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The relation of serum nesfatin-1 level with anthropometric and metabolic parameters in children and adolescents

A prospective observational study

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Abstract

Nesfatin-1, a recently discovered anorexigenic neuropeptide, seems to play an important role in hypothalamic pathways regulating food intake and energy homeostasis. The aim of this study was to evaluate the relation of serum nesfatin-1 level with metabolic and anthropometric parameters in children and adolescents.

This study prospectively included 78 Korean children and adolescents (42 obese/overweight group and 36 healthy control group). Fasting serum nesfatin-1 was quantitatively assayed by ELISA. Lipid profile, fasting blood glucose, fasting insulin, and the homeostasis model assessment of insulin resistance (HOMA-IR) were measured as metabolic parameters.

Serum nesfatin-1 levels were significantly lower in obese/overweight group than in control group (median 1.4 vs 2.0 ng/mL; $P = .003$). Pubertal subjects have the lower serum nesfatin-1 level than pre-pubertal subjects (median 1.5 vs 2.6 ng/mL; $P = .02$). Nesfatin-1 levels negatively correlated with chronological age ($r = -0.37$; $P = .001$), BMI ($r = -0.33$; $P = .003$), and BMI SDS ($r = -0.26$; $P = .02$).

In conclusion, our results suggest that serum nesfatin-1 negatively correlated with BMI in children and adolescents. It suggests that nesfatin-1 might have an important role in regulation of food intake in obese children and adolescents.

Abbreviations: BMI = body mass index, ELISA = enzyme-linked immunosorbent assay, HDL-C = high-density lipoprotein cholesterol, HOMA-IR = homeostasis model assessment of insulin resistance, LDL-C = low-density lipoprotein cholesterol, NUCB2 = nucleobindin-2, SDS = standard deviation score, TC = total cholesterol, TG = triglycerides.

Keywords: body composition, insulin resistance, nesfatin-1, obesity, overweight

1. Introduction

Obesity has achieved pandemic proportions and is an important cause of morbidity and mortality in the world.[1,2] The global epidemic of overweight and obesity is rapidly becoming a major public health problem in most countries because it increases the risk of chronic diseases such as insulin resistance, type 2 diabetes, hypertension, and coronary heart disease.[3] An imbalance between energy intake and expenditure and a sedentary lifestyle are the most common causes of obesity.[2] The hypothalamus is the key regulatory center for energy balance and has abundant peptides that regulate satiety.[2] Many of these peptides are found at peripheral sites such as the gut and adipose tissue where they are important for body weight homeostasis and contribute to the pathogenesis of insulin resistance and metabolic consequences including diabetes, dyslipidemia, hypertension, and cardiovascular disease.[2,4,5]

Nesfatin-1 is a recently identified anorexigenic peptide, originates from the precursor protein nucleobindin-2 (NUCB2), that is implicated in appetite regulation, weight loss, and malnutrition and energy metabolism modulation.[6,7] NUCB2 is expressed both in the central nervous system as well as in peripheral tissues, and nesfatin-1 can also cross the blood–brain barrier by non-saturable transmembrane diffusion, consistent with its low lipophilicity.[8] This finding suggests that peripheral nesfatin-1 (either endogenous or exogenous) may access the CNS the exert biological actions. Several studies showed that peripheral nesfatin-1 was found to be associated with body mass index (BMI), body fat, and blood glucose, and fat-free mass in obese adults.[9,10] However, there is limited data on nesfatin-1 secretion in obese children and adolescents. The aim of this study was to investigate the relationship between serum nesfatin-1

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levels and anthropometric and metabolic parameters in Korean children and adolescents.

2. Patients and methods

2.1. Participants

This cross-sectional study included 78 Korean children and young adolescents who visited the Department of Pediatrics, Yeouido St. Mary's Hospital from March 2013 through February 2014. Of the participants, 27 (34.6%) were obese, 15 (19.2%) were overweight, and 36 (46.2%) were healthy controls. Weight categories were defined by age and gender according to Korean Growth charts 2007 as BMI higher than or equal to the 95th percentile for obesity, the 85th to 94th percentile for overweight and the 15th to 84th percentile for normal weight.[11] Participants with chronic diseases (including cardiovascular, gastrointestinal, or respiratory disease), history of chronic drug use such as steroids or endocrine pathology with obesity were excluded. Informed consent was given by all participants. The study was reviewed and approved by the local Institutional Review Board, which has jurisdiction over the local study populations (IRB number: SC13TISE0174).

2.2. Anthropometry measurements and laboratory evaluations

All patients and controls underwent physical examinations and laboratory evaluations. Height was measured with a Harpenden's stadiometer. Weight and height were recorded to the nearest 0.1 kg and 0.1 cm, respectively. Weight and height standard deviation scores (SDSs) were calculated using the 2007 Korean National Growth Charts.[11] BMI was calculated as kg/m^2 and BMI SDS was expressed according to chronological age, according to the 2007 Korean National Growth Charts.[11] Puberty staging was evaluated by the standards of Marshall and Tanner.[12] A testicular volume of ≥4 mL in males and stages 2–5 breast development in females were considered consistent with puberty.

Blood samples for glucose, insulin, lipid profile, thyroid function tests, 25-hydroxy vitamin D, and nesfatin-1 were taken after 10–12 h overnight fasting. Cut-off points for abnormal lipid levels (total cholesterol [TC] ≥200 mg/dL, low-density lipoprotein cholesterol [LDL-C] ≥130 mg/dL, high-density lipoprotein cholesterol [HDL-C] ≤35 mg/dL, and triglycerides [TG]) ≥150 mg/dL) were from the Third Report of the National Cholesterol Education Program[13] and the American Diabetes Association.[14] Dyslipidemia was defined as presence of one or more abnormal serum lipid levels. The homeostasis model assessment of insulin resistance (HOMA-IR) was calculated using the equation: HOMA-IR = fasting insulin (μU/mL) × fasting glucose (mmol/L)/22.5. Different cutoff values for prepuberty and puberty stages were used to determine the status of insulin resistance (HOMA-IR) (prepuberty >2.5, puberty >4).[15]

2.3. Serum nesfatin-1 assays

Serum nesfatin-1 levels were measured using a commercially available enzyme-linked immunosorbent assay (ELISA, BioVendor, Norcross, GA, USA). Kits had a dynamic range between 0.1 and 20 ng/mL and a detection limit of 0.021 ng/mL. Spike and recovery experiments showed mean recoveries between 94% and 106%. Intra-assay and inter-assay coefficients of variation were <10% and <15%, respectively. Each assay was performed in duplicate, and the mean is used for analyses.

2.4. Statistical analysis

All statistical analyses used SPSS for Windows version 18 (SPSS Inc., Chicago, IL, USA).

Categorical variables are expressed as numbers and percentages and were compared by Fisher's exact test. Continuous variables are expressed as medians and ranges and were compared using Mann–Whitney *U* test. Relationships between fasting concentrations of serum nesfatin-1 and metabolic parameters (BMI, BMI SDS, weight SDS), fasting blood glucose, lipid profiles were examined by linear regression and Pearson's correlation coefficient analysis. Serum nesfatin-1 levels were log-transformed to achieve a normal distribution for these analyses. All *P* values <.05 were considered statistically significant.

3. Results

3.1. Clinical and laboratory characteristics

A total of 42 obese/overweight participants (27 obese and 15 overweight) and 36 healthy controls were included. The demographic, clinical, and laboratory data of the participants are in Table 1. Obese and overweight participants were combined to a single group because the group numbers were small with no difference in serum nesfatin-1 between the two groups (median 1.4 vs 1.5 ng/mL; $P=.75$) (supplementary Table 1, http://links.lww.com/MD/C966). Median ages were 10.1 years for the obese/overweight group and 10.8 years for the healthy controls ($P=.87$), with 17 (40.5%) girls in the obese/overweight group and 19 (52.8%) in the healthy control group ($P=.36$). Median BMIs were 24.8 for the obese/overweight group and 17.7 for healthy group ($P<.001$) with no differences between groups in fasting blood glucose. Dyslipidemia was more common in obese/overweight group than in control participants (24/42 [57.1%] vs 1/15 [6.6%]; $P<.001$).

3.2. Nesfatin-1 levels and clinical parameters

Serum nesfatin-1 levels were significantly lower in the obese/overweight group than in the control group (median 1.4 vs 2.0 ng/mL; $P=.02$) (Table 1). This trend was also observed among the prepuberty (median 2.2 vs 3.4 ng/mL; $P=.07$) and puberty subgroups (median 1.2 vs 1.7 ng/mL; $P=.11$), but the differences were not significant (Fig. 1). Nesfatin-1 levels were not significantly different between boys and girls (median 1.4 vs 2.2 ng/mL; $P=.22$). Participants in puberty had lower serum nesfatin-1 levels than prepuberty participants (median 1.5 vs 2.6 ng/mL; $P=.02$) (Table 2). Nesfatin-1 levels were not significantly different between participants with and without insulin resistance (median 1.2 vs 1.6 ng/mL; $P=.88$). Serum nesfatin-1 levels in dyslipidemia patients was lower than in patients without dyslipidemia (median 1.2 vs 2.7 ng/mL; $P=.047$).

Correlations between serum nesfatin-1 and continuous clinical parameters are in Table 3 and Fig. 2. Serum nesfatin-1 levels negatively correlated with chronological age ($r=-0.37$; $P=.001$), BMI ($r=-0.33$; $P=.003$), and BMI SDS ($r=-0.26$; $P=.02$) in all participants. The negative correlation between chronological age and serum nesfatin-1 was observed for both obese/overweight participants ($r=-0.37$; $P=.02$) and control

Table 1

The demographic, clinical and laboratory data for obese/overweight and control participants.

Characteristic	Obese/overweight (n = 42)	Control (n = 36)	*P* Value
Chronological age, years	10.1 (5.8–17.5)	10.8 (6.0–14.4)	.87
Female	17 (40.5)	19 (52.8)	.36
BMI, kg/m^2	24.8 (20.1–40.1)	17.7 (13.9–21.9)	<.001
BMI SDS	1.7 (1.2–3.2)	0.1 (-1.9–1.0)	<.001
Puberty	27 (64.3)	22 (61.1)	.82
Fasting blood glucose, mg/dL	94 (81–118)	94 (76–118)	.82
Insulin, mg/dL*	11.7 (0.7–60.5)	NA	NA
HOMA-IR*	2.8 (0.2–13.8)	NA	NA
Total cholesterol†, mg/dL	187 (119–281)	178 (143–226)	.22
LDL cholesterol†, mg/L	106 (14–198)	99 (94–130)	.96
HDL cholesterol†, mg/dL	47 (30–175)	57 (43–72)	.02
Triglycerides†, mg/dL	116 (32–339)	102 (51–142)	.11
Dyslipidemia	24/42 (57.1)	1/15 (6.6)	<.001
25-Hydroxy vitamin D, ng/mL	12.3 (5.2–22.3)	14.2 (6.0–26.4)	.06
Nesfain-1, ng/mL	1.4 (0.1–10.7)	2.0 (0.1–20.0)	.02

Data are median values (range) for continuous variables and number of cases (%) for categorical variables, unless otherwise specified.

BMI = body mass index, BMI SDS = standard deviation score of body mass index, HDL = high-density lipoprotein, HOMA-IR = homeostasis model assessment-insulin resistance, LDL = low-density lipoprotein, NA = not available.

* Measured in 44 obese/overweight participants.

† Measured in 54 participants: 42 obese/overweight and 12 controls.

participants ($r = -0.38$; $P = .02$). Serum nesfatin-1 was not correlated with fasting blood glucose, insulin, HOMA-IR, LDL-C, HDL-C, or TG.

4. Discussion

Based on a review of published studies, this is the first study to evaluate the relationship between serum nesfatin-1 levels and metabolic and anthropometric parameters in children and adolescents. Serum nesfatin-1 levels were negatively correlated with BMI. Our data suggests that low levels of the nesfatin-1 might contribute to inadequately controlled food intake in children and adolescents with obesity.

Animal studies strongly suggest that nesfatin-1 is a potential contributor to energy homeostasis.[16] Oh et al reported that in vivo deficiency of nesfatin-1 activity could cause overweight and obesity.[16] Chronic infusion of nesfatin-1 into the third ventricle of rats consistently reduced body weight gain. Meanwhile, rats

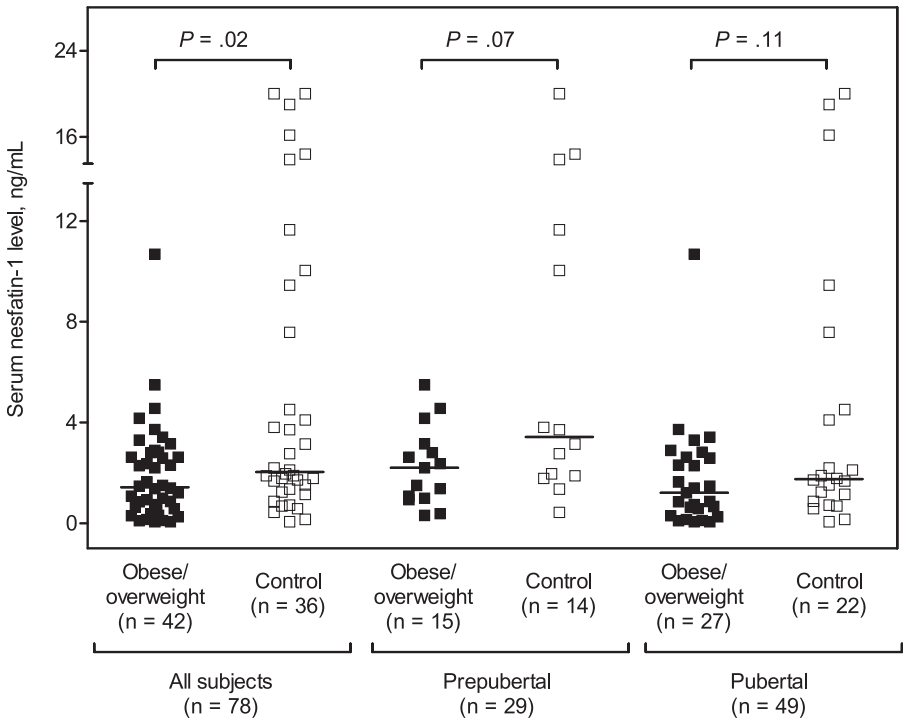

Figure 1. Serum nesfatin-1 levels in prepuberty and puberty groups. Closed and open and boxes indicate serum nesfatin-1 levels in obese/overweight and control groups, respectively. Horizontal bars indicate median values of serum nesfatin-1.

Table 2

Clinical and laboratory data for prepurbety and puberty subjects.

Characteristic	Prepuberty (n = 29)	Puberty (n = 49)	*P* Value
Chronological age, years	8.7 (5.8–11.9)	12.0 (7.4–17.5)	<.001
Female	11 (37.9)	25 (51.0)	.35
BMI (kg/m^2)	20.2 (13.9–27.5)	21.9 (14.2–40.1)	.03
BMI SDS	1.4 (−1.5–2.6)	1.3 (−1.9–3.2)	.65
Fasting blood glucose, mg/dL	94 (76–118)	93 (81–118)	.81
Insulin, mg/dL*	9.5 (0.7–32.0)	12.8 (4.8–60.5)	.17
HOMA-IR*	2.2 (0.2–8.1)	3.0 (1.0–13.8)	.20
Dyslipidemia	7/21 (33.3)	18/36 (50.0)	.17
25 (OH)vitamin D, mg/dL	13.1 (7.0–26.4)	13.3 (5.2–23.4)	.45
Nesfain-1, ng/mL	2.6 (0.3–20.0)	1.5 (0.1–20.0)	.02

Data are medians (range) for continuous variables and number of cases (%) for categorical variables, unless otherwise specified.

BMI = body mass index, BMI SDS = standard deviation score of body mass index, HOMA-IR = homeostasis model assessment-insulin resistance.

* Measured in 44 overweight/obese participants.

gain body weight after chronic intracerebroventricular administration of antibodies against the gene encoding nesfatin/NUCB2.[16] Nesfatin-1 can go through the blood–brain barrier via an unsaturable mechanism, thus, may influence the appetite through a central mechanism.[8,17] It was reported that nesfatin-1 suppresses food intake, even in obese mice with a knockdown leptin gene. This finding indicates the efficacy of nesfatin-1 as an appetite suppressant, as it works independently of the leptin pathway.[16] These data indicated that nesfatin-1 is involved in the physiological regulation of feeding behavior in rats and might be involved in body weight regulation.

Previous clinical studies have had conflicting results about the association between BMI SDS and serum nesfatin-1 levels. Initial studies showed a negative correlation between nesfatin-1 levels and BMI in healthy people.[9,18] Abaci et al found a significant negative correlation between BMI and serum nesfatin-1 levels in obese children.[19] In our study, nesfatin-1 was negatively correlated with BMI SDS in children and adolescents, consistent with previous studies conducted among adult population.[9,18,19] In contrast, other studies found a positive correlation between BMI and serum nesfatin-1 levels in adult population.[2,10] Anwar et al found a positive correlation between serum nesfatin-1 and BMI SDS in obese children.[20] Differences in assessment methods (such as ELISA for NUCB2 and nesfatin-1 vs sandwich-type ELISA that recognizes only nesfatin-1), experimental conditions, commercial kits, and populations might contribute to these discrepancies.

Levels of circulating serum nesfatin-1 and their relationship with age have not yet been fully investigated. Li et al reported that older healthy humans (average age, 47.3 years) had higher mean fasting plasma nesfatin-1 levels than younger healthy people (average age, 19.4 years).[18] Data are limited on the association between serum nesfatin-1 and chronological age among children and adolescents. A previous study showed that a marginal change was observed in plasma nesfatin-1 levels in mice aged 2 to 24 months, but the ratio of plasma nesfatin-1 levels to visceral fat decreased with advancing age.[21] This relationship has not been demonstrated in humans, but we found a negative correlation between serum nesfain-1 levels and chronological age. However, our study was limited to young children and we did not analyze visceral fat. Therefore, further studies should be performed to investigate the negative correlation between the ratio of serum nesfatin-1 to visceral fat and chronological age across the full ranges of ages, including children, adolescents, and adults of

Table 3

Correlations between serum nesfatin-1 levels and continuous clinical parameters*.

Variable	All subjects (n = 78)		Obese/overweight (n = 42)		Control (n = 36)	
	r	*P* Value	*r*	*P* Value	r	*P* Value
Chronological age, years	−0.37	.001	−0.37	.02	−0.38	.02
BMI, kg/m^2	−0.33	.003	−0.10	.53	−0.33	.048
BMI SDS	−0.26	.02	0.11	.49	−0.09	.60
Fasting blood glucose, mg/dL	0.06	.63	0.12	.44	−0.03	.88
Insulin, mg/dL†	−0.14	.38	−0.11	.50	−0.85	.07
HOMA-IR†	−0.13	.41	−0.10	.56	−0.88	.046
Lipid profiles						
Total cholesterol, mg/dL‡	−0.29	.03	−0.23	.15	−0.60	.04
LDL cholesterol, mg/dL‡	−0.01	.96	0.09	.60	−0.94	.001
HDL cholesterol, mg/dL‡	−0.17	.23	−0.25	.13	−0.01	.98
Triglycerides, mg/dL‡	−0.20	.16	−0.20	.20	0.05	.87
25-hydroxy vitamin D	0.12	.33	−0.01	.94	0.07	.71

BMI = body mass index, BMI SDS = standard deviation score of body mass index, HDL = high-density lipoprotein, HOMA-IR = homeostasis model assessment-insulin resistance, LDL = low-density lipoprotein.

* Serum nesfatin-1 levels were log-transformed to achieve a normal distribution for these analyses.

† Measured in 44 obese/overweight participants.

‡ Measured in 54 participants: 42 obese/overweight and 12 controls.

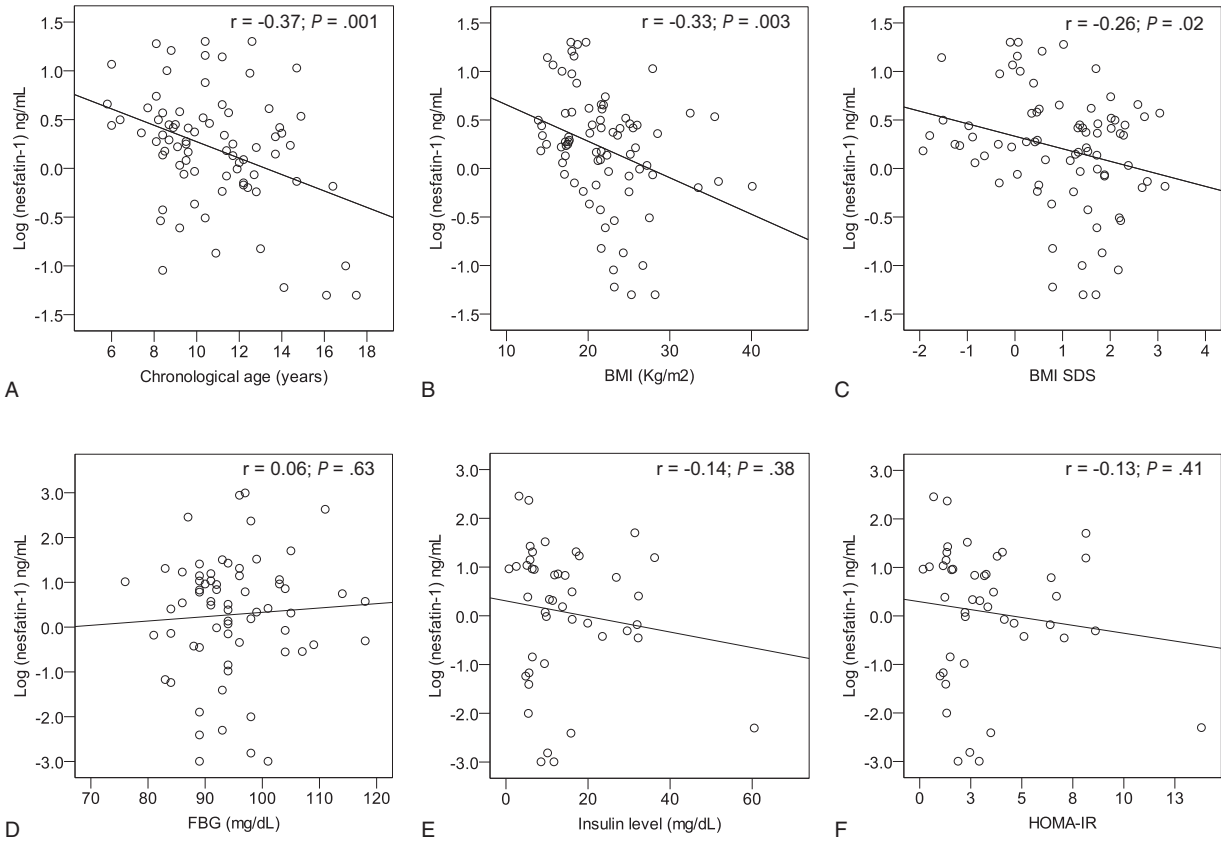

Figure 2. Correlation of serum nesfatin-1 levels with chronological age. (A), BMI (B), BMI SDS (C), FBG (D), insulin level (E), and HOMA-IR (F). BMI = body mass index, BMI SDS = standard deviation score of body mass index, FBG = fasting blood glucose, HOMA-IR = homeostasis model assessment-insulin resistance.

advanced age. In this study, serum nesfatin-1 levels were lower in pubertal subjects than in prepubertal children. A previous study reported that serum nesfatin-1 levels increased with puberty stage in patients and controls, but the increase was significant in the control group only.[20] Another study compared obese children for the presence of pubertal signs and found no significant differences by serum nesfatin-1 levels.[19] Garcia-Galiano et al examined the precursor protein, NUCB2 mRNA in human, rat, and mouse gonads.[22] They reported increased hypothalamic NUCB2/nesfatin-1 expression during the prepubertal transition. Intracerebroventricular administration of nesfatin-1 induced significant elevation of circulating gonadotropins in female rats during puberty.[22] Secretion of appetite-regulating peptides is different in prepuberty and puberty groups. Leptin, which is commonly associated with obesity, increases in men and women from Tanner stages I to III but falls significantly in men at Tanner states IV and V while continuing to rise in women.[23] Ghrelin levels are higher before puberty compared to puberty in normal weight and obese people.[24] Therefore, these regulatory peptides might be associated with the development of puberty as well as appetite control and metabolism. Characterization of specific neuroendocrine mechanisms and pathways by which nesfatin-1 regulates the gonadotropic axis at puberty remains to be completed and will require additional neuroanatomical and functional analysis.[22]

Another important feature of nesfatin-1 is its effect on insulin–glucose metabolism. Nesfatin-1 has direct, glucose-dependent insulinotropic action on β-cells of the pancreatic islets, enhancing both insulin secretion and insulin action.[25] Yang et al reported that intracerebroventricular infusion of nesfatin-1 improves glucose homeostasis by inhibiting hepatic glucose production in rats with obesity induced by diet.[26] Li et al found that plasma nesfatin-1 levels were lower in adults with type 2 diabetes compared to healthy adults.[18] In contrast, Anwar et al found positive correlations between nesfatin-1 and insulin and HOMA-IR.[20] Abaci et al reported no association between nesfatin-1 and insulin resistance in obese children.[19] Our study found no association between serum nesfatin-1 and insulin resistance among obese children and adolescents. In this study, nesfatin-1 levels were lower in people with dyslipidemia than in those without dyslipidemia. Li et al previously reported a positive correlation in patients with type 2 DM between HDL-C and fasting plasma nesfatin-1 levels.[18] Understanding the influence of nesfatin-1 on insulin–glucose metabolism requires further study.

This study had several limitations. First, age, sex, and puberty stage could not be matched between the obese/overweight group and the normal weight group because of the small number of cases. Further studies with a larger number of patients could resolve this limitation by matched case-control studies or stratified subgroup analysis. Second, serum insulin measurements were done in a small number of patients so conclusions could not be made about the relationship between serum nesfatin-1 levels and insulin resistance (i.e., HOMA-IR). Finally, although this study included patients with consecutive BMI SDS measurements, small number of patients with extreme values of BMI SDS (>2.0 and ≤ -2.0) were included. Therefore, the effect of BMI SDS on serum nesfatin-1 levels could not be sufficiently investigated.

5. Conclusion

This study suggests that serum nesfatin-1 is negatively associated with BMI and pubertal development during childhood and adolescence. Nesfatin-1 might be one of the important factors in the regulation of food intake in obese children and adolescents. Further studies with more participants are needed to evaluate the influence of puberty status, age, and insulin resistance on nesfatin-1 levels in children and adolescents and the pathological relevance of nesfatin-1 in obesity.

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