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Serum lipids in schizophrenia and other functional psychoses: a general population northern Finland 1966 birth cohort survey

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Objective: To compare fasting serum lipid concentrations of subjects with schizophrenia with a comparison group.
Method: The study sample consists of 5654 members of the northern Finland 1966 birth cohort who participated in the field study with blood samples after overnight fasting and clinical examination in 1997–98. Total cholesterol (TC), high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglycerides (TG) and glucose were analyzed. Analysis of variance were used for comparing differences in lipids means between diagnostic categories.
Results: Mean fasting TC in subjects with schizophrenia was 20 mg/dl higher than in the comparison group. TC and TG levels in the group of other psychoses resembled the schizophrenia group.
Conclusion: Blood lipid levels in subjects with schizophrenia and other functional psychoses were high. As these persons are at special risk for hyperlipidemia their lipid levels should be regularly monitored, and cholesterol lowering diet, as well as medication, should be considered.

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Introduction

Patients with schizophrenia tend be obese, and the antipsychotic-related weight gain is well documented in several studies (1–3). In addition, patients with schizophrenia are likely to have disturbances of glucose (4) and lipid regulation (5). The elevating effect of antipsychotics on serum lipids is well documented in several clinical-based studies involving typical neuroleptics (6, 7), and atypical neuroleptics (8–15) and recently in one large matched case–control study comprising 3.5 million subjects (16). Ryan et al (2003) (17) also showed that compared with the healthy subjects, the drug-naive, first-episode patients with schizophrenia had more often impaired fasting glucose tolerance and higher fasting plasma levels of glucose, insulin and cortisol. Hypercortisolemia may in turn explain hyperinsulinemia, hyperglycemia, and insulin resistance.

Hypercholesterolemia and hypertriglyceridemia are well known risk factors for coronary heart disease. Consequently, hyperlipidemia can have a negative effect on the prognosis in a patient with schizophrenia. The prognosis is often further adversely affected by other factors prejudicial to health, such as smoking and poor dietary habits (18). In subjects with schizophrenia the standardized mortality ratios (SMR) for disease of the circulatory, digestive, nervous and respiratory systems, in addition to suicides and accidental deaths, are higher than expected (19). In the case of circulatory disease this may be because of adverse metabolic disturbances in psychotic disorders (20).

In contrast to previous studies, we compared total cholesterol (TC), low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol and triglycerides (TG) in a prospective, geographically defined birth cohort at

age 31 years in subjects with schizophrenia and other functional psychoses with subjects never treated at the hospital because of any mental disorders. Lipid levels were controlled for Body Mass Index (BMI), alcohol consumption, smoking and sex.

Aims of the study

The aim of this study is to find whether there are significant differences in lipid levels: TC, LDL, HDL and TG, between patients with schizophrenia and other functional psychoses and subjects never treated at the hospital for any mental disorders.

Material and methods

Study sample

The northern Finland 1966 birth cohort is an unselected, general population birth cohort ascertained during mid-pregnancy. The cohort comprises 12058 live-born children in the two northern provinces of Lapland and Oulu with an expected delivery date during 1966 (21). The majority of the cohort members are Finns (white Caucasians) and $<1\%$ being Gypsies and Lapps. Permission to gather data was obtained from the Ministry of Social and Health. The study is reviewed by The Ethics Committee of the Faculty of Medicine of the University of Oulu.

In 1997, at the age of 31 years, 8463 of the members of the cohort currently living in northern Finland or in the capital area (Helsinki) were invited to a clinical examination. After complete description of the study to the subjects, written informed consent was obtained. Of those invited, 5983 subjects (71%) participated in the present study and gave written informed consent.

Psychiatric outcome

The national Finnish Hospital Discharge Register (FHDR) covers all general and mental hospitals. Its coverage and validity have been shown to be acceptable (22). Diagnoses in the FHDR during the period 1969–1986 were coded with the ICD-8 classification, in 1987–1995 with the ICD-9 along with DSM-III-R criteria (23), and since January 1, 1996 according to the ICD-10. All cohort members aged over 16 years appearing in the FHDR up till the end of 1997 with a FHDR diagnosis number 290–309 or 790.20 (ICD-8), 290–316 (ICD-9), or F00-F69 or F99 (ICD-10) were selected. All diagnoses were scrutinized and validated for the DSM-III-R criteria (24).

As non-fasting TG values differ significantly from fasting values (25), study subjects with non-fasting blood samples, as well as those with a failure in the laboratory tests, were excluded. Hence, the diagnostic categories and the final numbers in each were as follows:

1. Schizophrenia, defined as any individuals who at the time met DSM-III-R criteria ($n = 31$, 18 men) included: 295.11 ($n = 1$), 295.12 ($n = 2$), 295.30 ($n = 2$), 295.32 ($n = 3$), 295.90 ($n = 5$), 295.91 ($n = 2$), 295.92 ($n = 13$), 295.94 ($n = 3$).
2. Other psychoses, meaning all functional psychoses except DSM-III-R schizophrenia ($n = 21$, 11 men) included: 295.40 ($n = 7$), 295.70 ($n = 2$), 296.24 ($n = 1$) 296.34 ($n = 1$), 296.44 ($n = 4$), 297.10 ($n = 3$) 298.90 ($n = 3$).
3. Non-psychotic disorders ($n = 104$, 66 men): substance use disorders ($n = 42$), non-psychotic mood disorders ($n = 22$), anxiety disorders ($n = 15$), adjustment disorders ($n = 17$), personality disorders ($n = 17$), other non-psychotic diagnoses ($n = 17$). Multiple diagnoses were possible in this category, and the number of diagnoses exceeds the number of cases.
4. No psychiatric hospital treatment. A total of 5498 (2583 men) cohort members represented the unaffected population and served as the comparison group.

A more detailed description of the diagnostic validation and grouping is reported elsewhere (24, 26).

Lipid and glucose status

The participants were asked to fast overnight before a blood sample was taken. Serum glucose, TC, HDL and TG were determined by enzymatic methods using a Hitachi 911 Clinical Chemistry Analyzer (Boehringer Mannheim). Serum LDL was calculated by the Friedewald formula if the serum TG level was <354 mg/dl (27); if the TG level was ≥ 354 mg/dl, LDL was determined by precipitating LD-lipoproteins with heparin and measuring cholesterol in the liquid phase and subtracting it from TC. To translate SI units into US values the following conversion factors were used: for converting mmol/l to mg/dl the cholesterol values were divided by 0.02586, TG by 0.01129 and glucose by 0.0555.

Potential confounding and mediating factors

Overweight is associated with high blood cholesterol. In the field survey weight and height were

measured. The participants completed a questionnaire including items on body weight and height, alcohol consumption, smoking, and psychiatric medication. In cases without measured height or weight, BMI, (198 or 3.5% of cases, none in the schizophrenia or other psychoses groups) was calculated from the questionnaire answers. BMI < 25 was defined as normal, and ≥25 as overweight.

Smoking causes decreased HDL and hypertriglyceridemia (28). In our study subjects were considered smokers if they reported smoking at least occasionally, even if irregularly.

Alcohol increases HDL and TG (29). Alcohol consumption was also based on the questionnaire responses and converted to grams of absolute alcohol per day. Subjects were thereby divided into two categories: those drinking ≤15 g/day were considered light drinkers, and those drinking >15 g/day moderate drinkers. The cut-off points were adapted from Sillanaukee et al. (30).

Psychiatric medication at the time of blood sampling was identified on the basis of the questionnaire, referring to case records in cases of incomplete answers. The doses of antipsychotic medication were converted to chlorpromazine (CPZ) equivalent daily doses according to the Schizophrenia Patient Outcomes Research Team (PORT) Treatment Recommendations (31). Because these recommendations did not include CPZ equivalents of zuclopenthixol, its dosages were converted according to the Psychotropic Drug Directory 1999 (32).

Statistical methods

Hypotheses regarding differences in different diagnostic group means (serum lipid variables) were tested using analysis of variance (ANOVA). Potential confounding by sex, BMI, alcohol consumption and smoking was controlled in variance analysis. After performing ANOVA the following pairwise comparisons were used to compare schizophrenia, other functional psychoses and non-psychotic disorders with comparison group. Adjusting for multiple comparison was not performed. Caution should therefore be exercised over interpretation of marginally significant model. A chi-square test was used in analysis for categorical variables. TG was transformed to the natural logarithm to reduce skewness of the distribution. The non-parametric Kruskal–Wallis test was used in the analysis for glucose, and the Mann–Whitney *U*-test in the analysis of clinical course variables (days in hospital after diagnoses, proportion of time spent in hospital after diagnoses, number of treatment episodes in hospital after diagnoses, and age at onset). Two-tailed significance levels were used for all comparisons. All the statistical analyses were performed using the SAS software (version 8e) for Windows.

Results

In the schizophrenia group ($n = 31$) 16 had conventional medication, mean dosage 452 CPZ equivalents. Five subjects had atypical antipsychotic medication, mean dosage 725 CPZ equivalents per day. Five subjects had both atypical and conventional medication, mean dosage 580 CPZ equivalents. The mean daily dosage of antipsychotic medication with schizophrenia was 440 CPZ equivalents. In five of these 26 persons in the schizophrenia group we were able to identify the medicine in use but not the precise dose. These persons were not taken into account when mean dosages of medications were counted. Five persons did not report using any neuroleptic medication. Following data includes also persons with known type but not the precise dose of antipsychotic medication.

In the group of other psychoses ($n = 21$) five subjects had conventional medication, mean daily dosage 119 CPZ equivalents. One subject had atypical medication. The mean dosage of antipsychotic medication with other psychoses was 133 CPZ equivalents. Fifteen of 21 subjects did not report using any antipsychotic medication.

None of the subjects using antipsychotic medication reported taking any lipid lowering medication.

Missing data

Of all 8463 invited subjects 5983 (71%) participated in the field study. The rates of non-participants in different diagnostic categories were as follows: 51% in the schizophrenia group, 46% in the group of other psychoses, 48% in the group of non-psychotic disorders and 31% in the comparison group.

In order to evaluate possible selection bias in the groups with psychiatric hospital treatment we compared several clinical course variables between participants and non-participants: (i) days in hospital after diagnoses, (ii) proportion of time spent in hospital after diagnoses, (iii) number of treatment episodes in hospital after diagnoses, and (iv) age at onset. We found no major differences between non-participants and participants except in the schizophrenia group for days in hospital after diagnoses (median 381 days vs. 163 days,

respectively; $P = 0.078$) and proportion of time spent in hospital after diagnoses (median 0.11 vs. 0.06; $P = 0.059$), and in the group of other psychoses for the same variables (median 69 vs. 43; $P < 0.01$, and median 0.03 vs. 0.03, respectively; $P = 0.01$).

Mean TC (214 mg/dl) and TG (135 mg/dl) were significantly higher in the schizophrenia group than in the comparison group (196 mg/dl and 104 mg/dl, respectively) (Table 1). Mean TC (213 mg/dl) and TG (121 mg/dl) in the group of other functional psychoses were similar to schizophrenia group and TC and TG levels in hospital treated non-psychotic disorders (mean 194 mg/dl and 116 mg/dl, respectively) were similar to comparison group. No statistically significant differences were found in glucose levels between groups.

The proportions of sex, and overweight study subjects, light/moderate alcohol consumption, and smokers are presented in Table 2. Chi-Square test was used for analyzing potential confounding factors. Subjects with schizophrenia were more often overweight (58%) than subjects in the comparison group (40%). Subjects with schizophrenia were less often moderate drinkers (10% vs. 19%), and more persons with schizophrenia smoked (45% vs. 29%) than in the comparison group. All of these differences were statistically significant ($P < 0.01$).

In the schizophrenia group those who had both atypical and typical antipsychotic medication had the highest TC (Fig. 1) (median 243 mg/dl) and TG (Fig. 2) (median 154 mg/dl). Their median glucose level was 97 mg/dl. In schizophrenia subjects without any antipsychotic medication TC (median 198 mg/dl), TG (median 104 mg/dl) and glucose (median 92 mg/dl) were lower than in subjects using antipsychotic medication. The median glucose level in the group with atypical medication was 97 mg/dl. However, these differences were not statistically significant.

Discussion

As far as we know this is the first population based study of lipid and glucose levels among subjects with schizophrenia and other functional psychoses that also included subjects who did not use any antipsychotic medication for their psychotic disorder.

The TC and TG levels in subjects with schizophrenia were significantly higher compared with the comparison group. TC level was 8% higher in schizophrenia group than in the comparison group. A meta-analysis shows that a 10% change in the concentration of plasma TC is associated with 10%

Table 1. Serum total cholesterol, HDL- and LDL-cholesterol, and triglycerides in schizophrenia, other functional psychoses, non-psychotic disorders and the comparison group

					Analysis of variance†			
	Schizophrenia ($n = 31$) [mg/dl; mean (SD)]	Other functional psychoses ($n = 21$) [mg/dl; mean (SD)]	Non-psychotic disorders ($n = 104$) [mg/dl; mean (SD)]	Comparison group ($n = 5498$) [mg/dl; mean (SD)]	*F*-test between diagnostic categories $F_{(d.f.1,d.f.2)}$, *P*-value	Schizophrenia vs. comparison group $F_{(d.f.1,d.f.2)}$, *P*-value	Other functional psychoses vs. comparison group $F_{(d.f.1,d.f.2)}$, *P*-value	Non-psychotic disorders vs. comparison group $F_{(d.f.1,d.f.2)}$, *P*-value
Total cholesterol	214.1 (33.6)	212.8 (26.0)	194.2 (38.3)	196.4 (39.0)	$2.8_{(3,5413)}$, 0.038	$4.3_{(1,5413)}$, 0.039	$2.3_{(1,5413)}$, 0.130	$1.8_{(1,5413)}$, 0.180
HDL-cholesterol	55.9 (15.6)	58.1 (12.7)	57.0 (15.1)	60.5	$0.6_{(3,5413)}$, 0.622	$0.4_{(1,5413)}$, 0.527	$0.0_{(1,5413)}$, 0.900	$1.4_{(1,5413)}$, 0.242
LDL-cholesterol	131.5 (30.5)	130.6 (26.3)	115.6 (35.8)	116.3	$2.1_{(3,5397)}$, 0.101	$3.0_{(1,5397)}$, 0.082	$1.8_{(1,5397)}$, 0.176	$1.3_{(1,5397)}$, 0.251
Triglycerides	134.9‡	120.6	115.5	104.3	$1.8_{(3,5645)}$, 0.150	$4.8_{(1,5412)}$, 0.028	$0.2_{(1,5412)}$, 0.625	$0.3_{(1,5412)}$, 0.581

†Adjusted for sex, Body Mass Index, alcohol consumption and smoking.
‡Geometric mean.

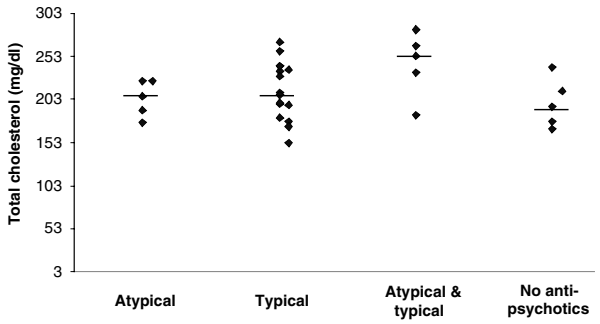

Fig. 1. Serum total cholesterol of subjects with schizophrenia according to type of medication.

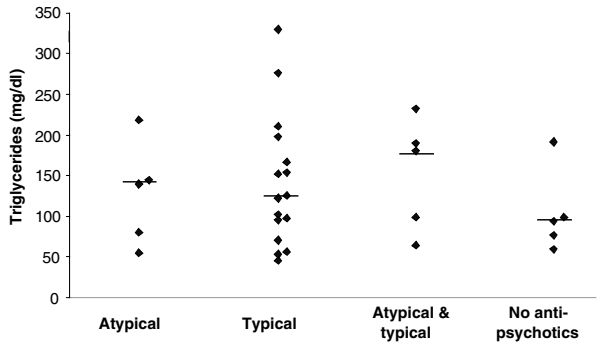

Fig. 2. Serum triglycerides of subjects with schizophrenia according to type of medication.

decrease of the odds of death (33). The effect of high plasma TG concentration on atherosclerosis and its complications is more controversial with some data supporting the role of plasma TG level as an independent risk factor (34). The higher TC level could be mainly because of higher LDL cholesterol. This is in accordance with the findings in many epidemiological studies. And also in this study the trend of the LDL cholesterol level across the various groups followed closely to that of the TC. The fact that the difference in LDL cholesterol between the schizophrenia and the comparison group did not reach statistical significance may simply reflect the lack of statistical power in the study. The correlation between TC and HDL cholesterol is much weaker and depends markedly on other confounders such as BMI and smoking which have a decreasing effect on HDL cholesterol (28) while alcohol consumption tends to increase it (29).

Lipid levels in the schizophrenia group resembled the group of other psychoses. This result is in concordance with the fact that most diagnoses in the group of other psychoses actually belong to the schizophrenia spectrum disorders. Some of the subjects in other psychoses group may have later met the criteria of schizophrenia.

Study subjects in the schizophrenia group with antipsychotic medication had higher TC and TG compared with those without any antipsychotic medication, and those with both atypical and typical antipsychotic medication had highest lipid levels. However, the within group analyses are somewhat unreliable when taking into account the small number of subjects. The results may also be confounded by different clinical profile of the subgroups. The mean dosage of antipsychotic medication in the schizophrenia group was in accordance with recommendations (31). Hence, high lipid levels were not because of excess dosage of antipsychotic medication.

Atypical neuroleptics are potent antagonists at both 5-HT_{2a} and 5-HT_{2c} receptors, with the latter implicated in hyperphagia and the subsequent development of obesity and adult-onset diabetes, although this does not seem to directly induce hyperlipidemia (10). In addition, study by Yamada et al. (1999) (35) suggest that 5-HT has a role in the regulation of leptin (an adiposity signal) secretion. Recently Baptista et al. (2001, 2002) (36, 37) suggested that neuroleptics may induce e.g. sudden body weight gain, insulin resistance and

Table 2. Gender, Body Mass Index, alcohol consumption, and smoking in schizophrenia, other psychoses, non-psychotic disorders and comparison group

	Schizophrenia ($n = 31$)	Other psychoses ($n = 21$)	Non-psychotic disorders ($n = 104$)	Comparison group ($n = 5498$)
Male	18 (58)	11 (52)	66 (63)	2583 (47)
Female	13 (42)	10 (48)	38 (37)	2915 (53)
BMI				
Normal (<25)	13 (42)	9 (43)	51 (50)	3292 (60)
Overweight (≥25)	18 (58)	12 (57)	52 (50)	2169 (40)
Alcohol consumption				
Light (≤15 g/day)	27 (90)	15 (75)	65 (66)	4313 (81)
Moderate (> 15 g/day)	3 (10)	5 (25)	34 (34)	1014 (19)
Smoking				
No	17 (55)	12 (71)	52 (50)	3842 (71)
Yes	14 (45)	9 (29)	52 (50)	1562 (29)

Values given are *n* (%).

increased appetite which, in turn, may be involved in the development of dyslipidemia in predisposed persons. However, we could not estimate the contribution of medication, diet and physical exercise, among other things, to lipid levels. In our study, subjects using conventional neuroleptics also had high lipid levels, although these medications are not 5-HT_{2c} receptor antagonists. Hence, the findings highlight the importance of health habits.

Our longitudinal data are unique and extensive, representing a geographically well defined and unselected general population. High rates of follow-up over three decades and the use of record linkage minimized selection, information and recall biases. There are number of methodological points to consider, however. The major weakness of the study is the small sample size of the psychiatric patients, which are further divided to subgroups according to the pharmacological treatment. The rarity of schizophrenia and other functional psychoses means that Type II statistical errors are possible. The beta value was 28%, i.e. slightly higher than generally accepted. There is also the possibility of Type I errors, as multiple comparisons were performed, and this was not taken into account in analyses. The self-reported smoking and alcohol use are somewhat unreliable but we do not believe that this has affected our results.

The higher level of TC, particularly its more atherogenic component LDL cholesterol, could have important clinical implications in the therapeutic management of schizophrenia and other functional psychoses. Although there are recommendations on the treatment of hyperlipidemia (38), there are not special recommendations for treating psychosis patients. Although healthier diet and physical exercise are recommended, there is currently very limited evidence available that behavioral interventions in overweight patients treated with antipsychotics actually work (1). Ideally, a weight restriction program that includes either habitual or formal exercise should be tailored to patient needs at the outset of antipsychotic treatment and the program should then be regularly monitored (2). Psychotic patients with lipid metabolism disorders can also be treated with e.g. statins, with careful consideration of potential interactions with antipsychotic medications. It is also important to remember that even if the initial dosage of antipsychotic medication to relieve an acute symptom episode exceeds the recommendations for the maintenance therapy, efforts should be made to reduce the dosage gradually. Moreover, because there may be a relationship between the dose of antipsychotic agent and weight gain (39), the lowest effective dose should be used. These are all important concerns in relation to the excess morbidity and mortality typical of persons with schizophrenia.

In conclusion, we found high lipid levels in subjects with schizophrenia and other functional psychoses, even among those in their early 30's and especially if taking both atypical and typical medication. Because of the small number of subjects in the subgroups further studies are needed to confirm our findings. High lipid levels are associated with increased morbidity from coronary heart disease among other things. Our results indicate the importance of including lipid status in the somatic examination. The combination of conventional and atypical neuroleptics should be very carefully considered, and specifically in these cases lipid levels should be monitored regularly.

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