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Dietary fatty acid and antioxidant intake in community-dwelling patients suffering from schizophrenia

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Abstract

Introduction: Brain phospholipids are uniquely rich in polyunsaturated fatty acids (PUFAs). Most PUFAs such as α-linolenic acid 18:3(n-3), eicosapentaenoic acid 20:5(n-3), and docosahexaenoic acid 22:6(n-3) are essential and must be provided through the diet. PUFAs are also very sensitive to oxidative stress. Decreased essential fatty acid content has been observed in cell membranes of various tissue types of schizophrenia patients, including neural cell membranes. A number of mechanisms may account for these deficits, such as inadequate dietary supply or increased oxidation. It is known that patients with schizophrenia make poor dietary choices. However, whether their dietary fatty acid or antioxidant intake is insufficient and contributes to the observed deficiencies has not been assessed.

Methods: After obtaining informed consent, a 24-h diet recall was administered to elicit nutritional information in 146 outpatients with schizophrenia. Intake of fatty acids and antioxidants including vitamins A, C, and E was compared to U.S. population standards according to the National Health and Nutrition Examination Survey Cycle III (NHANES III) results.

Results: Saturated and polyunsaturated fatty acid (PUFA) intake was significantly higher in schizophrenia patients than in controls ($p \leq 0.05$; $p \leq 0.005$, respectively). No differences were found with regard to dietary intake of γ-linolenic acid (18:3n-3), eicosapentaenoic acid (20:5n-3) and docosahexaenoic acid (22:6n-3). Similarly, antioxidant intake was not different between schizophrenia patients and controls.

Conclusion: The observed cell membrane deficits in PUFA and essential fatty acid content do not appear to derive from decreased dietary supply. Rather, intrinsic membrane phospholipid metabolism abnormalities may be causative. Overall increased fat intake in schizophrenia patients may contribute to the development of serious medical comorbidities, and further advance the risk for cumbersome metabolic side effects of antipsychotic treatment such as new-onset diabetes mellitus.

Keywords: Fatty acids; Nutrition; Schizophrenia; Dietary intake; Antioxidants

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1. Introduction

Saturated and monounsaturated fatty acids can be synthesized within the body. However, several polyunsaturated fatty acids (PUFAs), such as α-linolenic acid (18:3n-3), docosahexaenoic acid (22:6n-3) and eicosapentaenoic acid (20:5n-3), are essential and need to be supplied through the food chain. PUFAs constitute parts of various cell membrane phospholipids, especially neural cell membranes. Together with cholesterol, they form most of the cell membrane bilayer, and are closely associated with receptors, ion channels and other cell signalling entities.

One large-scale epidemiologic study has observed a highly significant correlation between fat intake and schizophrenic symptoms (Christensen and Christensen, 1988). The authors suggest that the ratio of saturated fat to PUFA in the diet correlates with the long-term outcome of schizophrenia. For example, they found that the saturated fat to PUFA ratio in the United states was 1.89: 1, whereas the ratio in India was 1: 0.29, and 1: 0.1 in Nigeria. Essentially, countries with a higher ratio and thus increased saturated fat intake from land animal and bird sources had worse outcome of schizophrenia than countries with relatively higher PUFA intake from sources such as fish, seafood and vegetables, thereby confirming the observation of a better outcome of schizophrenia in developing countries than in industrialized countries (World Health Organization, 1979).

Recently, abnormalities in cell membrane phospholipid metabolism of patients with schizophrenia have been described, including abnormally low in vivo and post-mortem PUFA brain content (Yao et al., 2002; Pettegrew et al., 1991; Yao et al., 2000); or low PUFA content of red blood cell membranes (Assies et al., 2001; Peet et al., 1995) and skin fibroblasts (Mahadik et al., 1996). Clinically, outcome of patients who had improvements in PUFA levels of RBC membranes was more favourable (Evans et al., 2003). Importantly, neuronal cell membrane PUFA content may modify neural function (Fenton et al., 2000) through at least two mechanisms. First, both receptors and ion channels are embedded in a phospholipid matrix and changes in the local microenvironment may be followed by physical disposition changes with subsequent altered binding characteristics (Peet, 2003). Second, essential fatty acids (EFA) are the precursors of prostaglandins, leukotriens, and eicosanoids; and via the phospholipase A2 and cyclo-oxygenase cycles, they are involved in countless signalling processes throughout the body; with the eicosanoids likely fulfilling a special role in long-term synaptic plasticity (Wainwright, 1997). Horrobin et al. (1994) proposed a disorder of membrane phospholipid metabolism as a biochemical basis for schizophrenia. Specifically, excessive loss of polyunsaturated fatty acids through increased phospholipase A2 activity has been implicated, involving increased EFA release from phospholipids that are normally used for cell signalling and prostaglandin synthesis. This would eventually lead to EFA depletion of cell membranes and change the physical cell membrane composition (Horrobin, 1998), since EFAs are replaced by non-essential fatty acids with different stereochemical structures.

The theoretical framework has received support through several clinical trials supplementing PUFAs along with regular antispychotic treatment (Freeman, 2000). While only few trials did not show efficacy of PUFA supplementation (Fenton et al., 2001), most trials have produced promising additional improvements in schizophrenia symptomatology along with conventional pharmacotherapy (Mellor et al., 1996; Emsley et al., 2002; Peet et al., 2001). One trial has used PUFAs as monotherapy for the treatment of schizophrenia with partial success (Peet et al., 2001). For a systematic review of trial results, please refer to Joy et al. (2003).

Brain PUFAs are also exquisitely sensitive to oxidation. This is especially important, since the brain has a very active aerobic metabolism, and, at the same time, relatively poor antioxidant defenses. There is evidence that oxidative stress may contribute to PUFA depletion and cell membrane damage in schizophrenia (Mahadik et al., 2001), both through excessive free radical generation and impaired antioxidant defenses (Reddy et al., 2003; Mahadik and Mukherjee, 1996). Additionally, some antipsychotics such as haloperidol have oxidative capabilities per se, and long term extrapyramidal side effects from these compounds may in part be explained by neuronal degeneration through oxidative cell membrane damage (Jeding et al., 1995; Sachdev et al., 1999; Gunne and Arden, 1993). The potent antioxidant vitamin E has been

used to ameliorate symptoms of tardive dyskinesia (TD) with some success (Egan et al., 1997; Michael et al., 2002). At the same time, lack of treatment success has also been reported (Shiriqui et al., 1992). Moreover, the same group reported conflicting results on the efficacy of vitamin E in the treatment of TD (Adler et al., 1998, 1999). Overall, reviews provide modest evidence that vitamin E may be beneficial in the treatment of TD (Barak et al., 1998); and protect against deterioration of TD (Soares and McGrath, 2000). More recent studies have supported the findings of a positive effect of vitamin E in the treatment of TD (Zhang et al., 2004).

Since there is evidence that dietary fatty acid composition may influence cell membrane phospholipid composition (Wainwright, 2002; Abedin et al., 1999; Kwon et al., 1991; Lopez et al., 1991), and that antioxidants may exert direct neuroprotective functions and ameliorate side effects introduced through routine antipsychotic treatment, we decided to examine the actual dietary intake of various fatty acids and the most common dietary antioxidants vitamins A, E, and C in schizophrenia patients. Similarly, given the reported association between intake of certain fats and long-term outcome parameters in patients with schizophrenia (Christensen and Christensen, 1988), a quantification of factual intakes of various fats and fatty acids may prove useful for eventual translation into clinical treatment considerations such as choice of specific PUFAs for supplementation or provision of specific dietary recommendations for reduction of i.e. saturated fat intake.

2. Methods

Informed consent was obtained according to procedures approved by the University of Pittsburgh Institutional Review Board. The sample was one of convenience and consisted of outpatients at the Comprehensive Care Services (CCS) at Western Psychiatric Institute and Clinic. This outpatient facility is devoted to the treatment of patients with schizophrenia, and related disorders. As the only such specialized treatment program in Western Pennsylvania, the clinic draws patients from all across this region. It also serves a disproportionate number of poor and minority individuals. Sociodemographic data were obtained by open ended questions and, in case of missing information: data were completed by patient chart review. The first author conducted 24-h diet recalls using standardized food models to collect the nutritional information and estimate portion sizes; after receiving thorough training and instruction by a registered dietician. The 24-h recall method is widely regarded as suitable for the purpose of gathering dietary intakes (Madden et al., 1976; Young et al., 1952) and has been employed in the NHANES National Health and Diet Surveys (Kohlmeier, 1992). Nutritional values (total fat, saturated fat, vitamin E, etc.) were computed using the commercially available ESHA Food Processor Nutrition software 7.5 (Lee et al., 1995) and compared to nutritional data for the general population of similar age from NHANES III (National Health and Nutrition Examination Survey, Cycle III). Importantly, both the NHANES surveys and the ESHA Food Processor calculate nutritional values according to values obtained from the vast USDA (United States Department of Agriculture) database.

SPSS (for windows) software was employed for data analysis. Descriptive analysis including mean, range and standard deviation for continuous variables was carried out to determine whether the variables were normally distributed and frequency counts for categorical data (for example gender, race, etc.) were done to examine the proportions of various sociodemographic characteristics. The measures obtained through the 24-h diet recall were examined for the whole group, for males and females and for Caucasians and African-Americans. Individual micronutrient intakes such as intake of α-linolenic acid, eicosapenaeonic acid, docosahexaenoic acid, and of the antioxidants vitamins A, E and C were compared to corresponding dietary intakes observed in the National Health and Nutrition Examination Survey, Cycle III (McDowell et al., 1994; Alaimo et al., 1994; Bialostosky et al., 2002). Student *t*-tests and where appropriate Fisher's Exact Tests were employed to look for statistical differences between the means of 2 variables. Total omega-3 and omega-6 fatty acid intakes in our sample–which was not available for comparison through NHANES III population data–were analyzed descriptively. Confidence interval was 95% throughout.

3. Results

One-hundred and forty-six subjects were recruited. Average age in the study sample was 43.3 (±8.9) years. Seventy-eight patients (53.4%) were male. Regarding ethnicity, seventy-nine (54.1%) were Caucasian. DSM-IV diagnoses were Schizophrenia ($n=69$, 47.3%) Schizoaffective Disorder ($n=53$, 36.3%), Psychotic Disorder NOS ($n=24$, 16.4). Mean body mass index was 32.8 (±7.8). Mean BMI of male subjects was 30.8 (±7.3), and of female subjects 35.1 (±8). Eighty-seven patients (59.6%) were smokers; they smoked 23.4±14.4 cigarettes per day on average. Twelve subjects were married (8.2%).

Table 1 shows micronutrient intake of schizophrenia patients compared to the U.S. population sample.

Similar to the pattern observed for population and gender, saturated fat intake of both Caucasian (41.71±26.36 g) and African-American schizophrenia patients (42.33±21.29 g) was higher than in the corresponding Caucasian (30.41±0.78 g) and African American (28.88±0.88 g) population ($p\leq0.001$, respectively). Total PUFA intake was also significantly higher in Caucasian (41.71±26.36 g; $p\leq0.029$) and African-American patients (42.33±21.29 g; $p\leq0.037$) than in the population (30.41±0.78 g and 28.88±0.88 g, respectively). No differences in fatty acid intake were found with respect to smoking status. No significant negative correlations between number of cigarettes smoked and PUFA intake were observed.

There were significant correlations between BMI and intake of saturated fat ($r=0.526$, $p\leq0.001$), monounsaturated fat ($r=0.605$, $p\leq0.001$), trans-fatty acids ($r=0.242$, $p=0.003$), vitamin E ($r=0.293$, $p\leq0.001$), and 18:3n-3 ($r=0.369$, $p\leq0.001$). BMI and intake of 20:5n-3, 22:6n-3, vitamins A and C was not correlated.

Saturated fat to total PUFA ratios observed were 1.77:1 in the population versus 2.07:1 in the study sample. The male population had a ratio of 1.79:1 compared to 2.13:1 in males with schizophrenia. The female population ratio of saturated fat to PUFA intake was 1.69:1. Female schizophrenia patients ingested twice as much saturated fat as PUFAs, corresponding to a ratio of 2:1.

Table 1
Micronutrient intake

	Group			Males			Females		
	Population[a] S.D.	Patients S.D.	p	Population S.D.	Patients S.D.	p	Population S.D.	Patients S.D.	p
Saturated fat (g)	29.93±0.68	41.99±24.13	0.001	36.37±1.05	44.50±27.91	0.012	23.83±0.61	39.11±18.68	0.001
Monounsaturated fat (g)	33.76±0.72	37.28±22.42	0.059	40.75±1.15	38.49±25.35	0.426	26.61±0.67	35.89±18.58	0.001
Trans fat (g)	5.43±0.16	2.58±3.66	0.001	6.56±0.26	2.81±4.24	0.001	4.40±0.16	2.32±2.86	0.001
Polyunsaturated fat (g)	16.89±0.41	20.26±13.44	0.003	20.32±0.65	20.89±14.08	0.755	14.10±0.43	19.54±12.74	0.001
18:03(n-3) (g)	1.405±0.032	1.330±1.062	0.362	1.750±0.050	1.340±0.995	0.507	1.206±0.038	1.319±1.141	0.364
20:05(n-3) (g)	0.047±0.006	0.031±0.117	0.625	0.054±0.008	0.043±0.151	0.499	0.040±0.006	0.017±0.055	0.441
22:06(n-3) (g)	0.088±0.010	0.062±0.209	0.271	0.106±0.013	0.082±0.266	0.310	0.075±0.011	0.038±0.109	0.421
Vitamin A IU	6062.5±231.3	5633.1±6495.3	0.423	6621.8±366.8	5117.2±4716.7	0.006	5540.7±279.9	6224.9±8066.6	0.484
Vitamin C (mg)	106.38±3.59	131.66±162.80	0.062	116.08±5.21	134.54±122.09	0.333	96.50±3.98	128.35±200.52	0.192
Vitamin E (α-tocopherol EQ)	9.73±0.34	9.75±6.98	0.634	11.32±0.49	10.31±7.28	0.230	8.24±0.34	9.10±6.61	0.284

[a] Population data from the National Health and Nutrition Examination Survey, Cycle III (McDowell et al., 1994; Alaimo et al., 1994; Bialostosky et al., 2002).

Table 2
ω-3 and ω-6 fatty acid intake in grams (g)

		Omega-3 (g)	±S.D.	Omega-6 (g)	±S.D.	Ratio
All	$n=146$	1.15	1.073	14.11	12.451	1:12.27
Males	$n=78$	1.156	1.065	14.75	13.918	1:12.76
Females	$n=68$	1.143	1.09	13.39	10.6	1:11.71

Table 2 depicts total ω-3 and ω-6 fatty acid intake and corresponding ω-3 to ω-6 ratios observed in our patient sample.

No ethnic differences with respect to ω-3 or ω-6 fatty acid intake were observed. There were significant correlations between BMI and both ω-3 ($r=0.256$, $p=0.002$) and ω-6 intake ($r=0.316$, $p\leq0.001$). Intake of ω-3 and ω-6 fatty acids was correlated as well ($r=0.632$, $p\leq0.001$). No significant differences in ω-fatty acid intake with respect to smoking status existed. There was a trend towards significancy ($p=0.65$) for male smokers to have lower ω-3 fatty acid intake.

4. Discussion

As a group, schizophrenia patients ate more fat than persons in the general population. The pattern was observed for intake of both saturated fat and polyunsaturated fat. There was also a strong trend towards higher monounsaturated fat intake. The tendency for outpatients with schizophrenia to have increased caloric intake including a higher total dietary fat consumption than healthy individuals has been established previously (Strassnig et al., 2003). The moderate consumption of trans-fatty acids in our schizophrenia patient sample is remarkable, and may even exert weak protective effects, since certain serious health risks such as Coronary Artery Disease have directly been related to high trans-fat intake (Ascherio and Willet, 1997). Total PUFA intake was higher in patients than healthy controls, whereas intake of Omega-3 essential fatty acids such as á-linolenic acid (18:3n-3), eicosapentaenoic acid (20:5n-3) and docosahexaenoic acid (22:6n-3) was not different between patients and healthy controls. Thus, it may be speculated that the increased total PUFA intake observed in our patient population derived from increased omega-6 intake. There is already a well-described disparity between omega-3 and -6 fatty acid contents in the average American diet; and this disparity has been increasing (Simopoulos, 2002). It is known that patient with schizophrenia make poor dietary choices (Brown et al., 1999), thereby possibly aggravating such a difference. There was also a close association between higher PUFA intake and increase in BMI.

Based on our results we hypothesize that the proposed PUFA metabolism deficiencies in our sample of schizophrenia patients may not necessarily derive from a decreased baseline dietary intake of these fatty acids. Rather, intrinsic metabolic deficits such as accelerated PUFA loss through increased phospholipase A2 activity (Horrobin, 1996), alterations in polyenoic pathways through defects in PUFA desaturation and elongation (Reddy et al., in press) or increased oxidative cell membrane damage (Mahadik and Scheffer, 1996) may be responsible for the observed PUFA deficits of cell membranes. Yet, a relative dietary lack of certain PUFA might still contribute to the observed membrane deficits in schizophrenia. The modern Western diet is generally deficient in ω-3 fatty acids (Simopoulos, 2000; Holman, 1997). Optimal ratios of dietary ω-6 to ω-3 fatty acids have been proposed, and range from 5–10:1 (WHO, 1995) to 1: 1 to 2: 1 (Simopoulos, 1991). In fact, the average diet in industrialized countries contains tenfold less ω-3 than ω-6 fatty acids, with a mean ratio estimated at 1:9.8 in the United States (Kris-Etherton et al., 2000). We observed a slightly higher ratio of 1:12.27 in our study subjects, only emphasizing this relative ω-3 fatty acid dietary deficiency. It is known that ω-6 to ω-3 fatty acids competitively inhibit cellular elongase and desaturase enzymes and thus, a high ω-6 intake may down-regulate ω-3 metabolism (Emken et al., 1994). Predominance of dietary ω-6 fatty acids with a relative paucity of ω-3 PUFA, therefore, may contribute to subnormal cellular membrane concentrations of ω-3 fatty acids. Biochemical investigations have shown that a ω-3 to ω-6 ratio of 1:2.3 yields a maximum conversion of the prevalent dietary ω-3 fatty acid α-linolenic acid (ALA) into docosahexaenoic acid (DHA; Masters, 1996). Among cell membranes, DHA is especially abundant in neural cell membranes and has been closely associated with normal biophysical properties of membrane-bound proteins including receptors, transporters, and adhesion and cytoskeleton proteins (Champeil-Potokar et al., 2004).

Similarly, therapeutic ω-3 and ω-6 PUFA supplementation may not be equally effective in the treatment of schizophrenia. Rather, ω-3 fatty acids seem to have better efficacy (Peet, 2003), which may partially be effected by a correction of the observed ω-3 to ω-6 ratios, apart from substitution for increased intrinsic metabolic demand (Emsley et al., 2003). In fact, initial trial results incorporating add-on treatment with the ω-3 fatty acid EPA (20:5n-3) in the range from 1 to 3 g show promising results (Puri et al., 2000; Emsley et al., 2002; Arvindakshan et al., 2003; Peet, 2003).

Dietary antioxidant intake was less homogenous. Whereas vitamin C intake was slightly higher in schizophrenia patients than in the population, vitamins A and E intake was similar. However, an average antioxidant supply may not be adequate, since patients with schizophrenia may be exposed to increased oxidative stress when compared to the population (Prabakaran et al., 2004). Intrinsically impaired antioxidant defenses per se in patients suffering from schizophrenia (Phillips et al., 1993), increased peroxidative stress during acute schizophrenic episodes (Reddy et al., 2003; Lohr, 1991), increased smoking rates (McCreadie, 2000) or prolonged treatment with antipsychotic medication (Lohr et al., 2003), especially with classic compounds such as haloperidol or chlorpromazine (Jeding et al., 1995) have been implicated. Thus, antioxidant supplementation may help to preserve cell membrane PUFAs from oxidative stress (Tsay et al., 2000). Additional antioxidant supplementation may arguably be beneficial to the patient suffering from schizophrenia (Mahadik et al., 2001; Elkashef and Wyatt, 1999; Lohr, 1991).

Apart from this, new-onset type II diabetes during treatment with antipsychotic medication has become increasingly problematic in clinical settings (Melkersson and Dahl, 2004). Evidence exists that dietary composition modulates insulin resistance. Relatively high saturated fat intake increases the likelihood to developing type 2 diabetes mellitus (-Hlt98271824 [Rivellese and Lilli, 2003) and decreases insulin sensitivity (Hu et al., 2001). Essential fatty acid intake may exert direct effects on insulin sensitivity. For example, dietary substitution of polyunsaturated fatty acids for saturated fat enhances insulin sensitivity (Vessby et al., 2001), and ω-3 fatty acid content in muscle cell membranes correlates to insulin sensitivity in animal models (Storlien et al., 1991). There is convincing evidence that cutting down saturated fat intake per se improves insulin sensitivity (Summers et al., 2002). Consumption of a low fat diet promotes ω-3 fatty acid content in blood plasma (Raatz et al., 2001) and may directly lead to improved insulin sensitivity (Rivellese et al., 2002).

Health benefits of a low fat diet are apparent (Kuller, 1997). This may hold true especially for patients suffering from schizophrenia, who a priori may have an even higher fat intake than reference populations (McCreadie, 2000; Brown et al., 1999). The observed high fat intake in schizophrenia patients is worrisome and contributes to the development of serious medical comorbidities as well as further advances the risk for cumbersome metabolic side effects of antipsychotic treatment such as new-onset diabetes mellitus. Development of dietary interventions to promote low-fat diets seem necessary (Strassnig et al., in press).

5. Limitations

The study was a cross-sectional analysis of an outpatient population suffering from schizophrenia. Data have been compared to cross-sectional population data from the National Health and Nutrition Survey, Cycle III. While we believe that the reported dietary intakes of our subjects were stable at time of assessment, the validity of a dietary recall in our particular population with schizophrenia has not been established. Additionally, patients in our sample were predominantly overweight or obese. However, this was not a representative sample obtained by random sampling, but rather a sample of convenience made up of volunteers from our outpatient program. Therefore, the results may not be applicable to the entire patient population, but may be appropriate for the large number of overweight or obese patients with schizophrenia encountered in outpatient settings.

It should also be noted that the standard deviation of the mean intake of for almost all nutrients measured were several fold higher in the group of schizophrenia patients as compared to the controls. While this is not surprising considering the differences in the sample sizes of the groups compared, it does not rule out the existence of subgroups of patients, among the patient group with distinct dietary intake profiles. Studies with

larger samples, preferably sampled randomly, might help resolve this.

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