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Association between depression, parameters of adiposity and genetic polymorphisms of pro-inflammatory cytokines: *IL-1α, IL-1β, IL-2* and *IL-6* in subjects over 55 years old

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Background. During the last few decades, adiposity has become a relatively common phenomenon worldwide. The available data on the effects of pro-inflammatory factors in both depression and adiposity has been attracting great attention. Aim. We sought to assess the prevalence of -889C>T IL-1α, -31T>C and -511C>T IL-1β, -330T>G IL-2 and -174G>C IL-6 genes and their association with adiposity and depression in Polish subjects. Methods. A cohort study was conducted in 2013/2014, covering a sample of 297 individuals (217 female and 80 male). Anthropometric data was handled using the BIA analysis method, while for genotyping PCR-RFLP techniques were used. Results. A positive correlation between depression and anthropometric parameters: adipose tissue (in kg) and adipose tissue (in %) (R=0.135 and *p*=0.02, R=0.114 and *p*<0.05, respectively) was found. No association between studied polymorphisms and depression was observed. Conclusion. Although it was not possible to demonstrate any influence of the studied polymorphisms as the genetic modulator of depression, authors believe that the presented data are noticeable and may provide the basis for future studies on larger groups.

Key words cross sectional study, genetic variants of cytokines, obesity, depression

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INTRODUCTION

In recent decades, the lifestyle of Europeans has changed, resulting in an increase in both adiposity and depression. The epidemic of adiposity (body mass index (BMI) ≥ 30) and depression is not limited to Europe, it is happening worldwide, and is a problem with serious public health implications (Luppino *et al.*, 2010). Adiposity is linked to chronic diseases such as hypertension, diabetes, coronary heart disease, liver disease, cancers and depression (Akbaraly *et al.*, 2009; Simon *et al.*, 2009; Takeuchi *et al.*, 2009; Clement & Basdevant, 2010; Cohen *et al.*, 2010). The World Health Organization has ranked depression as the 4th cause of diseases worldwide, and research shows that by 2020 depression and myocardial infarction will become the main causes of disability (www.who.int/mediacentre/factsheets/fs311/en/).

Differences in genetic and environmental background as well as the age and sex structure of the population influence the prevalence of adiposity (Ujcic-Voortman *et al.*, 2012). It was found that the prevalence of adiposity resulting from accumulation of visceral fat is age-dependent, starting at 30 years of age and that the risk of adiposity increases in different populations from 7–11% to 54–89% (Ogbera, 2010).

An increase in prevalence of depression with age is observed in different populations. The source of inflammatory cytokines is the gut with intestinal microorganisms influencing immune responses (Lee & Mazmanian, 2010). The role of keratinocytes, myocytes, including cardiomyocytes and fibroblasts, as well as neuronal and glial cells of the brain on the production of cytokines was also indicated in review by Ufnal & Wolynczyk-Gmaj (Ufnal & Wolynczyk-Gmaj, 2011). One of the major environmental factors which may interact with cytokines and genetic predisposition to depression, is stress. Oversupply of food and calories has long been considered to be a stress for the organism (Haroon *et al.*, 2012). Increased exposure to food allergens due to the oversupply of food, and stress may contribute to the loss of protective microorganisms and increase inflammation in the gut, thus contributing to behavioral symptoms associated with increased inflammatory cytokines (Arrieta *et al.*, 2006; Buret, 2006). As early as in 2004 and 2005, Khaodhiar *et al.* (2004) and Lim *et al.* (2005) argued that adiposity is linked to an increase in circulating cytokines while BMI has a significant influence on concentrations of inflammatory cytokines, behavioral alterations, and depression. Recently published data suggested the crucial role of IL-1α, IL-1β, IL-2 and IL-6 in the regulation of inflammation, hematopoiesis and the immune response, as well as in metabolic processes and depression (Cartier *et al.*, 2009;

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Genetic investigations were carried out in the laboratory of the Department of Gerontobiology, Pomeranian Medical University, Szczecin, (Poland).

Abbreviations: ANOVA, analysis of variance; BDI, Beck depression inventory; BIA, bioelectrical impedance analysis techniques; BMI, body mass index; GDS, geriatric depression scale; GP, *general practitioner;* HPA, hypothalamic-pituitary adrenal; IL, interleukin; PCR–RFLP, polymerase chain reaction–restriction fragment length polymorphism; SNPs, single nucleotide polymorphisms; TNF-α, tumor necrosis factor α; WC, waist circumference; WHR, waist-to-hip ratio

Table 1. Description of genotyped polymorphisms and references of PCR-RFLP conditions

Gene/Abbreviations/ Location	Nucleotide	db SNPs	NCBI Reference sequence	Reference PCR-RFLP
IL-1α (Interleukin-1 alpha) 2q13-21	-889 C>T	Ex1+12C>T	1800587	Paz Aparicio *et al.*, 2011
IL-1β (Interleukin-1 beta) 2q13-21	-31 T>C -511 C>T	-31 T>C -511C>T	1143634 16944	September *et al.*, 2011
IL-2 (Interleukin-2) 4q26–27	-330 T>G	-384G>T	2069762	Gao *et al.*, 2009
IL-6 (Interleukin-6) 7p21	-174 G>C	-174 G>C	1800795	Todhunter *et al.*, 2005

Bosker *et al.*, 2011; Bufalino *et al.*, 2012; Howe *et al.*, 2013; Raison and Miller 2013). It is believed that adiposity, especially visceral adiposity, is associated with depression because it increases the levels of pro-inflammatory cytokines. On the other hand, the cytokines released from adipose tissue may affect the brain and behavior (Miller *et al.*, 2003; Weisberg *et al.*, 2003; Park *et al.*, 2005; Suganami, 2010; Martinac *et al.*, 2014).

Data on the links between polymorphisms -889C>T *IL-1a*, -330 T>G *IL-2* and -174 G>C *IL-6* gene, adiposity, and depression in Polish subjects as well as in other populations, is either sparse or the issue has not been researched. The objective of this study was to verify whether there is a link between depression, adiposity, and the distribution of genotypes and alleles of pro-inflammatory cytokines: *IL-1a, IL-1β, IL-2* and *IL-6* in subjects over 55 years old.

MATERIAL AND METHODS

The study was conducted in accordance with the Declaration of Helsinki (1975, revised 2000) and was approved by the Regional Ethics Committees (decision reference numbers KB-0012/174/13). Written, informed consent was obtained from all participants. The current study was conducted in Department of Civilization Diseases, Pomeranian Medical University, Szczecin, Poland. Samples and data were collected in the years 2013-2014. Patients, during a visit to a GP received the invitation to the project, in which the participation was voluntary. In our study group female-to-male imbalance was due to the fact that females joined the study more willingly than males. Coexistence of any serious illness (hepatic, pulmonary, renal, cancer) was an exclusionary criterion. Anthropometric measurements, surveys and level of lipids were determined for all the subjects, but genotyping was performed only for subjects, who declared any antidepressant treatment.

Study population. The study group consisted of 297 individuals (215 female and 82 male). The mean age of the group was 63.5 (±5.9) years, with the mean age of females of 63.3 (±5.7) and of 63.9 (±6.4) for males.

Anthropometric measurements. The participants measurements were recorded following fasting overnight. Body composition was measured using bioelectrical impedance analysis techniques (BIA), (Jawon Segmental Body Composition Analyzer, Medical IOI-353, Korea). Waist circumference (WC) was measured with a tape measure midway between the lowest rib and the pelvis in position of expiration, hip circumference was measured at the widest circumference of the hip. Different anthropometric measures were calculated: BMI was calculated as weight divided by height squared (kg/m^2), waist circumference (WC, in cm), waist-to-hip ratio (WHR): WC divided by hip circumference. Adiposity, weight, height, waist and hip circumference were measured in accordance with a written, standardized manual.

Measurement of depression. To assess the severity of depressive symptoms among the study group, the original 30-item version of Geriatric Depression Scale (GDS) by Yesavage *et al.* was used (Yesavage *et al.*, 1983). It consists of thirty short questions with two possible answers (yes / no) to choose from. Geriatric Depression Scale scores between 0 and 10 points indicate no depression, between 11 and 20 points — slight depression, while the result between 21 and 30 points suggests the presence of deep depression. Geriatric Depression Scale was used because the sensitivity and specificity of the GDS is 84 and 95%, respectively. (Albiński *et al.*, 2011). Moreover, the high accuracy of the converging GDS and Beck Depression Inventory (BDI) was proved. The correlation between the two tools is r=0.91. On the other hand, the results indicated that, answering questions of the GDS caused much less difficulty than answering questions of the BDI. Thirdly, while completing the BDI respondents chose more than one answer more frequently than while completing GDS (Albiński *et al.*, 2011).

Genotyping of -889C>T *IL-1α*, -31T>C and -511C>T *IL-1β*, -330T>G *IL-2* and -174 G>C *IL-6* genes. Peripheral venous blood samples were collected into sterile tubes containing EDTA solution, using a standard venipuncture. Genomic DNA was isolated using the membrane-based QIAamp DNA extraction protocol (Qiagen, Hilden, Germany). Genetic investigations were carried out in the laboratory of the Department of Gerontobiology, Pomeranian Medical University, Szczecin, (Poland). DNA samples were stored at 4°C for further analyses. Genotypes were determined by PCR-RFLP using a Hightech Thermocycler Cycler-Technology for Life (SensoQuest, Gottingen, Germany). Protocols for -889T>C *IL-1a*, -31T>C and -511C>T *IL-1β*, -330 T>G *IL-2* and -174 G>C *IL-6* polymorphisms followed previously described PCR-RFLP techniques (Todhunter *et al.*, 2005; Gao, 2009; Paz Aparicio *et al.*, 2011; September *et al.*, 2011) (see Table 1).

Statistical analysis. To determine whether there are statistically significant differences in genotypes and allele frequencies between groups, we used the $\chi 2$ test. In order to analyze genotypes and allele frequencies effect on depression and adipose tissue, we applied the analysis of variance (ANOVA), followed by GDS multiple range tests for comparison among groups. Correlations between continuous variables were performed with either Spearman rank (R) or Pearson's test. The data presented below follows the convention mean (standard deviation). The level of significance was set at $p < 0.05$. All statistical analyses for this study were performed using the StatView computer software version 5.0 (SAS Institute Inc. Cary, NC, USA).

Table 2. Subjects characteristics, body composition and depression in study group

Group, sex, n	Age, years	WHR	Adipose tissue, kg, %	BMI, kg/m^2	No depression	Low depression n, (%)	Deep depression
Male, n=82	63.9 (±6.4)	0.99 (±0.08)	26.6 (±8.5), 31.1 (±6.1)	29.7 (±4.9)	65 (79.3)	12 (14.6)	5 (6.1)
Female, n=215	63.3 (±5.7)	0.92 (±0.07)	28.4 (±8.5), 37.1 (±5.3)	29.5 (±5.3)	141 (65.6)	63 (29.3)	11 (5.1)
Sum/ n=297 average	63.5 (±5.9)	0.96 (±0.08)	27.9 (±8.6) 35.5% (±6.2)	29.6 (±5.2)	206 (69.4)	75 (25.3)	16 (5.3)

RESULTS

In 297 individuals, 206 subjects did not have depression (69.4%; 65 males and 141 females) while 91 subjects did (30.6%; 16 males and 75 females). In males and females with depression 12 and 63 had low depression, and 5 and 11 deep depression, respectively. Additionally, low depression was significantly more frequent in females than in males ($p = 0.04$). To compare two nominal variables we applied $\chi 2$ test. Average GDS scores for 297 subjects were 8.3 (±6.3) with min. 0 and max 29.0 points.

For all 297 individuals the average adipose tissue was 27.9 kg (±8.6) and accounted for 35.5% (±6.2) of body mass, with an average BMI of 29.6 (±5.2). Subjects' characteristics of anthropometric parameters and depression are presented in Table 2.

Subjects' characteristics of adipose tissue and depression, sorted by BMI values are presented in Table 3.

Body mass index is widely used as a proxy for body fat and has been shown to correlate with other parameters of adiposity (Bouchard, 2007). In numerous studies, BMI emerges as the favorite, but some researchers consider that it is a relatively crude index of adiposity, predominantly due to the fact that it is limited by differences in body fatness for a given BMI across age, sex, and race, (Jackson *et al*., 2002; Camhi *et al*., 2011). To resolve this limitation, Barreira *et al.* (2011) developed the body adiposity index (BAI) in Mexican-American and Afro-American subjects. However, it is unknown how well BAI performs in Caucasian individuals, including elder subjects. Therefore, we decided to use BMI. The study group was divided into two subgroups, based on BMI: those with BMI $\geq$ 30 kg/m^2 (37 males and 94 females) and those with BMI $<$ 30 kg/m^2 (45 males and 121 females). We decided to apply WHO (WHO, 2000) criteria to define obesity. Correlation between all: low and deep depression and the mass of adipose tissue (in kg) was found (p=0.0345).

Our study represented all genotypes for polymorphisms -889C>T *IL-1a*, -31T>C and -511C>T *IL-1β*, -330 T>G *IL-2* and -174 G>C *IL-6*. We received: 69 CC homozygotes, 147 GC heterozygotes and 81 GG homozygotes of -889C>T *IL-1a* polymorphism, resulting in G allele frequency of 52.0%; 140 TT homozygotes, 130 TC heterozygotes and 27 CC homozygotes of -31T>C *IL-1β* polymorphism, resulting in C allele frequency of 31.0%; 144 CC homozygotes, 130 CT heterozygotes and 23 TT homozygotes of -511C>T *IL-1β*, polymorphism, resulting in T allele frequency of 27.0%; 123 TT homozygotes, 141 TG heterozygotes and 33 GG homozygotes of -330T>G *IL-2* polymorphism, resulting in G allele frequency of 34.8%; 81 GG homozygotes, 147 GC heterozygotes and 69 CC homozygotes of -174G>C *IL-6* polymorphism, resulting in G allele frequency of 48.0%.

We obtained 100% concordance between the genotyped duplicate samples for the SNPs (single nucleotide polymorphisms). We presented the prevalence of genotype and mutated allele frequency in the study group, divided by BMI, in Table 4.

DISCUSSION

During the last two centuries, changes in lifestyle and diet have caused people around the world to be obese. Several studies found an increased prevalence of depression in obese subjects (Heo *et al*., 2006; Herva *et al*., 2006; Baumeister & Harter, 2007; de Wit, 2010).

Table 3. Subjects' characteristics, study group divided by body mass index

Subjects	Group		Age, years (± S.D.)	Adipose tissue, kg, %	No depression	Low depression n, (%)	Deep depression
With BMI≥30	Male,	n=37	62.5 (±12.2)	33.4 (±6.9), 34.2 (±5.4)	29 (78.4)	7 (18.9)	1 (2.7)
	Female,	n=94	62.1 (±8.3)	35.0 (±5.7), 41.0 (±3.8)	58 (61.7)	29 (30.9)	7 (7.4)
Sum/average		n=131	62.2 (±9.6)	35.3 (±6.2), 39.1 (±5.3)	87 (70.1)	36 (24.9)	8 (5.1)
With BMI<30	Male,	n=45	64.2 (±6.5)	21.1 (±4.8), 28.6 (±5.6)	36 (80.0)	5 (11.1)	4 (8.9)
	Female,	n=121	63.3 (±8.3)	22.4 (±4.8), 34.1 (±4.4)	83 (68.6)	34 (28.1)	4 (3.3)
Sum/average		n=166	63.5 (±7.8)	22.1 (±4.8), 32.6 (±5.3)	119 (74.3)	39 (19.6)	8 (6.1)

sex *vs* depression for BMI≥30; p=0.17; sex *vs* depression for BMI<30; p=0.03

Table 4. Prevalence of genotype and mutated allele frequency in study group, divided by BMI

Subjects characteristics	With BMI≥30	With BMI<30	No depression	Low depression	Deep depression
-889 C>T IL-1α					
n	131	166	206	75	16
CC	56	89	102	35	8
CT	64	63	84	35	8
TT	11	14	20	5	0
T	0.33	0.27	0.3	0.3	0.25
Chi² *p*-value	0.15		0.59		
-31 T>C IL-1β					
TT	61	79	91	39	10
TC	57	73	93	31	6
CC	13	14	22	5	0
C	0.32	0.30	0.33	0.27	0.19
Chi² *p*-value	0.9		0.35		
-511 C>T IL-1β					
CC	64	80	93	41	10
CT	57	73	94	30	6
TT	10	13	19	4	0
T	0.29	0.30	0.32	0.25	0.19
Chi² *p*-value	0.99		0.32		
-330 T>G IL-2					
TT	51	72	81	36	6
TG	68	73	100	31	10
GG	12	21	25	8	0
G	0.35	0.35	0.36	0.31	0.31
Chi² *p*-value	0.35		0.24		
-174 G>C IL-6					
GG	34	47	57	20	4
GC	67	80	106	31	10
CC	30	39	43	24	2
C	0.48	0.48	0.47	0.53	0.43
Chi² *p*-value	0.86		0.24		

One of the features of adiposity is chronic inflammation, which is characterized by increased cytokine production in adipose tissue (Wellen & Hotamisiligil, 2003; Chung *et al*., 2004; Chung *et al*., 2006). As we mentioned in the introduction, the gut with intestinal microorganisms related to immune responses, keratinocytes, myocytes, as well as neuronal and glial cells of the brain are also the source of inflammatory cytokines (Lee & Mazmanian, 2010; Ufnal & Wolynczyk-Gmaj, 2011). In recent years, the inflammatory hypothesis attracted great attention and has become one of the most prevalent issues concerning depression (Felger & Lotrich, 2013). It is supported by the fact that in some patients with depression, an activation of the immune system is observed; several pro-inflammatory cytokines activate brain serotonergic systems, which are involved in depression, while the use of antidepressant therapy leads to decreased levels of cytokines in these patients (De Berardis *et al*., 2010). Additionally, it was found that cytokines activate cerebral noradrenergic systems (Sluzewska *et al*., 1996; O'Brien *et al*., 2004; Basterzi *et al*., 2005; Dunn *et al*., 2005; Schiepers *et al*., 2005). In a publication by Khairova et al. (2009) the participation of inflammation in the development of mood disorders was explained by the influence of cytokines on modulation of synaptic plasticity linked with changes in the metabolism of neurotransmitters involved in the regulation of mood. Recently, research showed that inflammatory processes *inter alia* are associated with elevated concentrations of pro-inflammatory cytokines, such as: IL-1, IL-2, IL-6 and TNF-α and influence the development and progression of depression (Howren *et al*., 2009; Dowlati *et al*., 2010; Maes *et al*., 2012; Schmidt *et al*., 2014). In people with depression excessive stimulation of the hypothalamic-pituitary adrenal (HPA) was observed (Pizzagalli *et al*., 2009). The administration of IL-1 and IL-6 increases the

secretion of corticotrophin and activation of the HPA axis (Besedovsky &, del Rey, 1996). These cytokines also affect the transcription of glucocorticoid receptor genes and thereby interfere with the feedback inhibition of the hypothalamus and pituitary gland. This phenomenon may explain the pathological mechanism of the HPA axis deregulation in depression, similar as during infection/inflammation caused by bacteria and viruses, which also result in excessive activation of the HPA axis (Beisel, 1981; Silverman *et al.*, 2005). Miller *et al.* and Raison *et al.* (each 2009) reported influence of inflammatory cytokines on the synthesis and the reuptake of serotonin, norepinephrine and dopamine, whose disturbances are observed in depression. It was reported that in humans undergoing immunotherapy high doses of IL-2 induce neuropsychiatric symptoms, including depression. On the other hand, interestingly, with alleviation of depression in response to antidepressant treatment, normalization is evident with respect to levels of IL-1β, IL-6 (Miller *et al.*, 2009; Raison *et al.*, 2009).

Data on association between depression, parameters of adiposity and genetic polymorphisms of pro-inflammatory cytokines in population of Poland and generally are sparse. To our knowledge, this is the first comprehensive evaluation of whether parameters of adiposity increase the risk of developing depression and whether it is associated with pro-inflammatory cytokines in Polish subjects over 55 years old.

Borkowska and coworkers (2001) examined polymorphisms -31T>C and -511C>T *IL-1β* gene in Polish subjects with depression and concluded that there is a link between genotypes TT and CC (at -31T>C and -511C>T *IL-1β* gene, respectively) and depression.

In our study we found a positive correlation between depression and anthropometric parameters: adipose tissue (in kg) and adipose tissue (in %) ($p<0.05$), but we did not find a link between polymorphisms -31T>C and -511C>T IL-1β gene and depression.

Analysis of this connection, conducted by Hwang *et al.* in the Asian population showed an association between TT homozygote at -31T>C *IL-1β* polymorphism and CC homozygote at -511C>T *IL-1β* polymorphism and depression. However, no association between -511C>T *IL-1β* polymorphism and depression in elderly Chinese subjects was found (Hwang *et al.*, 2009). Hwang *et al.* (2009) found that -511 TT homozygotes of *IL-1β* gene are linked to depression in elderly subjects, but our observations did not confirm it. In another study, there was no relationship between polymorphisms of *IL-1a, IL-1β, and IL-1RA* and childhood-onset mood disorders (Misener *et al.*, 2008). Study conducted by Yu *et al.* (2003) showed a link between polymorphisms, *IL-1β* gene, and the risk of developing depression and study conducted by Hwang and coworkers (2009) indicated a possible role of these polymorphisms in development of depression.

Biochemical parameters, such as serum cytokine concentrations, which are associated with polymorphisms of cytokines genes, also suggested the role of polymorphism in cytokine genes in the development of depression. In a study by Diniz and coworkers (2010) higher serum concentrations of IL-1β in elderly depressed patients compared to non depressed elderly controls were found.

The later study by Maes and coworkers (2012) also presented significantly higher serum IL-1 concentrations (IL-1a plus IL-1b) in majorly depressed patients, compared to volunteers without depression. However, other authors found that increased urinary IL-1 β levels in early postnatal period are linked to an increased risk of postpartum depression (Corwin *et al.*, 2008).

Moreover, animal studies concluded that obese mice have higher level of IL-1 α than slim mice. IL-1α regulates the differentiation of pre-adipocytes and may have a critical function in the development of inflammation linked to adiposity, while BMI is closely related to adipose tissue both in kg and in percentage of the body mass (Um *et al.*, 2011).

CONCLUSION

All in all, the results of our study suggest lack of influence of the studied polymorphisms as the genetic modulator of depression. We concluded that further research is required to confirm our findings, because we believe that the better understanding of the role of cytokines in the pathophysiology of depression and adiposity may help in development of the new therapeutic strategies both in adiposity and depression.

Declaration of interest

The authors state no conflict of interests.

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