the notion that the initiation of antipsychotic treatment in patients with first-episode psychosis (FEP) leads to early metabolic deterioration and significant weight gain. The marked increases in total cholesterol, LDL, and triglycerides are consistent with previous observations in similar cohorts treated with olanzapine and risperidone, where a strong obesogenic effect has been reported within the first twelve weeks of treatment (Pérez-Iglesias et al., 2007; Correll et al., 2023). In addition, the rise in leptin - an indicator of insulin resistance and early adipocyte dysfunction in psychosis (Pillinger et al., 2023) - adds further support to this pattern.

Although no significant changes were detected in fasting glucose or HOMA-IR (a clinical score of insulin resistance), the slight increase in HbA_1c suggests that glycemic control may begin to deteriorate even before basal insulin levels show alterations. This underlines the importance of incorporating long-term glycemic markers such as HbA_1c into early monitoring protocols from the beginning of treatment.

The increase in systolic blood pressure and the average weight gain of 4.85 kg over just three months reinforce the concept of a “critical window” during which cardiovascular risk rapidly escalates (Pérez-Iglesias et al., 2014). Additionally, 50.5% of patients experienced clinically significant increases in both weight and BMI (defined as >7%), a threshold associated with higher risk of metabolic complications, cardiovascular disease, and type 2 diabetes. Longitudinal studies in FEP cohorts have shown that such early weight gain tends to persist or even increase over the following 10 years after the psychotic onset (Vázquez-Bourgon et al., 2022), emphasizing the urgent need to implement weight gain prevention strategies from the earliest stages of psychosis. Behavioral interventions - including supervised exercise programs and nutritional counseling - could mitigate part of this metabolic burden, as suggested by early intervention studies in FEP (Coentre et al., 2022).

Our study also revealed sex-based differences: men showed significantly greater increases in triglycerides and glucose, suggesting a higher early cardiovascular risk under antipsychotic treatment. In contrast, women exhibited a more pronounced increase in HDL and leptin, indicating a differential response in lipid and endocrine regulation, possibly mediated by hormonal factors. These results highlight the need to tailor metabolic monitoring by sex, with specific thresholds and control frequencies adapted to male and female profiles.

Moreover, we observed a progressive increase in both total cholesterol and leptin in relation to the degree of BMI gain (<7%, 7–20%, and >20%). This "dose-response curve" was not as evident for other parameters once covariates were adjusted for, suggesting that cholesterol and leptin are the most sensitive markers of weight gain. Stratifying patients by percentage BMI increase may allow early identification of those at higher metabolic risk and help prioritize targeted interventions (dietary, exercise-based, or pharmacological).

Among the limitations of this study is the heterogeneity in the type and dosage of antipsychotics used, which prevents attribution of the observed changes to a single agent. Additionally, the proportion of missing data in some hormonal variables (e.g., insulin) reduced the statistical power for those outcomes. Future research should stratify analyses by specific antipsychotic and dosage, incorporate behavioral intervention groups, and extend follow-up beyond three months to determine whether metabolic alterations stabilize or continue to progress over time.

This study presents several strengths that support the robustness of its findings. Firstly, systematic clinical follow-up was conducted with high adherence rates, allowing for the collection of consistent and reliable data throughout the observation period. Additionally, the data were obtained from real-world clinical practice, with broad inclusion criteria in terms of both age range and clinical characteristics, which enhances the representativeness and applicability of the results.

The prospective design enabled real-time data collection, minimizing recall bias and allowing for a rigorous assessment of metabolic changes from the onset of antipsychotic treatment. Furthermore, objective and standardized measures were used to evaluate all clinical and analytical parameters - such as weight, BMI, lipid profile, and hormone levels - according to validated protocols, ensuring strong internal comparability of the results.

From a statistical standpoint, a robust multivariate adjustment was applied through ANCOVA analyses, controlling for baseline values, age, sex, and other relevant covariates, which strengthens the validity of the associations observed. Finally, the integration of anthropometric, biochemical, and hormonal variables allows for a more comprehensive and coherent interpretation of the findings, suggesting possible underlying biological mechanisms in the metabolic impact of treatment.

CONCLUSIONS

This study demonstrates that during the first three months of antipsychotic treatment in patients with first-episode psychosis:

1. There is a significant deterioration in the lipid profile (total cholesterol, LDL, and triglycerides), along with increases in leptin and HbA_1c, highlighting the early onset of adipocyte dysfunction and glycemic disturbances.
2. Early weight gain is evident (mean +4.85 kg), along with increases in BMI, waist circumference, and systolic blood pressure - confirming the existence of a "critical window" of heightened cardiovascular risk.
3. A total of 50.5% of patients experienced a clinically significant increase in both weight and BMI (>7%), a threshold associated with greater risk of metabolic syndrome, type 2 diabetes, and long-term cardiovascular complications.
4. Sex-based differences were observed: men showed more marked increases in triglycerides and glucose, while women exhibited greater rises in HDL and leptin. These findings support the need for sex-specific strategies for metabolic monitoring and prevention.
5. A dose-response relationship was observed with BMI gain: total cholesterol and leptin levels increased progressively with higher percentages of BMI increase (<7%, 7–20%, >20%), identifying high-risk subgroups who may benefit from targeted interventions.
6. No significant changes were observed in fasting glucose, insulin levels, or HOMA-IR.

Clinical implications:

- Implement intensive, personalized monitoring and prevention protocols tailored to sex and degree of BMI increase.
- Include long-term glycemic control markers (e.g., HbA_1c) from the outset of treatment.
- Promptly evaluate non-pharmacological interventions (diet, exercise) in high-risk groups identified through early metabolic screening.

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ANNEXES

Annex 1. Paired samples t-test table for clinical and metabolic variables (Baseline - 3 months)

Variable	Mean Difference	Standard Deviation	95% CI		t	p (2-tailed)
			Lower	Upper		
Glucose	-1,09	14,45	-3,16	0,97	-1,047	0,297
Triglycerides	-8,72	50,36	-16,05	-1,4	-2,349	0,020
Total cholesterol	-17,14	33,04	-22,04	-12,24	-6,90	<0,001
HDL	-6,62	40,99	-12,78	-0,47	-2,13	0,035
LDL	-13,37	27,95	-17,58	-9,17	-6,28	<0,001
Insulin	-0,042	4,52	-1,80	1,71	-0,05	0,960
Leptin	-2,51	8,14	-4,02	-1,01	-3,31	0,001
HOMA-IR	0,13	1,02	-0,28	0,56	0,67	0,510
HbA1c	0,05	0,27	0,01	0,10	2,38	0,019
Baseline Weight- 3 months	-4,85	5,53	-5,63	-4,07	-12,26	<0,001
Usual Weight- 3 months	-2,94	7,48	-3,99	-1,89	-5,51	<0,001
Waist circumference	-2,28	7,06	-3,27	-1,28	-4,51	<0,001
Systolic BP	4,57	16,57	2,23	6,90	3,86	<0,001
Diastolic BP	1,29	12,44	-0,47	3,04	1,45	0,150
BMI	-1,68	1,99	-1,96	-1,40	-11,80	<0,001

Annex 2. Distribution of weight gain (%) after 3 months

Weight Gain Percentage			
	Frequency	Percentage	Valid Percentage

Percentage weight Gain	< 7%	97	44,3	49,5
	7-20%	82	37,4	41,8
	>20%	17	7,8	8,7
	Valid Total	196	89,5	100,0
Overall Total		219	100,0	

Annex 3. Distribution of BMI increase (%) after 3 months

Aumento IMC en porcentaje				
		Frequency	Percentage	Valid Percentage
Percentage BMI Gain	< 7%	97	44,3	49,5
	7%-20%	81	37,0	41,3
	>20%	18	8,2	9,2
	Valid Total	196	89,5	100,0
Overall Total		219	100,0	