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Polyunsaturated fatty acids deficits are associated with psychotic state and negative symptoms in patients with schizophrenia

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ABSTRACT

The study was aimed to examine membrane polyunsaturated fatty acids (PUFAs) profile in patients with schizophrenia (SZ) before and after antipsychotic medication and test their association with psychopathology. Erythrocyte membrane fatty acids were analysed by gas chromatography in 36 drug-free patients with SZ and 36 controls. Psychometric evaluation and blood sampling were achieved at baseline and after 3 months of antipsychotic treatment. At enrolment, levels of total PUFAs and arachidonic (AA) and docosahexaenoic (DHA) acids were significantly lower, but ω6/ω3 PUFAs ratio was higher in patients. AA and DHA were negatively related to the Andreason's scale for assessment of negative symptoms (SANS) score. DHA was inversely related to "alogia", "anhedonia", "avolition", and "blunted affect" subitems of SANS. After 3 months under typical antipsychotic drugs, fatty acid profile turned into comparable to controls in parallel with psychopathology improvement. Data indicate that PUFAs deficits are associated with psychotic state and negative symptoms of SZ.

1. Introduction

Polyunsaturated fatty acids (PUFAs) are important components of membrane cells and neurological tissue. PUFAs, especially arachidonic acid (AA) and docosahexaenoic acid (DHA) are particularly important for the central nervous system structure and function [1]. Since the hypothesis originally issued by David Horrobin almost 30 years ago [2], the accumulated evidence suggests an altered phospholipids and PUFAs metabolism in patients with schizophrenia (SZ). Most studies reported that SZ is associated with PUFAs deficiency [3–10]. However, there is disagreement about which PUFAs are deficient [ω6, ω3 or both], and about the association between PUFAs deficits and psychotic state and symptoms. Studies were conducted in chronically medicated, drug-free or never-medicated patients that may explain variability of findings. Furthermore, the clinical significance of altered PUFAs levels in SZ is not clear and its underlining mechanisms are not well understood. Whether PUFAs alterations are a part of the biological predisposition to SZ or are associated only with existing psychotic state is unclear. Also, whether antipsychotic drugs modify fatty acid metabolism in SZ patients and how is unsolved. These questions may be addressed by studying PUFAs profile in a cohort of drug-free patients during the psychotic state and after stabilization under antipsychotic medication. This study was aimed at examining erythrocyte membrane fatty acids profile in drug-free patients with SZ, to test the association between PUFAs deficit and the symptoms of SZ, and to tag on eventual change in PUFAs levels after improvement of psychopathology under antipsychotic drugs.

2. Methods and materials

2.1. Subjects

This case–control study included 36 male patients with SZ and 36 healthy male subjects matched according to age and smoking habits. Patients were consecutive male subjects responding to DSMIV-TR criteria of SZ [11], admitted in Psychiatry Department (Razi Hospital Manouba, Tunisia), who were in withdrawal of antipsychotic drugs for over 3 months. Diagnosis was confirmed by two senior experienced psychiatrists. At enrolment, clinical assessment and blood collection were achieved in all patients and psychometric tests were completed in 32 patients. Patients were started with antipsychotic and were asked to attend the service after 12 weeks. Antipsychotic medication consisted of typical antipsychotic with most of patients were taking phenothiazine.

Abbreviations: PUFAs, polyunsaturated fatty acids; SZ, schizophrenia; AA, arachidonic acid; DHA, docosahexaenoic acid; SANS, Andreason's scale for assessment of negative symptoms; SAPS, Andreason's scale for assessment of positive; PANSS, the positive and negative syndrome scale; GAF, the global assessment of functioning; CGI, the clinical global impression scale

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After 12 weeks of treatment, only 16 patients went back to the service. Among these, 12 patients were taking phenothiazine and 4 patients were taking haloperidol.

The control group was composed of 36 healthy subjects with no personal or familial history of psychiatric trouble. Exclusion criteria for both patients and controls were acute or chronic physical or mental illness (except SZ for patients), history of severe cranial trauma, substance abuse or dependence (except tobacco) according to the DSMIV-TR criteria [11] and mental deficiency based on the axe II of the DSMIV-TR [11]. Patients with important maniac or depressive symptoms were also excluded. The study was approved by the Razi Hospital Ethic Committee. Written informed consent was obtained from all participants in this study. The family's consent was required when the patient's mental status did not allow him to give his consent.

2.2. Psychometric evaluation

At enrolment, before administration of antipsychotic drugs, and after 3 months under antipsychotic treatment, patients were assessed by the following psychometrics instruments: Andreason's scale for assessment of positive symptoms (SAPS), Andreason's scale for assessment of negative symptoms (SANS); the positive and negative syndrome scale (PANSS); the global assessment of functioning (GAF) and the clinical global impression scale (CGI).

2.3. Erythrocyte fatty acids analysis

Fasting venous blood specimens were drawn into tubes containing EDTA, and centrifuged at 4000 rpm for 10 min. Buffy coats and plasma were removed and the erythrocytes were washed three times in isotonic saline and stored at −80 °C until analysis. The packed cells (400 μl) were lysed with 10 ml of cold distilled water and centrifuged at 4000 rpm for 20 min to form a tight pellet. Supernatant was removed, and the above procedure was repeated until supernatant was clear. FAs were transformed to their methyl esters in the presence of acetyl chloride, according to the method by Moser and Moser [12]. Briefly, 100 μl of heptadecanoic acid (C17:0) (400 mg/l) as internal standard was added to erythrocyte membranes. Then 1 ml of 25% (v/v) methylene chloride in methanol and 200 μl of acetyl chloride were added and heated for 1 h at 75 °C. After cooling, 4 ml of 7.0 wt% K_2CO_3 was added to stop the reaction. The resulting fatty acid methyl esters were extracted with 5 ml of hexane, followed by extraction with 2.5 ml of acetonitrile to remove polar compounds. The hexane layer was collected and evaporated to dryness under nitrogen. The dry residue was reconstituted in 20 μl of hexane to be analysed by gas chromatography.

2.4. Gas chromatography analysis

Analyses were performed with a gas chromatograph model 6890N (Agilent Technologies), equipped with a split/splitless capillary Intel system and a flame ionization detector. The injector and detector temperatures were 230 and 280 °C, respectively. Sample (1 μl) was injected into an Innowax capillary column; dimensions 30 m × 0.25 mm; I.D., 0.25 μm film thickness (Agilent Technologies). The flow-rate of nitrogen as the carrier gas was set to 1.5 ml/min in a constant flow mode. The oven temperature was held at 150 °C for 1 min, then programmed at a rate of 15 °C/min increase up to 210 °C and kept constant during 5 min then subsequently programmed to 250 °C at a rate of 4 °C/min. The method was calibrated by injecting the standard fatty acid mixture in approximately equal proportions under identical conditions. Values of FAs are reported as the percent of total fatty acids.

2.5. Statistical analysis

The difference between groups was compared by ANOVA analysis or the Mann–Whitney *U* test. Association between continuous variables was tested by Pearson correlation analysis. Reported *p*-values were based on two-tailed calculations, and all statistical analyses were carried out using SPSS for windows 11.0 software (SPSS Inc., Chicago, USA).

3. Results

Clinical characteristics of patients and psychometric measures at enrolment and after 3 months of antipsychotic treatment are shown in Table 1. At enrolment, erythrocyte membrane fatty acids profile showed significant increase in saturated fatty acids levels and decrease in PUFAs levels in patients compared to controls. Levels of AA and DHA were significantly lower in patients with SZ. No significant difference was observed for others PUFAs between the two groups. The ω6/ω3 ratio was significantly higher in patients with SZ (Table 2).

The search for correlation between PUFAs and psychometric scores showed that SANS was negatively related to dihomo-gamma linolenic acid ($r=-0.411$; $p=0.019$), AA ($r=-0.345$; $p=0.05$), DHA ($r=-0.541$; $p=0.001$) and total PUFAs ($r=-0.375$; $p=0.034$) (Fig. 1). DHA was inversely related to subitems of SANS alogia ($r=-0.350$; $p=0.05$), anhedonia ($r=-0.490$; $p=0.004$), avolition ($r=-0.370$; $p=0.037$), disturbed attention ($r=-0.400$; $p=0.023$) and blunted affect ($r=-0.414$; $p=0.018$). AA was inversely related to disturbed attention ($r=-0.406$; $p=0.021$) (Fig. 2). Moreover, levels of AA, DHA, and total PUFAs tended to

Table 1
Clinical characteristics at baseline and psychometrics scores in antipsychotic drugs free schizophrenia patients at baseline (SZ-BL) and after 3 months of treatment (SZ-3).

	Controls ($n=36$)	SZ-BL ($n=36$)	SZ-3 ($n=16$)	p
Age, years	34.2 (9.6)	36.6 (9.1)	34.4 (8.6)	0.51
Smokers, %	55.6	58.3	56.3	0.88
Age of onset, years	–	26.4 (6.4)	26.7 (6.3)	0.87
Duration of disease, years	–	10.3 (7.95)	9.4 (7.3)	0.70
SAPS[a]	–	81.56 (26.15)	27.47 (22.78)	< 0.001
SANS[a]	–	64.81 (23.69)	42.07 (19.28)	0.002
PANSS[a]	–	110.5 (20.95)	65.27 (17.05)	< 0.001
GAF[a]	–	29.48 (4.88)	58.6 (7.89)	0.002
CGI[a]	–	5.83 (0.83)	1.75 (0.68)	< 0.001

Results are expressed as means (SD) or percent; SAPS, Andreason's scale for assessment of positive symptoms; SANS, Andreason's Scale for assessment of negative symptoms; PANSS, the positive and negative symptoms scale; GAF, global assessment of functioning; CGI, the clinical global impression scale; *p*, SZ-3 compared to SZ-BL.

[a] Psychometrics scores was performed in 32 patients at enrolment and 16 patients after antipsychotic treatment.

Table 2
Red blood cell membrane fatty acids profile in drug-free schizophrenia patients at baseline (SZ-BL) and after 3 months of antipsychotic treatment (SZ-3) compared with controls.

	SZ-BL ($n=36$)	SZ-3 ($n=16$)	Controls ($n=36$)	p	P^a
C16:0	32.54 (4.57)	30.33 (3.91)	29.98 (1.49)	0.003	0.74
C18:0	23.15 (3.3)	21.41 (2.99)	22.95 (3.03)	0.787	0.11
C18:1 ω9	15.99 (2.04)	16.50 (2.96)	15.81 (2.13)	0.726	0.36
C18:2 ω6	11.83 (2.4)	12.59 (2.17)	12.00 (1.76)	0.729	0.32
C20:3 ω6	1.24 (0.6)	1.54 (0.54)	1.41 (0.41)	0.156	0.36
C20:4 ω6	9.07 (4.79)	10.28 (4.56)	11.07 (2.90)	0.036	0.46
C20:5 ω3	0.51 (0.53)	0.36 (0.23)	0.41 (0.12)	0.28	0.39
C22:5 ω3	0.99 (0.58)	1.29 (0.69)	1.09 (0.41)	0.398	0.30
C22:6 ω3	1.88 (1.05)	2.33 (1.40)	2.81 (0.56)	<0.001	0.24
SFAs	57.71 (7.53)	52.96 (6.34)	53.77 (3.9)	0.041	0.66
MUFAs	16.8 (2.11)	17.36 (3.14)	16.58 (2.13)	0.654	0.31
PUFAs	26.49(8.78)	29.67 (8.32)	29.65 (4.61)	0.06	0.99
ω6 PUFAs	22.88 (7.20)	25.28 (6.45)	25.27 (4.17)	0.029	0.99
ω3 PUFAs	3.61 (1.84)	4.39 (2.05)	4.39 (0.69)	0.020	0.99
ω6/ω3 ratio	7.55 (3.58)	6.74 (2.63)	5.80 (0.83)	0.006	0.21

Values represent mean (SD) of the percent of total fatty acids; SFAs, saturated fatty acids; MUFAs, monounsaturated fatty acids; PUFAs, polyunsaturated fatty acids; p, SZ-BL compared to controls; P^a, SZ-3 compared to controls.

decline through the SANS tertiles. This decrease was significant for DHA (2.48 ± 1.20; 1.71 ± 0.92 and 1.23 ± 0.80; $p=0.02$) and ω3 PUFAs (4.49 ± 2.28; 3.36 ± 1.44 and 2.50 ± 1.47; $p=0.05$), for the first, the second and the third tertile of SANS values, respectively (Fig. 3). No correlation was observed between PUFAs levels and other psychometric test's scores.

After 3 months under antipsychotic drugs, in parallel with psychopathology improvement, fatty acid profile turned to be comparable with controls (Table 2). No significant correlations persisted between PUFAs and psychometric scores.

4. Discussion

This study showed decreased erythrocyte membrane PUFAs levels in patients with SZ. These data are in accordance with numerous studies [3–10] and support the hypothesis of altered PUFAs metabolism in SZ. PUFAs, mainly AA and DHA, are concentrated in neuronal membranous phospholipids, including the myelin sheath [1,13]. They are important in the regulation of many biochemical events including neurotransmitter release and uptake, receptor function and various processes in the central

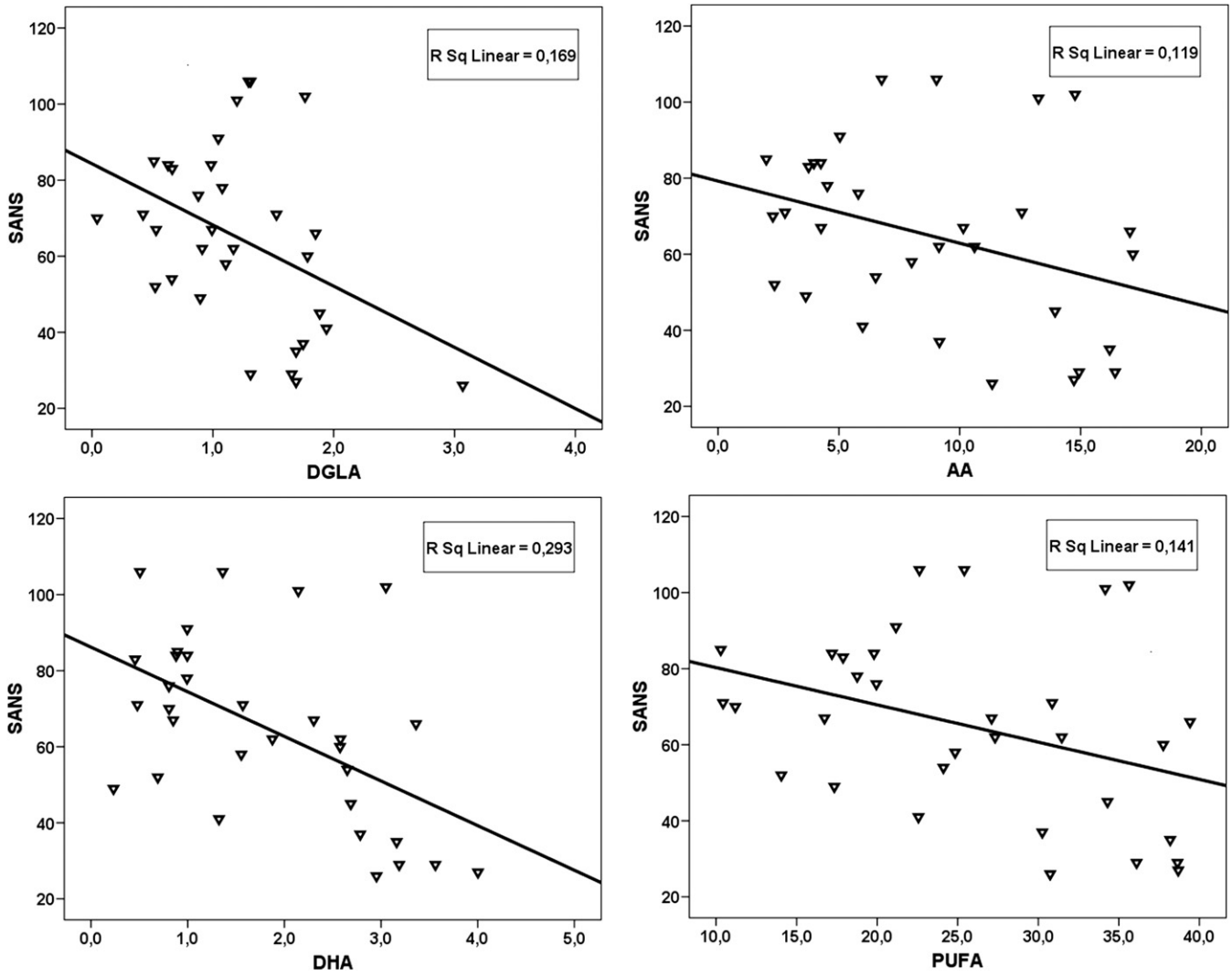

Fig. 1. Correlations between Andreason's scale for assessment of negative symptoms (SANS) and dihomo-gamma linolenic (DGLA), arachidonic (AA), docosahexaenoic (DHA) acids and total polyunsaturated fatty acids (PUFAs) levels in patients with schizophrenia ($n=32$).

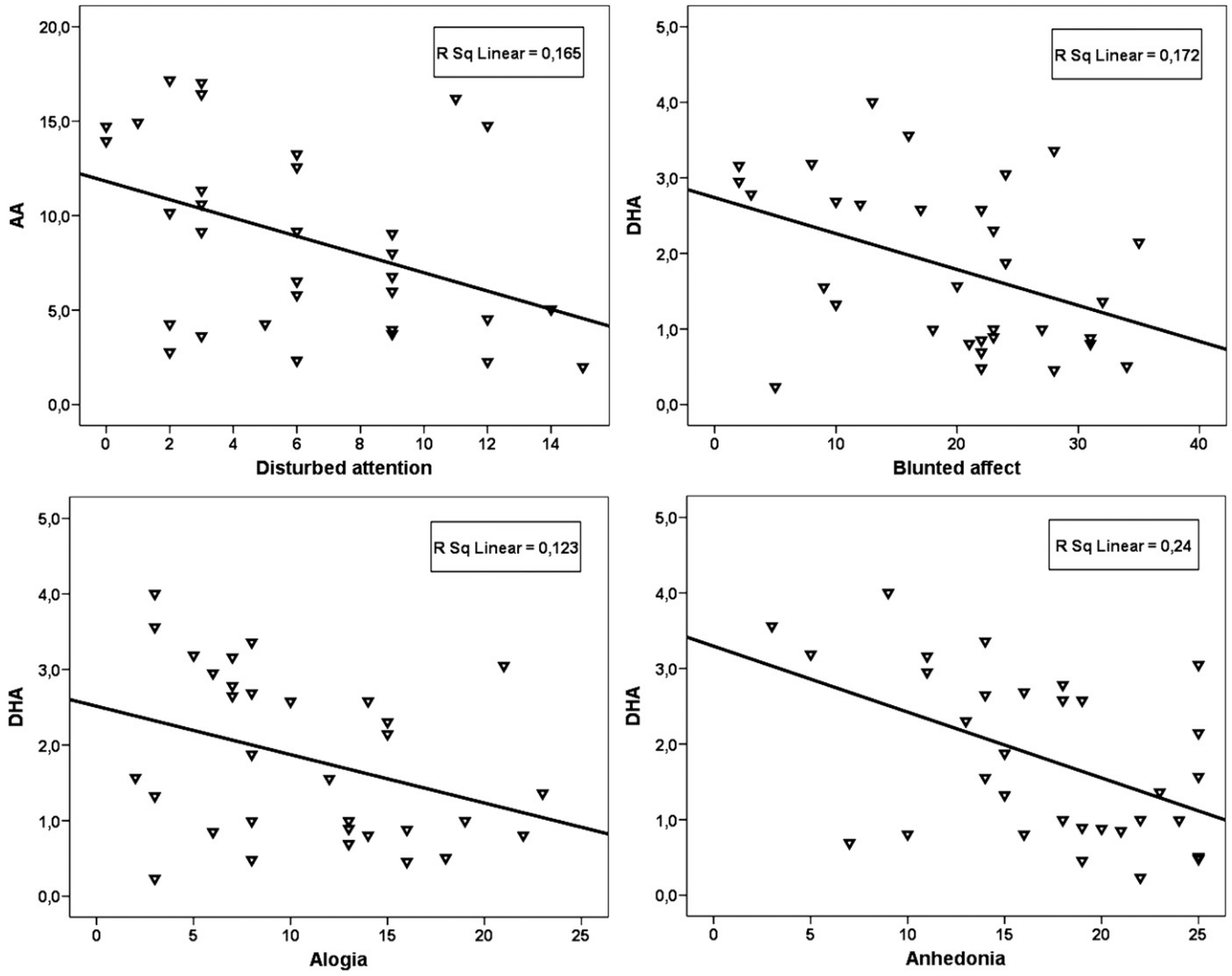

Fig. 2. Correlations of some subitems of Andreason's scale for assessment of negative symptoms (SANS) with arachidonic (AA) and docosahexaenoic (DHA) acids and in patients with schizophrenia ($n=32$).

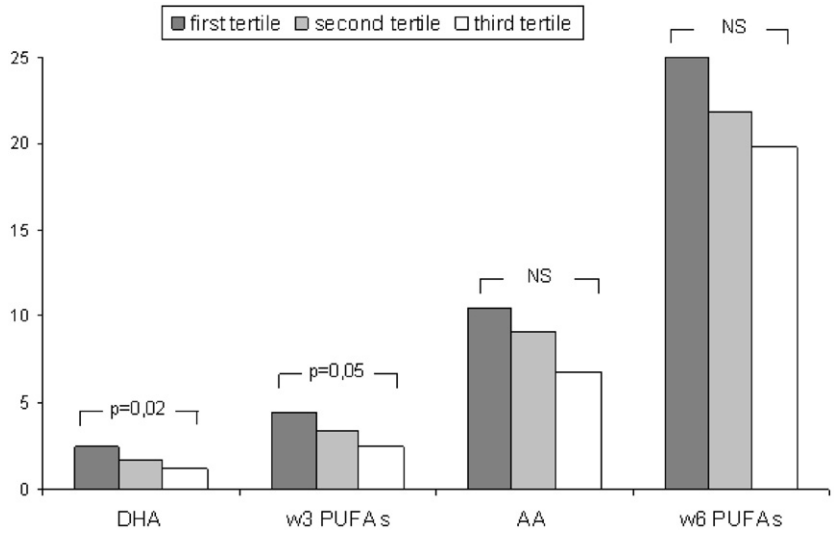

Fig. 3. Variation of erythrocyte membrane arachidonic (AA), docosahexaenoic (DHA) acids and ω3 and ω6 polyunsaturated fatty acids (PUFAs) levels in patients with schizophrenia according to Andreason's scale for assessment of negative symptoms tertiles ($n=32$).

nervous system [14–17]. Accordingly, the link between membrane PUFAs deficits and SZ is understandable.

A number of mechanisms may account for these deficits such as inadequate dietary supply, smoking, decreased desaturation and incorporation in cell membranes, oxidative stress-induced degradation and high phospholipids breakdown through increased phospholipase A2 activity [6,9,18–22]. Nevertheless, the exact cause of altered PUFAs metabolism in SZ is still unknown and whether PUFAs deficit is a contributor, a consequence, or an epiphenomenon of SZ remains unclear. Smoking may contribute to PUFAs deficit in patients with SZ [18,23]. However, it is unlikely that the erythrocyte PUFAs deficit observed in this study are related to smoking since the patients and controls were well-matched according to smoking status.

Some studies reported decreased levels of both ω6 and ω3 PUFAs [3–6,10]. Others showed that only ω3 PUFAs are decreased [7,8,22]. Discrepancies may be linked to the confounding effect of disease-related factors such state of illness, duration of disease and antipsychotic medication. Other factors such as age, body mass, tobacco consumption, fish intake and genetics may affect PUFAs status, which would explain the reduced omega-3-index (RBC EPA+DHA) in Tunisians compared to other populations [24,25]. In this study, both ω6 (AA) and ω3 (DHA) PUFAs were decreased, but ω6/ω3 ratio was increased. As omega-3 fatty acids have been considered a cardio-metabolic protector agent [26], the increase of ω6/ω3 ratio in patients with SZ may explain the higher cardio-metabolic risk in SZ [27,28].

This study showed an inverse relationship of PUFAs, especially DHA and AA with SANS, and its subitems alogia, anhedonia, avolition, disturbed attention and blunted affect, suggesting that PUFAs deficits are associated with negative symptoms of SZ. Accordingly, it was demonstrated that supplementation with ω3 rich fish oil results in significant improvement of negative, but not positive symptoms [29]. In SZ, it is assumed that hypofunction of the cortical and prefrontal dopamine systems contributes to negative symptoms and cognitive disorders and that hyperactivity of the subcortical and limbic dopamine systems causes positive symptoms [30]. Otherwise, it was demonstrated that ω3 PUFAs deficiency is associated with impairment in dopamine neurotransmission [31]. McNamara and colleagues [32] showed that PUFAs levels are reduced in the orbitofrontal regions of brains of patients with SZ that may explain the association between PUFAs deficits and negative symptoms.

An interesting finding of this study was the correction of PUFAs deficits, in parallel with symptoms improvement, under antipsychotic medication. These findings suggest that PUFAs deficit is related to psychotic state, but not to schizophrenic illness. In agreement with this assumption, Richardson and colleagues [33] found no PUFAs deficits in subjects with schizotypal traits. Our data also suggest an effect of antipsychotics on PUFAs metabolism. Early studies by Yao et al. [3] found that erythrocyte PUFAs composition was reduced by the typical antipsychotic haloperidol, whereas later studies using either typical or atypical medications found positive effects [6,8,9], similar to those of present study. It was shown that antipsychotic medication increases peripheral and central PUFAs levels in SZ patients by increasing PUFAs biosynthetic enzyme expression and/or activities [34–36]. However, it is not clear whether the correction of PUFAs profile is related to the direct effect of antipsychotic or to the improvement of psychopathology under antipsychotics.

Some limitations of the current study are to be mentioned, especially a small sample size. In reality, the constraint of including only drug-free patients had limited their number. The well-known tendency of most patients with SZ to break their treatment and monitoring [37] explain the reduced number of patients reviewed after antipsychotic treatment. Dietary intake that may influence fatty acid profile was not assessed. In practice, assessing dietary habits in patients with schizophrenia is complicate.

In summary, this study showed an altered PUFAs metabolism in free antipsychotic drugs patients with SZ. Data clearly indicate that PUFAs deficits are associated with the psychotic state, in particular with the negative symptoms of SZ. Antipsychotic drugs seem to normalize PUFAs levels in parallel with improvement of psychopathology. However the underlying mechanisms remain unclear. Further investigations are needed to fully understand the complex relationship between phospholipids and fatty acids metabolisms, psychopathology, and the effects of antipsychotic medication.

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