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ORIGINAL INVESTIGATION

Incidence of non-alcoholic fatty liver disease and metabolic dysfunction in first episode schizophrenia and related psychotic disorders: a 3-year prospective randomized interventional study

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Abstract
Rationale Patients with schizophrenia spectrum disorders have increased morbidity and mortality, largely due to cardiovascular disease, which is associated with antipsychotic treatment.
Objectives Because of the link between cardiometabolic risk, non-alcoholic fatty liver disease (NAFLD), and antipsychotics, we aimed to investigate the development of NAFLD during the first 3 years of antipsychotic treatment in first episode non-affective psychosis patients.
Results A sample of 191 subjects was included in final analyses, randomly assigned to aripiprazole ($N = 83$), risperidone ($N = 12$), quetiapine ($N = 46$), and ziprasidone ($N = 50$). At intake, 180 patients were antipsychotic naïve. The NAFLD fibrosis score, FIB-4 score, and the fatty liver index (FLI) were calculated at baseline, at 3 months, and then yearly for 3 years. None of the patients showed significant liver fibrosis according to the mentioned scores at baseline, prior to randomization. At 3 years follow-up, 25.1 % individuals showed a FLI score ≥60, which is a predictor of steatosis. Of the individuals considered indeterminate at baseline, 64.7 % developed a FLI score ≥60 and only 16.6 % who had a FLI score <30 at baseline, showed a FLI score predictor of steatosis at endpoint. The FLI score ≥60 at endpoint was associated with an increase of more than 7 % of the body mass index (FLI score ≥ 60, 91.7 %; FLI < 60, 55.9 %; $p < 0.001$), increased triglyceride levels (FLI score ≥ 60, 54.2 %; FLI < 60, 5.6 %; $p < 0.001$), decreased HDL levels (FLI score ≥ 60, 41.7 %; FLI < 60, 17.5 %; $p = 0.001$), hypertension (FLI score ≥ 60, 19.5 %; FLI < 60, 4.5 %; $p = 0.002$), and waist circumference increase (steatosis 68.8 %; FLI < 60, 14.0 %; $p < 0.001$).
Conclusions Our results support the importance of assessing the potential development of NAFLD in schizophrenia spectrum patients receiving antipsychotic medication.

Keywords Psychosis · Metabolic syndrome · Antipsychotics · Cardiometabolic risk · Lipids · Hepatic steatosis

María Teresa Arias-Loste and María José Morlán-Coarasa have ?contributed equally to the manuscript.

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Introduction

Patients with schizophrenia spectrum disorders are associated with excess premature mortality and lower life expectancy compared to the general population, and the increase in cardiovascular morbidity and mortality is a critical risk factor (Correll

et al. 2014). Antipsychotics play a decisive role in diminishing acute psychotic symptoms (Leucht et al. 2012) and also in preventing relapses during the maintenance phase (Caseiro et al. 2012). Nonetheless, weight gain and metabolic side effects are frequently associated with antipsychotic medications, particularly in young people during the early phases of the illness (De Hert et al. 2012; Perez-Iglesias et al. 2014). Disturbingly, obesity and insulin resistance have been identified as key factors associated with non-alcoholic fatty liver disease (NAFLD) (Targher 2007). Approximately 20 % of adults in the general population in Western countries have NAFLD, which is the current main cause of liver disease in these countries (Angulo 2002). The clinical significance and spectrum of lesions that encompass NAFLD vary widely from simple steatosis, with a mainly benign course and prognosis, to non-alcoholic steatohepatitis (NASH), which may lead to liver cirrhosis or hepatocellular carcinoma (Bugianesi et al. 2002).

Although NAFLD is accepted to be a component of the metabolic syndrome, it has been shown that its presence may itself constitute a cardiovascular risk factor independent from the classic risk factors such as insulin resistance or obesity (Targher et al. 2010). The increased morbidity and mortality associated with schizophrenia is largely due to cardiovascular disease (Foley and Morley 2011).

To our knowledge, no studies have been performed to analyze the potential development of NAFLD in individuals with schizophrenia. Because fatty liver disease has been demonstrated to be an independent cardiovascular risk factor, its early identification may lead to a closer follow-up in this cluster of patients, with better prevention and treatment of the cardiometabolic outcomes. The aim of the present study is to investigate the potential development of NAFLD during the first 3 years of antipsychotic treatment in a large epidemiological cohort of drug-naïve patients with first episode non-affective psychosis.

Methods

Study setting and financial support

The participants were drawn from an ongoing longitudinal intervention program of patients with first-episode psychosis, *Programa Asistencial de Fases Iniciales de Psicosis* (PAFIP), University Hospital Marqués de Valdecilla, Spain. In accordance with international standards for research ethics, the local institutional review board approved this program.

Subjects

The patients recruited into this study were drawn from a consecutive sample of patients with psychosis who were referred to our psychiatric unit from October 2005 to January 2012 and met the following criteria: (1) age 15–60 years; (2) living in the catchment area; (3) experiencing their first episode of psychosis; (4) no prior treatment with antipsychotic medication or, if previously treated, a total period of adequate antipsychotic treatment of less than 6 weeks; (5) meeting the DSM-IV criteria for brief psychotic disorder, schizophreniform disorder, schizophrenia, schizoaffective disorder, or psychotic disorder not otherwise specified; and (6) they understood the nature of the study and signed an informed consent document. Patients were excluded for any of the following reasons: (1) meeting the DSM-IV criteria for drug dependence, (2) meeting the DSM-IV criteria for mental retardation, and (3) having a history of neurological disease or head injury.

The diagnoses were confirmed using the Structured Clinical Interview for DSM-IV, which was performed by an experienced psychiatrist 6 months after the baseline visit.

Study design

This is a prospective, randomized, flexible-dose, open-label study. The patients who agreed to participate were randomly assigned to the treatment groups. We used a simple randomization procedure and a computer-generated randomization list that was generated by a statistician. At study intake, 180 patients were antipsychotic naïve. The mean duration of prior treatment in those patients (N = 11) who had minimally treated before randomization was 2 weeks (SD = 1.5; range = 0.4–4.0 weeks). The patients who were taking antipsychotics at intake underwent a 2–5-day washout period before initiating the treatment protocol. The dose ranges were 3–6 mg/day of risperidone, 5–30 mg/day of aripiprazole, 100–600 mg/day of quetiapine, and 40–160 mg/day of ziprasidone. At the treating physician's discretion, the dose and type of antipsychotic medication could be changed based on clinical efficacy and the profile of side effects during the follow-up period. Certain concomitant medications (lormetazepam and clonazepam) were permitted for the management of agitation, general behavior disturbances, and/or insomnia. Only if clinically significant extrapyramidal signs occurred was anticholinergic medication (biperiden at dose of up to 8 mg/day) allowed. Antidepressants (SSRIs) and mood stabilizers were permitted if clinically needed. During the 3-year follow-up period, the patients were regularly assessed in the psychiatric outpatient clinic by experienced psychiatrists. All patients were informed about potential weight gain and were given advice on their diet, exercise, and lifestyle.

Assessments

The patients' weight and waist circumference were determined at baseline, 3 months, and then yearly for 3 years. The patients' wore lightweight clothing when their body weights were measured. The patients' height was measured at the time of enrollment. The patients' body mass index

(BMI) was computed as their body weight (kg) divided by height in square meters.

The data collected at the first or at 3-month visit ($N = 136$ and $N = 55$, respectively) were considered as baseline measurements, and those obtained at 1 ($N = 15$), 2 ($N = 13$), or 3 years ($N = 163$) were considered endpoint measurements.

The fasting venous blood samples were collected at baseline, 3 months, and then yearly for 3 years. All determinations were performed in our hospital. The glucose, triglycerides, total and HDL cholesterol levels were measured by automated methods on a Technicon Dax (Technicon Instruments Corp., USA) using the reagents supplied by Boehringer-Mannheim (Germany). A complete blood count and liver function tests based on standard values were performed at each visit (data not shown).

The insulin levels were measured by an immunoradiometric assay (Immunotech, Beckman Coulter Company, Czech Republic) with an average interassay coefficient of variation (CV) of 3.3 % and intra-assay CV of 2.8 %. The sensitivity of the method was 0.5 μU/mL. The values for normal weight subjects are 2.1–22 μU/mL. This assay does not show any cross-reactivity with human proinsulin or C-peptide. A non-invasive assessment of NAFLD was retrospectively applied. Based on the available clinical, anthropometrical, and analytical data, the NAFLD fibrosis score and the FIB-4 score were calculated as previously described (Angulo et al. 2007; Sterling et al. 2006) to assess the degree of liver fibrosis. Moreover, the fatty liver index (FLI) was applied to determine the presence of liver steatosis (Bedogni et al. 2006). The hepatic scores were determined yearly during the 3-year follow-up period. The FLI consists of an algorithm that predicts fatty liver disease based on the BMI, waist circumference, and triglyceride and gamma-glutamyltransferase levels, with an accuracy of 0.84 (95 % CI 0.81–0.87). The FLI varies from 0 to 100. A score lower than 30 rules out fatty liver disease (negative likelihood ratio = 0.2), and a score greater than or equal to 60 suggests fatty liver disease (positive likelihood ratio = 4.3). FLI scores ≥30 and <60 were considered indeterminate. Based on the FLI, the patients were classified into two subgroups: patients with FLI ≥ 60 at any time during the follow-up, with no abnormalities in the liver function tests at baseline, and patients who did not have an FLI that suggested steatosis (<60) throughout the follow-up period. The mean time between the start of the trial and the endpoint was 1003.2 +/− 223.3 days (range 266–1257 days); therefore, we considered a total follow-up period of 1300 days.

Statistical analysis

The statistical analyses were performed using the SPSS software, 19.0 (Armonk, NY: IBM Corp.). All data were tested for a normal distribution using the Kolmogorov-Smirnov test. To compare the continuous variables among groups, one-way analysis of variance was used for the normally distributed data and the Mann-Whitney U test was used for the non-normally distributed data. The categorical data were analyzed using the chi-squared test. All of the hypotheses were tested using a two-sided significance level of 0.05.

The primary aim of this study was to test the hypothesis that antipsychotic treatment would result in an increase incidence of liver steatosis. Kaplan-Meier survival curves and a log-rank test were used to assess time to hepatic steatosis. The percentages of emergent steatosis between groups were examined using chi-squared tests.

Results

Out of the 295 individuals who were referred to PAFIP from October 2005 to January 2012, 239 met the inclusion criteria and were randomly assigned to the treatment groups. Of these, 34 individuals were excluded because they did not have both the start and endpoint measurements needed to determine the FLI, so we calculated the FLI on 205 patients. Based on the FLI, 14 patients (6.8 %; 14/205) had a basal score that predicted hepatic steatosis (FLI ≥ 60) and, therefore, were also excluded. Thus, a sample of 191 subjects was included in the final analyses and showed either an indeterminate score (FLI ≥ 30 and <60) (34/191; 17.8 %) or were ruled out for steatosis (FLI < 30) (157/191; 82.2 %) at baseline.

The mean age at study intake was 31.7 years (SD 10.1), and 53.4 % were males. Most of the subjects were Caucasian (97.4 %) and lived with their families (70.2 %). 47.1 % of the patients were diagnosed with schizophrenia, 33 % with schizophreniform disorder, 12.6 % with brief psychotic disorder, 6.3 % with unspecified psychotic disorder, 0.5 % with schizoaffective disorder, and 0.5 % with delusional disorder. The mean duration of psychosis was 14.1 months (SD 34.0) (Table 1).

At baseline, prior to randomization, none of the patients showed significant liver fibrosis based on the NAFLD fibrosis score or FIB-4 score. The following parameters mean values were obtained at baseline in our sample: weight 64.0 (SD 12.1), glucose 88.1(SD 22.6), insulin 10.4 (SD 10.1), triglycerides 78.0 (SD 36.1), HDL 53.8 (SD 15.1), total cholesterol 174.4 (SD 36.6), GGT 21.7 (SD 51.0), waist circumference 81.3 (SD 9.9), systolic blood pressure 118.2 (SD 16.5), and diastolic blood pressure BP 68.0 (SD 10.8).

Eighty-three individuals were initially randomized to aripiprazole, 12 to risperidone, 46 to quetiapine, and 50 to ziprasidone treatment. The dose and type of antipsychotic medication changed through the follow-up.

At the end of the follow-up, 25.1 % (48/191) of the individuals displayed a FLI ≥ 60, a predictor of the presence of steatosis. The rest of the 191 subjects had either an

Table 1 Demographic and clinical characteristics: comparison between patients with baseline FLI < 30 and with baseline FLI ≥ 30 and <60

	Total		Baseline FLI < 30		Baseline FLI ≥ 30 and <60			
	N = 191		*N* = 157		*N* = 34			
Characteristics	Mean	SD	Mean	SD	Mean	SD	U	*p*
Age at admission (years)	31.7	10.1	31.0	10.0	34.8	10.5	2073.0	0.041
	N	%	*N*	%	*N*	%	χ^2 (df = 1)	*p*
Diagnosis*								
Schizophrenia	90	47.1	73	46.5	17	50.0	0.138	0.711
Other schizophrenia spectrum diagnoses	101	52.9	84	53.5	17	50.0		
Brief psychotic disorder	24	12.6	22	14.0	2	5.9		
Unspecified psychotic disorder	12	6.3	8	5.1	4	11.8		
Schizophreniform disorder	63	33.0	53	33.8	10	29.4		
Schizoaffective disorder	1	0.5	1	0.6	0	0.0		
Delusional disorder	1	0.5	0	0.0	1	2.9		
Sex (male)	102	53.4	76	48.4	26	76.5	8.845	0.003
Race (white)	186	97.4	152	96.8	34	100.0	1.112	0.292
Socioeconomic status (not/low qualified worker)**	83	44.1	65	41.9	18	54.5	1.755	0.185
Urban area (yes)***	134	70.5	114	73.1	20	58.8	2.728	0.099
Living with family (yes)	134	70.2	106	67.5	28	82.4	2.938	0.086
Unemployed (yes)	74	38.7	63	40.1	11	32.4	0.712	0.399
Tobacco use (yes)	116	60.7	97	61.8	19	55.9	0.408	0.523
Cannabis use (yes)	74	38.7	60	38.2	14	41.2	0.103	0.748
Alcohol use (yes)	103	53.9	86	54.8	17	50.0	0.257	0.612

*All the diagnoses df = 5 $p = 0.130$

**"Baseline FLI ≥ 30 and <60" = 33

***"Baseline FLI < 30" = 156

indeterminate FLI (37/191; 19.4 %) or a FLI < 30, suggestive of absence of steatosis (106/191; 55.5 %).

As shown in the Fig. 1, 64.7 % of the individuals considered indeterminate at baseline, developed a FLI predictor of steatosis, most within the first 2 years. In contrast, only 16.6 % of the individuals who had a FLI < 30 (absence of steatosis) at baseline displayed a FLI predictor of steatosis during the follow-up period.

According to basal FLI, the group of higher risk of developing a predictor of steatosis (baseline FLI ≥30 and <60) was composed of a significant higher proportion of males (76.5 %; $p = 0.003$) and a mean age of 34.8 (SD 10.5) compared to the low risk group (baseline FLI < 30) (Table 1). A FLI predictor of steatosis developed significantly more frequently in men (75 %; $p < 0.001$), but there were no significant differences between the groups that showed a FLI ≥ 60 at endpoint and the remaining study population with respect to age, socioeconomic status, diagnosis, employment, place of residence, and consumption of tobacco, cannabis, or alcohol.

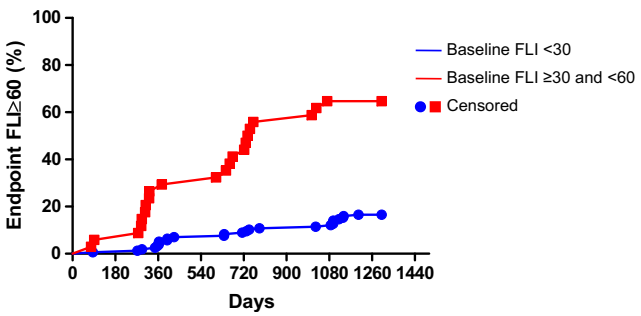

Fig. 1 Endpoint FLI ≥ 60 development according to basal FLI

As shown in Table 2, an endpoint FLI predictor of steatosis was significantly associated with changes in some of the metabolic syndrome criteria, as defined by the American Heart Association (Grundy et al. 2005), and in other biochemical and clinical parameters, compared to those in which steatosis was ruled out. Interestingly, we found a significantly higher proportion of patients with hyperinsulinemia, a surrogate marker of insulin resistance, in the FLI ≥ 60 group. The American Heart Association criteria for clinical diagnosis of metabolic syndrome are waist circumference ≥102 cm in men and ≥88 cm in women; tryglicerides ≥150 mg/dL; HDL <40 mg/dL in men and <50 mg/dL in women; systolic blood pressure ≥130 mmHg or diastolic blood pressure ≥85 mmHg;

Table 2 Metabolic and biochemical parameters comparison between patients with FLI ≥ 60 and <60 at endpoint

	Total		Endpoint FLI ≥ 60		Endpoint FLI < 60			
	N = 191		*N* = 48		*N* = 143			
Characteristics	*N*	%	*N*	%	*N*	%	χ^2 (df = 1)	*p*
Weight > 7 %	124	64.9	44	91.7	80	55.9	20.137	0.000
Glucose ≥ 100	22	11.5	7	14.6	15	10.5	0.591	0.442
GGT > 50	18	9.4	12	25.0	6	4.2	18.222	0.000
Triglycerides ≥ 150	34	17.8	26	54.2	8	5.6	57.944	0.000
HDL < 40 (<50 women)	45	23.6	20	41.7	25	17.5	11.671	0.001
Total cholesterol > 200	79	41.4	25	52.1	54	37.8	3.039	0.081
SBP ≥ 130 or DBP ≥ 85	14	8.1	8	19.5	6	4.5	9.422	0.002
Waist ≥ 102 (≥88 women)	53	27.7	33	68.8	20	14.0	53.758	0.000
Insulin > 17	22	11.8	10	22.2	12	8.5	6.243	0.012
Metabolic syndrome	13	6.8	12	25.0	1	0.7	33.457	0.000

Weight >7 % refers to the increase in weight during follow-up from baseline

Weight (kg), glucose (mg/dL), triglycerides (mg/dL), total cholesterol (mg/dL), waist circumference (cm), insulin (μU/mL)

GGT gamma glutamyl transferase (mg/dL), *HDL* high-density lipoprotein (mg/dL), *SBP or DBP* systolic or diastolic blood pressure (mm Hg)

and fasting glucose ≥100 mg/dL (Grundy et al. 2005). We did not find significant differences in these metabolic and biochemical parameters with respect to groups of treatment.

Discussion

We found that a significant proportion of patients develop a predictor of NAFLD in a somewhat short period of time after the first episode of their illness. Although none of the patients included in the analysis displayed significant liver fibrosis, it is remarkable how early a risk indicator of liver steatosis seems to appear in a considerable proportion of patients during the follow-up period. Because of the link between cardiometabolic risk, NAFLD, and antipsychotic medication, early detection of potential NAFLD development in clinical practice using non-invasive techniques could be worth considering, as these patients should be monitored to treat liver disease and the potential underlying cardiovascular disease risk factors (Liu and Nonalcoholic 2014). This constitutes a health problem that has still not been described in patients with schizophrenia spectrum disorders, who have a shorter life expectancy and a two- to threefold higher risk of dying from a cardiovascular disease than the general population.

Several limitations should be taken into account when interpreting our results. First, the lack of a placebo controlled group since all the subjects included in the sample were undergoing their first episode of psychosis and it was not possible to provide placebo from an ethical point of view. Second, although we have utilized a non-invasive assessment of NAFLD development in patients receiving antipsychotic medication, we are fully aware that these clinical data should be further confirmed using imaging techniques, liver stiffness and/or liver biopsy. Nevertheless, as it has been stated in current European guidelines on the diagnosis and management of NAFLD (EASL-EASD-EASO 2016) although ultrasound is the preferred first-line diagnostic procedure for the assessment of steatosis, in settings where imaging tools are not available or feasible, as in large epidemiological studies, validated serum biomarkers and scores (i.e., FLI) are an acceptable alternative for the diagnosis of steatosis. Third, the impact of diet and physical activity in our findings herein cannot be ruled out since a thorough description of these variables in our sample during follow-up was not available. Finally, we suggest that the results showed related to differences by groups of treatment should be considered cautiously, as our investigation design is an intention-to-treat study.

Our results support the importance of monitoring the potential NAFLD development in patients receiving antipsychotic medication for schizophrenia spectrum disorders. The early detection of features of NAFLD may lead to a more careful and accurate cardiovascular surveillance and management in this subset of patients.

Compliance with ethical standards The participants were drawn from an ongoing longitudinal intervention program of patients with first-episode psychosis, *Programa Asistencial de Fases Iniciales de Psicosis* (PAFIP), University Hospital Marqués de Valdecilla, Spain. In accordance with international standards for research ethics, the local institutional review board approved this program.

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