Plasma fatty acid profile in depressive disorder resembles insulin resistance state

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Abstract

BACKGROUND: Depressive disorder is related to an increased risk of type 2 diabetes mellitus (DM2) and cardiovascular disease (CVD). Insulin resistance (IR), connected with altered fatty acid (FA) composition, namely with decreased proportion of polyunsaturated FA could participate in these associations. The aim of the study was to investigate the composition of FA in plasma cholesterol esters (CE) and phosphatidylcholine (PC) as well as indices of insulin resistance and oxidative stress in the patients with depressive disorder.

MATERIALS AND METHODS: Parameters of lipid and glucose homeostasis, concentrations of FA in plasma cholesteryl esters (CE) and phosphatidylcholine (PC) and conjugated dienes in LDL were investigated in a group of 47 patients (9M/38F) with depression and compared with 47 control persons (16M/31F). Delta-9 desaturase (D9D) and D6D desaturase were estimated as product to precursor fatty acid ratios.

RESULTS: In depressive patients increased concentrations of palmitoleic acid and total monounsaturated FA with decreased proportion of total polyunsaturated FA n-6 (PUFA n-6) (all $p<0.05$) in CE were found, while in PC increased proportion of saturated FA was observed ($p<0.05$). Moreover, index of D6D activity was significantly increased in PC and CE ($p<0.05$). Concomitantly, in depressive patients higher levels of plasma triacylglycerols ($p<0.05$), conjugated dienes in LDL ($p<0.001$) and HOMA index of IR ($p<0.05$) were found.

CONCLUSIONS: Esterified FA composition of depressive patients revealed changes, similar to those, usually observed in insulin resistance. Dysregulation of FA could participate in the pathogenesis of depression and be associated with an increased risk of CVD and DM2.

ORIGINAL ARTICLE

Abbreviations:
CD - conjugated dienes
FA - fatty acids
PUFA - polyunsaturated fatty acids
HOMA-IR - homeostasis model assessment of insulin resistance
D9D - Δ-9-desaturase
D6D - Δ-6-desaturase
D5D - Δ-5-desaturase
TAG - triacylglycerols
LDL - low density lipoproteins

INTRODUCTION

It is commonly assumed that abnormal composition of polyunsaturated fatty acids (PUFA), especially PUFA n-3 in human tissues, takes part in the pathogenesis of depressive disorder (DD). It was suggested that PUFA n-3 deficit could be associated with several factors affecting neurobiology of DD, e.g. disruption of the biophysical properties of neuronal membranes, signal transduction, or altered neurotransmitter biosynthesis (Hibbeln & Salem 1999). Altered metabolism of fatty acids (FA) including PUFAs is characteristic for metabolic syndrome (MetS) (Warensjö 2007), which is a cluster of metabolic and hormonal changes, e.g. visceral obesity, insulin resistance (IR), dyslipidaemia, arterial hypertension, glucose homeostasis abnormalities, but also low-grade inflammation and/or increased oxidative stress (Eckel *et al.* 2005). Features of MetS were observed also in the patients suffering from DD (Zeman *et al.* 2009). MetS is considered a marker of an increased risk of cardiovascular disease (CVD) and type 2 diabetes mellitus (DM2) (Wannamethee *et al.* 2005). The FA profile in persons with IR and MetS is characterised by high proportions of saturated FA (SFA), such as palmitic acid (PA, 16:0), low levels of PUFAs, e.g. linoleic acid (LA,18:2n-6), and a higher proportion of palmitoleic (POA, 16:1n-7) and dihomo-γ-linolenic (DGLA, 20:3n-6) (Warensjö 2007; Žák *et al.* 2007). Altered activities of desaturases, enzymes catalyzing the endogenous synthesis of long-chain unsaturated FAs, are found in IR and MetS as well (Warensjö 2007; Žák *et al.* 2007). Increased estimates of activity of delta-9-desaturase (D9D) and D6D, while decreased activity of D5D are findings, typical for IR (Warensjö 2007).

In most studies investigating depressive patients only n-3 and n-6 PUFA levels were investigated. Studies, relating SFA or monounsaturated (MUFA) content, as well as indices of desaturase activities with depression are sparse, with inconsistent results (Assies *et al.* 2010; Tsuboi *et al.* 2012). The aim of this study was to analyze entire FA profile in serum phosphatidylcholine (PC) and cholesteryl esters (CE), including estimated activities of D9D, D5D and D6D in the group of patients with DD.

MATERIAL AND METHODS

We have investigated 47 drug naïve patients (9 M/38F) from Psychiatric Clinic of 1st Faculty of Medicine, Charles University in Prague with depression and compared with 47 control persons (16M/31F). The

Tab. 1. Relevant fatty acids and estimated indices in plasma lipids of the investigated groups.

Parameter	Phosphatidylcholine		Cholesteryl esters	
Fatty acid	Depression (n=47)	Controls (n=47)	Depression (n=47)	Controls (n=47)
16:0	30.02±2.44	29.59±1.24	9.96±2.24	9.33±1.18
16:1n-7	0.57±0.22	0.51±0.12	0.44±0.15	0.36±0.16*
18:1n-9	10.04±1.72	9.67±1.84	18.70±1.72	17.90±1.84
18:2n-6	22.58±3.56	24.21±2.88	56.11±4.56	58.56±4.88
20:3n-6	3.18±0.88	2.88±0.60	0.71±0.17	0.63±0.12
20:4n-6	11.55±2.82	11.90±2.02	5.89±2.67	5.69±2.05
20:5n-3	0.88±0.41	1.10±1.01	0.37±0.40	0.36±0.32
22:6n-3	3.36±1.06	3.60±1.20	3.36±1.06	3.60±1.20
Σ SFA	44.05±1.90	43.40±1.16***	11.59±2.251	10.74±1.18
Σ MUFA	12.31±1.93	11.83±1.97	23.63±3.62	22.11±3.82*
Σ PUFAn-6	38.36±1.84	39.04±2.74	63.59±4.93	66.06±5.87*
Σ PUFAn-3	5.28±1.16	5.73±1.95	1.09±0.59	1.08±0.51
D9D (16:1n-7/16:0)	0.204±0.007	0.180±0.005	0.35±0.15	0.34±0.14
D6D (18:3n-6/18:2n-6)	0.005±0.002	0.003±0.001*	0.015±0.009	0.012±0.004*
AI	0.56±0.07	0.54±0.03	0.15±0.03	0.14±0.03

mol % (ave ± S.D.); ANCOVA, adjusted for gender and age; corrected P for multiple test: * $p<0.05$; *** $p<0.001$; AI= atherogenic index; [(12:0+4*14:0+16:0)/(Σ PUFAn-6+Σ PUFAn-3+Σ MUFA)]

patients did not differ significantly from controls in age (60.9±15.7 vs. 57.8±12.3 yrs) and BMI (26.6±15.7 vs. 25.1±4.0 kg/m^2). The controls consisted of 47 healthy persons (medical staff of the 1st Faculty of Medicine). The routine biochemical parameters were analyzed by conventional methods on automatic analyzers according to standard procedures. The insulin concentrations were analysed by radioimmunological method (Immunotech, Prague, Czech Republic). The FA in plasma PC and CE were analyzed by capillary gas chromatography. For the assessment of IR, we used the homeostasis model assessment index (HOMA-IR), calculated by the formula: insulin (μU/ml)* glucose (mmol/l)/22.5. Concentrations of conjugated dienes (CD) in precipitated LDL were measured as it was published previously (Kodydková *et al.* 2009). For statistical analysis, BMDP Statistical Software was used. We used the Benjamini-Hochberg (exploratory Simes) method for adjusting p in multiple test procedure.

RESULTS

In the group of depressive patients compared with controls we have found increased plasma triacylglycerols (TAG), 1.69±0.91 vs. 1.11±0.30 mmol/l, HOMA-IR, 3.34±2.86 vs. 2.69±0.60, both $p<0.05$, and CD in LDL 62.95±24.34 vs. 42.93±12.96, $p<0.001$. Concentrations of relevant FA in plasma PC a CE are shown in Table 1. In depressive patients increased concentrations of POA ($p<0.05$) in CE were found. Decreased content of total PUFA n-6 while increased content of MUFA in CE were observed (both $p<0.05$) whereas increased proportion of total SFA in PC ($p<0.001$) was found as well. Moreover, index of D6D activity was significantly increased in PC and CE (all $p<0.05$).

DISCUSSION

The main findings of our study were increased concentrations of POA in CE, SFA in PC, concomitantly with decreased proportions of PUFA n-6 and increased of MUFA in CE of persons with DD. Moreover, index of D6D activity was found to be increased in the patients. Increased TAG, HOMA-IR index and CD-LDL were other findings. Interestingly, similar plasma FA profiles as in this study are usually found in MetS (Warensjö 2007; Žák 2007). Hypertriglyceridemia, increased oxidative stress and IR were found in the patients with DD in our previous work (Kodydková *et al.* 2009; Zeman *et al.* 2009). In prospective study, increased POA, DGLA, increased D6D, decreased LA were predictors of MetS development (Warensjö 2007). A high proportion of POA, a surrogate marker of *de novo* lipogenesis, in serum CE was an independent predictor of high glycaemia in another study (Lindgarde *et al.* 2006). High DGLA proportion and D6D activity correlated with IR (Warensjö 2007) and with the risk of DM2 (Kröger & Schulze 2012). Only a few of studies dealt with FA other than PUFA n-3 and PUFA n-6 in DD. In one study, the concentrations of most of the SFAs and MUFAs with a chain length 20 carbon atoms of depressive patients were significantly lower, whereas D9D activity significantly higher than in the controls (Assies *et al.* 2010). Tsuboi *et al.* (2012) found depressive symptoms positively correlating with PA percentages and negatively with arachidonic acid (20:4n-6) percentages. Positive correlation of PA with depressive symptoms could be connected with a chronic low-grade inflammation or oxidative stress increased by PA (Tsuboi *et al.* 2012). Liu & McNamara (2011) found significantly elevated gene expression for D6D in the prefrontal cortex of bipolar disorder (BD) patients and suggested that this may contribute to dysregulated central PUFA biosynthesis and pro-inflammatory signaling implicated in the BD. Increased SFA in our DD patients corresponded with an observed trend to increased atherogenic index of FA in PC (Ulbricht & Southgate 1991).

Limitation of our study was that among the patients with DD women prevailed in compare to control group, however the differences in the FA profiles remained statistically significant even if adjusted on gender. Nevertheless, the results require confirmation in a larger cohort with proportional rate of both genders. In conclusion, esterified FA composition of lipid classes of plasma in depressive patients revealed changes similar to those usually observed in insulin resistance. Dysregulation of FA could participate in the pathogenesis of depression and be associated with an increased risk of CVD and DM2.

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REFERENCES

1 Assies J, Pouwer F, Lok A, Mocking RJ, Bockting CL, Visser I, et al (2010). Plasma and erythrocyte fatty acid patterns in patients with recurrent depression: a matched case-control study. PLoS One. **5**: e10635.
2 Eckel RH, Grundy SM, Zimmet PZ (2005). The metabolic syndrome. Lancet. **365**: 1415–1428.
3 Hibbeln JR, Salem N, Jr (1995). Dietary polyunsaturated fatty acids and depression: when cholesterol does not satisfy. Am J Clin Nutr. **62**: 1–9.
4 Kodydková J, Vávrová L, Zeman M, Jirák R, Macášek J, Staňková B, et al (2009). Antioxidative enzymes and increased oxidative stress in depressive women. Clin Biochem. **42**: 1368–1374.
5 Kröger J, Schulze MB (2012). Recent insights into the relation of Δ5 desaturase and Δ6 desaturase activity to the development of type 2 diabetes. Curr Opin Lipidol. **23**: 4–10.
6 Lindgärde F, Vessby B, Ahrén B (2006). Serum cholesteryl fatty acid composition and plasma glucose concentrations in Amerindian women. Am J Clin Nutr. **84**: 1009–1013.

7 Liu Y, McNamara RK (2011). Elevated Delta-6 desaturase (FADS2) gene expression in the prefrontal cortex of patients with bipolar disorder. J Psychiatr Res. **45**: 269–272.
8 Tsuboi H, Watanabe M, Kobayashi F, Kimura K, Kinae N. Associations of depressive symptoms with serum proportions of palmitic and arachidonic acids, and α-tocopherol effects among male population – A preliminary study. Clin Nutr. 2012 Aug 5. [Epub ahead of print]
9 Ulbricht TL, Southgate DA (1991). Coronary heart disease: seven dietary factors. Lancet. **338**: 985–992.
10 Wannamethee SG, Shaper AG, Lennon L, Morris RW (2005). Metabolic syndrome vs Framingham risk score for prediction of coronary heart disease, stroke, and type 2 diabetes mellitus. Arch Intern Med. **165**: 2644–2650.
11 Warensjö E (2007). Fatty Acid Desaturase Activities in Metabolic Syndrome and Cardiovascular Disease. Special Reference to Stearoyl-CoA-Desaturase and Biomarkers of Dietary Fat (dissertation). Sweden: Uppsala Univ.
12 Žák A, Tvrzická E, Vecka M, Jáchymová M, Duffková L, Staňková B, et al (2007). Severity of metabolic syndrome unfavorably influences oxidative stress and fatty acid metabolism in men. Tohoku J Exp Med. **212:** 359–371.
13 Zeman M, Jirák R, Jáchymová M, Vecka M, Tvrzická E, Žák A (2009). Leptin, adiponectin, leptin to adiponectin ratio and insulin resistance in depressive women. Neuro Endocrinol Lett. **30**: 387–395.