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Short Communication

Association of serum ferritin level and depression with respect to the body mass index in Korean male adults

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BACKGROUD/OBJECTIVES: Obesity is globally a major public health issue. Evidence suggests that elevated ferritin levels are associated with obesity, dyslipidemia, insulin resistance, and metabolic syndrome. This study was undertaken to examine the relationship between the serum ferritin level and depression in Korean male adults with respect to classification of the prevailing obesity.
SUBJECTS/METHODS: This was a case-control study; subjects were classified into obese group ($\geq$ 25.0 kg/m^2, 28 subjects) and normal group (18.5-22.9 kg/m^2, 27 subjects). A survey was conducted to assess the depression levels as per the guidelines suggested by the Center program for Epidemiological Studies-Depression (CES-D). Blood was collected from each group for assessing biomarkers, and isolated plasma was evaluated for fasting glucose, insulin, quantitative insulin sensitivity check index, and ferritin levels. Data were analyzed, and groups were compared with respect to Body Mass Index (BMI), depression scale and biomarkers.
RESULTS: The average depression score of the obesity group was 16.86, which was higher than the normal group (12.56). Subjects scoring more than 16 points comprised 53.6% of the population in the obese group, which was more than double that in the normal group, as assessed by the CES-D program. Furthermore, the serum ferritin level of the obesity group was 207.12 ng/mL, which was higher than that of the normal group (132.66 ng/mL). Lastly, the BMI appeared to be significantly correlated with both depression ($r = 0.320$, $P = 0.017$) and elevated ferritin levels ($r = 0.352$, $P = 0.008$).
CONCLUSION: This study provides evidence of existing correlation between ferritin and depression with obesity.

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INTRODUCTION

The prevalence of overweight adults and obesity has increased worldwide [1,2]. Obesity-related comorbidities, including mental disorders, result in an impaired health-related quality of life [3-6]. Previous researches studying the association of obesity with depression have revealed that obesity is associated with depressive symptoms, and there is growing evidence that the Body Mass Index (BMI) is an independent predictor of mental disorders [7]. Importantly, public health intervention programs that aim to achieving an ideal body weight or BMI in the population can benefit both the physical and mental health status of an individual [2].

Adipocytes are known to have enhanced serum ferritin levels in obesity, suggesting a role in the outcome of the disease. Given the ideas, studies have investigated the role and status of iron in obesity and related mental health [8].

In recent years, numerous studies have examined the association between serum ferritin level and various types of adiposity [9-11]. The BMI and waist-to-thigh ratio are reported to be the strongest predictors of the serum ferritin level [12]. Two analyses from the National Health and Nutrition Examination Survey shows that serum ferritin levels are associated with abdominal obesity and other indices of body fat distribution [13,14]. Recently, the waist-to-hip circumference ratio was reported to be related to the serum ferritin levels in obese patients with metabolic syndrome [15] in US [14] and Chinese adults [16], suggesting a close relationship between obesity as a metabolic syndrome and iron storage concentration.

Some reports in Korea have also suggested an association between the serum ferritin level and abdominal obesity [17] and metabolic syndrome [18,19].

This study aimed to determine the association with serum ferritin level and depression based on the BMI status in young male subjects. Consequently, data on body weight, age, and blood analysis were collected after performing a self-rating depression scale survey. Male subjects were chosen after excluding individuals with anemia or those receiving treatment for anemia.

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SUBJECTS AND METHODS

Research design

This study performed a descriptive analysis of the BMI, depression, and serum ferritin levels in Korean male adults to determine their correlation. Male subjects in their twenties were enrolled for this study, and they were examined in a nearby university. Data was collected from September to October, 2016. The research purpose was socially publicized as obesity prevention and management. In the primary screening, all voluntary participants were assessed for their weight and height. Based on the Cohen [20] Power analysis formula at a significance level (α) of 0.05, the required number of subjects was calculated to be 24 per group, comparison group of 2, medium effect size of 0.30, and statistical power (1-β) of 0.80. Hence, we required a minimum total of 48 subjects. Considering wastage rates of 10-15%, 58 people were ultimately targeted.

The primary screening document classified the 58 enrolled subjects into the obese and normal groups. The subjects were divided into the two groups, based on the standard of the Korean Obesity Academic Society: BMI $\geq$ 25.0 kg/m^2 (obese group, 28 subjects) and 18.5-22.9 kg/m^2 (normal group, 27 subjects). All subjects undertook a survey, and relevant blood tests were conducted. Finally, 55 subjects were included in the analysis; 2 subjects who had undergone treatment due to hemolysis, and 1 subject who dropped out, were excluded.

The purpose of the study, progress, security and anonymity of the data, and the possibility of withdrawal, was explained to all participants by the researcher. Written consent was obtained from all subjects who agreed and understood the study participation (IRB No:AFMC-15065-IRB-15-054).

Assessment of BMI

BMI was assessed on the height and weight of the subject, as described elsewhere [21]. Briefly, height and weight were measured after overnight fasting, with the participants shoeless and wearing a lightweight gown. The BMI was calculated as the weight (kg) divided by the square of the height (m).

Assessment of self-rating depression sale

Depression levels were assessed using self-rating scale methods, as described previously [22]. To measure depression, the Center program for Epidemiological Studies-Depression (CES-D) developed by Radloff [23], was modified by Chon and Rhee [22] for applying to the Korean population. We employed the revised survey in our study, which contains 20 questions for measuring the behavior, physical, and cognition areas related to depression. Each section was divided into a 4-point scale as follows: 'rarely, 0 point', 'sometimes, 1 point', 'considerably, 2 points', and 'mostly, 3 points'. Ranging from a minimum score of 0 to a maximum of 60, the score obtained was proportional to the level of depression.

Based on the scores achieved, the subjects were classified as depression group (over 16) and normal group (under 16), based on the Boyed *et al*. [24] standard. The reliability of the measurement was Cronbach's $\alpha = 0.84$ in Radloff [23] and Cronbach's $\alpha = 0.85$ by Chon and Rhee [22]. In this study, the Cronbach's α was assessed as 0.90.

Blood biochemical analysis

Briefly, using a 22G syringe, blood samples were collected after overnight fasting. The biochemistry tests included variables of glucose, insulin, and serum ferritin in plasma. All analysis were performed by the Korea Green Cross Biotherapeutics Inc. The quantitative insulin sensitivity check index (QUICKI) for insulin sensitivity were calculated using the equation, 1 / (log (fasting insulin μU/mL) + log (fasting glucose mg/dL)). QUICKI determines the range below 0.339 as unhealthy individuals with low insulin sensitivity, and below 0.30 as diabetes. The serum ferritin levels were measured using specific enzyme linked immunoassays (Green Cross Biotherapeutics Inc, Korea), where a reference value of the ferritin assay was 5-600 ng/mL.

Data analysis

Data were analyzed using the SPSS WIN 22.0 program (SPSS Inc. Chicago, IL, USA). General characteristics of subjects were analyzed by descriptive statistics (Frequency, or mean and standard deviation). The difference between the subjects' depression and serum ferritin level was analyzed using the *t-test and* χ^2-test. The Pearson correlation coefficient was applied for the final analysis. *P*-values less than 0.05 are considered significant.

RESULTS

General characteristics of the subjects

The average age of the participants was 20.9 years and BMI was 25.9 kg/m^2. Elementary school period revealed the duration showing highest weight increase (23.6%). Familial assessment revealed the father (18.2%) to be the most obese, followed by the mother (10.9%), and lastly the siblings (7.3%) (See Table 1). The revised self-rating depression scale survey for Koreans is commonly used in healthy people and is applied freely (See Supplemental Table 1). Based on the self-rating depression scale (CES-D) survey, depression was classified at a score of more than 16. The average score achieved was 14.75. Totally, 40% of subjects (22 out of 55) surveyed in our study were found to be depressive.

Higher serum ferritin levels and depression scores on obesity

Obese people are often observed to be afflicted with accompanying emotional disorders or depression. To examine the factors affecting obesity and the depression status in these participants, the subjects were classified according to their BMI status and factors analyzed.

The obese group had a higher BMI (mean: 30.86 kg/m^2) than the normal group (mean: 20.69 kg/m^2) ($t = 26.258$, $P < 0.001$), as presented in Table 2. The weight increasing period in the obese group was 7.1% in the group less than 7 years, 46.4% in the elementary school, 17.9% in the middle school, and 14.3% in the high school and University. The level of depression was higher in the obese group (mean: 16.86 scores) than in the normal group (mean: 12.56 scores) ($t = 3.363$, $P = 0.001$). As expected, depression was higher in the obese group, with the depression rate being more than double in the obese group than the normal group (53.6% vs. 25.9%, for obese group vs. normal group, $\chi^2 = 4.377$, $P = 0.036$).

Table 1. General characteristics of the subjects (n = 55)

Variables	Category	Mean±SD n (%)	Acquired score range
Age, yrs (mean±SD)		20.38 ± 0.782	19-23
BMI (kg/m^2)		25.87 ± 5.32	19-33
Weight increasing period	Prior to age 7	2 (3.6)	
	Elementary school	13 (23.6)	
	Middle school	5 (9.1)	
	High school	4 (7.3)	
	University	4 (7.3)	
	None	27 (49.1)	
Obese person in family	Father	10 (18.2)	
	Mother	6 (10.9)	
	Both of parent	3 (5.5)	
	Brothers and sisters	4 (7.3)	
	None	27 (49.1)	
Depression		14.75 ± 5.17	4-28
Classification of depression	Normal group	33 (60)	
	Depressive group	22 (40)	

Table 2. The analysis of depression between normal and obese group (n = 55)

Variables	Category		Normal (BMI = 18.5-22.9) n = 27 (%)	Obese (BMI ≥ 25) n = 28 (%)	t/χ^2 (*P*-value)
BMI (kg/m^2)			20.69 ± 1.25	30.86 ± 1.59	26.258 (< 0.001)
Obese person in family	Father	Yes	4 (14.8)	6 (21.4)	0.404 (0.729)
		No	23 (85.2)	22 (78.6)	
	Mother	Yes	3 (11.1)	3 (10.7)	0.002 (0.648)
		No	24 (88.9)	25 (89.3)	
	Both of parent	Yes	0 (0.0)	3 (10.7)	3.063 (0.236)
		No	27 (100)	25 (89.3)	
	Siblings	Yes	2 (7.40)	5 (17.9)	1.351 (0.422)
		No	25 (92.6)	23 (82.1)	
Depression			12.56 ± 4.45	16.86 ± 5.00	3.363 (0.001)
Classification of depression	Normal group		20 (74.1)	13 (46.4)	4.377 (0.036)
	Depressive group		7 (25.9)	15 (53.6)	

Table 3. Blood biochemical analysis of subjects Mean±SD

Variables	Normal (BMI = 18.5-22.9) n = 27	Obese (BMI ≥ 25) n = 28	Total	Reference value
Glucose (mg/dL)	78.6 ± 4.9	84 ± 6.0**	81.3 ± 6.1	70-100
Insulin (μU/mL)	4.2 ± 1.6	7.8 ± 3.3***	6.0 ± 3.2	3.00-28.00
QUICKI	0.40 ± 0.33	0.36 ± 0.28***	0.39 ± 0.05	0.339-0.45
Serum ferritin (ng/mL)	132.66 ± 63.15	207.12 ± 104.61**	170.57 ± 4.8	20-400

** P< 0.01 *** P< 0.001

QUICKI: quantitative insulin sensitivity check index

Fasting blood was analyzed for glucose, insulin, QUICKI of insulin sensitivity, and ferritin levels. As expected, the obese group had a higher level of glucose and insulin, and a lower level of QUICKI (index of insulin sensitivity), as compared to the normal group (Table 3). The average serum ferritin level was 170.57 ng/mL in the subjects. Consistently, the serum ferritin level was higher in the obese group (mean: 207.12 ng/mL) than in the normal group (mean: 132.66 ng/mL) (t = 3.181, P = 0.002, Table 4).

Correlation of BMI, depression, and serum ferritin levels

We analyzed the relationship between serum ferritin level and depression on either the BMI status or other variables, such as insulin sensitivity. Interestingly, BMI appears to be significantly correlated to depression (r = 0.320, P = 0.017) and the serum ferritin level (r = 0.352, P = 0.008). Furthermore, depression also appears to be correlated to the serum ferritin level (r = 0.472, P = 0.001, See Table 4A). As expected, the insulin sensitivity of subjects did not correlate with depression (r =

Table 4. Correlation of the subject's BMI, depression and blood analysis

(A) Correlation between BMI, depression and serum ferritin (n = 55)

Variables	BMI	Depression	Serum ferritin
	r (*P*-value)		
BMI	1		
Depression	0.320 (0.017)	1	
Serum ferritin	0.352 (0.008)	0.472 (0.001)	1

(B) Correlation between insulin sensitivity, depression and serum ferritin (n = 55)

Variables	Insulin sensitivity	Depression	Serum ferritin
	r (*P*-value)		
Insulin sensitivity	1		
Depression	-0.110 (0.428)	1	
Serum ferritin	-0.302 (0.026)	0.472 (0.001)	1

-0.110, $P = 0.428$). However, insulin sensitivity appears to have a correlation with serum ferritin levels (r = -0.302, $P = 0.026$, Table 4B)

DISCUSSION

Results of this study indicate that serum ferritin and depression levels of young male adults are dependent on the BMI status, and higher BMI levels correlate with depression. The mean depression score in the obese group (18.86 points) was higher than the normal group (12.56 points); furthermore, the depressive group, which had a score of more than 16 points based on the Boyed *et al*. [24] standard, contained twice as many subjects in the obese group (53.6%) as compared to the normal group (25.9%).

A previous study reported that obese individuals were 38% more likely to experience current depression, and 40% were more likely to have lifetime diagnosed depression among men, after fully adjusting for several factors such as demographics, obesity-related comorbidities, and psychosocial or lifestyle factors [7]. Indeed, the relationship between obesity and mental health has been conclusively correlated. This has been reported in an important study examining BMI as a predictor of the mental health status [7]. In addition, our results support the conclusion of the previous study in that there exists an association between BMI and depression. Moreover, our results also demonstrate a correlation between BMI and serum ferritin levels, which were found to be higher in the obese group (207.12 ng/mL) than in the normal group (132.66 ng/mL). Furthermore, we observed that obesity increases both the depression status and serum ferritin level.

Serum ferritin is used as a biomarker of the quantitative state of iron in the body, and is the most reliable indicator of iron in the body [25]. The association between the serum ferritin level and obesity in Japanese subjects [10] and Chinese subjects [11] was found to be positive. In addition, elevated serum ferritin levels were discovered to be a risk factor for metabolic syndrome [26], and a predictive factor for obesity during the 5 year follow up of men [27]. A previous study showed that 3,839 subjects with higher serum ferritin concentrations were more likely to be male, and have a higher BMI and WBC count [28].

On the other hand, obesity is considered to be a chronic inflammatory state, and ferritin is a reactant that is observed in the acute phase of inflammation [29]. In recent years, increased serum ferritin levels are recognized as a consequence of a chronic inflammatory reaction caused by obesity, and not just the result of an increase in iron stores [30]. An increased serum ferritin concentration in clinical patients is associated with depressive symptoms [31], with inflammation being the key explanation for the association. In addition, normal or increased ferritin levels play significant roles in the onset and development of depression since they are important components of the inflammatory process [32], which is consistent with the results of this study.

This study has several limitations. First, the research was a cross-sectional study. The depression stages of the subject based on his weight loss or gain were not known. Second, females were excluded from this study, due to the possibility of hormones affecting depression. Nevertheless, we determined there exists a relationship between depression and serum ferritin levels with the BMI status, which would thereby overcome the bias of sex-related hormones. Third, the study focused on the status of young males only, which is contradictory to a previous study by Veltman *et al*. [33] who reported that older people have a tendency to increased depression in the community. The fourth limitation of this study is that the correlation between depression and serum ferritin was confirmed according to the BMI status only. Therefore, there is a limitation in confirming the correlation between insulin sensitivity, blood glucose, and blood insulin. There is also a limitation for adjustment of potential confounding factors such as BMI, in the correlation of depression and ferritin.

Despite these limitations, the available data conclusively indicates that depression and obesity interact reciprocally. Further studies are required to examine the relationship between the serum ferritin level and depression by expanding the number of subjects. Also, we suggest a future study that includes adjustment factors such as BMI, glucose, and insulin levels as potential confounding factors, as it is necessary to confirm the correlation between depression and serum ferritin, including BMI, as well as variables such as insulin sensitivity, blood glucose, and blood insulin. This study provides valuable public health data to confirm the association between depression and the serum ferritin level according to the BMI of young adult males. We believe these results indicate the potential of serum ferritin to be used as a biomarker for measuring the depression status in obesity.

CONFLICT OF INTEREST

The authors declare no potential conflicts of interests.

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