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Serum levels of phoenixin and nesfatin in patients with iron, vitamin B12 or vitamin D deficiency: a comparative study

Níveis séricos de fenixina e nesfatina em pacientes com deficiência de ferro, vitamina B12 ou vitamina D: um estudo comparativo

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ABSTRACT

Objective
Micronutrient deficiencies are recognized as critical factors contributing to the global burden of disease. Phoenixin-14 and nesfatin-1 newly discovered neuropeptides which have been related to various physiological processes and potential therapeutic applications. This study was conducted to test whether circulating concentrations of nesfatin-1 and phoenixin-14 were altered in individuals with iron, vitamin B12, vitamin D and combined deficiencies.

Method
Our study group consists of 33 patients with iron deficiency, 30 patients with vitamin B12 deficiency, 33 patients with vitamin D deficiency, 32 patients with combined deficiency, 24 patients who received vitamin D supplementation and 32 control subjects. Serum nesfatin-1 and phoenixin-14 concentrations were determined measured by Enzyme-Linked ImmunoSorbent Assay method.

Results
Serum phoenixin-14 values were significantly lower in subjects with iron, vitamin B12, vitamin D and combined deficiency compared with the healthy group. After vitamin D supplementation, serum phoenixin-14 levels did not differ significantly with the healthy group. Serum nesfatin-1 concentrations were significantly lower in subjects with iron, vitamin B12 and combined deficiency compared with the healthy group. There was no significant difference in nesfatin-1 values between those with vitamin D deficiency, those taking vitamin D3 supplements and the healthy controls.

Conclusion
Significant differences in phoenixin-14 and nesfatin-1 levels between iron, vitamin D, vitamin B12 deficiency and the healthy control group supports that these molecules related to the pathogenesis of micronutrient deficiencies. Phoenixin-14 and nesfatin-1 may be considered potential biomarkers of micronutrient deficiencies.

Keywords: Iron Deficiency. Nesfatin-1. Phoenixin-14. Vitamin B12 deficiency. Vitamin D deficiency.

RESUMO

Objetivo
As deficiências de micronutrientes são reconhecidas como fatores críticos que contribuem para a carga global de doenças. Neuropeptídeos recém-descobertos Phoenixin-14 e nesfatin-1 que foram relacionados a vários processos fisiológicos e potenciais aplicações terapêuticas. Este estudo foi realizado para testar se as concentrações circulantes de nesfatina-1 e fenixina-14 estevam alteradas em indivíduos com deficiência de ferro, vitamina B12, vitamina D e combinada.

Método
Nosso grupo de estudo consiste em 33 pacientes com deficiência de ferro, 30 pacientes com deficiência de vitamina B12, 33 pacientes com deficiência de vitamina D, 32 pacientes com deficiência combinada, 24 pacientes que receberam suplementação de vitamina D e 32 controles. As concentrações séricas de nesfatina-1 e fenixina-14 foram determinados pelo método Enzyme-Linked ImmunoSorbent Assay.

Resultados
Os valores séricos de fenixina-14 foram significativamente menores em pacientes com deficiência de ferro, vitamina B12, vitamina D e combinada em comparação com o grupo controle. Após a suplementação de vitamina D, os níveis séricos de fenixina-14 não diferiram significativamente com o grupo controle. Os valores séricos de nesfatina-1 foram significativamente menores em pacientes com deficiência de ferro, vitamina B12 e combinada em comparação com o grupo controle. Não houve diferença nos níveis de nesfatina-1 entre aqueles com deficiência de vitamina D, recebendo vitamina D3 ou aqueles controles saudáveis.

Conclusão
Nosso estudo observou diferenças significativas nas concentrações de fenixina-14 e nesfatina-1 entre ferro, vitamina D, deficiência de vitamina B12 e o grupo controle. A fenixina-14 e a nesfatina podem estar relacionadas à patogênese das deficiências de micronutrientes.

***Palavras-chave**: Falta de ferro. Nesfatina-1. Phoenixin-14. Deficiência de vitamina B12. Deficiência de vitamina D.*

INTRODUCTION

Vitamins and minerals are essential to human metabolism. Deficiencies of these micronutrients may lead to increased risks of pathlogies in physiological functions [1]. Micronutrient Deficiencies (MNDs) contribute significantly to the global burden of disease [2].

Vitamin D deficiency is a global health problem affecting more than one billion children and adults worldwide. Vitamin D plays a regulatory role in the immüne and endocrine system, as well as maintaining calcium and phosphate homeostasis. Vitamin D regulates intestinal mucosal immunity and intestinal barrier integrity [3,4]. Low levels of Vitamin D is closely associated with cardiovascular diseases, inflammatory processes, and cancer. In addition vitamin D deficiency is implicated in the development of a number of metabolic disorders, including İnsulin Resistance (IR), Type 2 Diabetes *Mellitus* (T2DM), obesity and metabolic syndrome [5].

Iron is a necessary trace element for all mammals and involve in many essential metabolic processes, such Deoxyribonucleic Acid (DNA) synthesis, oxygen transport, and energy metabolism [6]. Worldwide, iron deficiency is a common micronutrient deficiency with a high individual and societal cost [2]. Iron deficiency is caused by hemorrhage, decreased dietary iron and decreased iron absorption, genetic disorder, cancer, inflammation, and chronic diseases [6,7].

Vitamin B12 is a micronutrient that plays a significant role as a cofactor in essential biochemical reactions in cellular metabolism. Vitamin B12 deficiency primarily affects the hematopoietic system and the nervous system. Most common causes of vitamin B12 deficiency are malabsorption and impaired bioavailability, as well as inadequate dietary intake [8].

Nesfatin-1 is an anorexigenic peptide derived from the precursor protein Nucleobindin2 (NUCB2), discovered in the hypothalamus in 2006 [9]. It is generally expressed in central nervous system as well as peripheral tissues such as adipose tissue, pancreas, reproductive organs and predominantly gastic mucosa. Different bodily functions of nesfatin-1 have been reported including modulation of food intake, gastrointestinal functions, energy expenditure, and emotion related functions [10]. It has been suggested that peripheral nesfatin-1 may enter the brain and control appetite and feeding response. It has also been reported that nesfatin-1 reverses the negative effects of oxidative stress and modulates the intestinal microbiota composition and the structure of the intestinal barrier in various intestinal disorders. Additionally nesfatin-1 decreases stomach and intestinal motility [11].

Phoenixin (PNX) is a recently identified neuropeptide that produced mainly in the hypothalamus by the proteolytic cleavage of a small integral membrane protein 20 [12]. Immunohistochemical studies revealed co-expression of PNX-14 and nesfatin-1. PNX and nesfatin-1 exhibit counterbalancing interaction in various physiological processes [13]. PNX is also widely expressed in peripheral tissues, beginning from the heart, thymus, gastrointestinal tract, and ovary. Studies on PNX vary from regulation of the reproductive system to its relationship with food intake, memory, sensory processes and energy homeostasis [12,13]. PNX and nesfatin-1 also exerts anti-inflammatory, and cytoprotective effects [11,14,15). Despite the increasing knowledge about the nesfatin-1 and PNX-14, more research is needed to understand their place in general physiology and therapeutic potential.

Micronutrient deficiencies are common in our country and all over the world. We thought that PNX and nesfatin-1 neuropeptides might also play a role in micronutrient deficiencies because they affect a wide range of physiological and pathological mechanisms such as food intake and energy homeostasis. Therefore, we aimed to demonstrate and compare the concentrations of nesfatin-1 and PNX-14 in patients with iron deficiency, vitamin B12 deficiency, vitamin D deficiency, combined deficiency and healthy controls.

METHODS

Participants and Study Design

In this case-control study, 33 patients with iron deficiency, 30 patients with vitamin B12 deficiency, 33 patients with vitamin D deficiency, 24 patients who received vitamin D supplementation, 32 patients with combined deficiency (participants with concurrent deficiencies of vitamin D, vitamin B12 and iron) and 32 controls matched age and body mass index (BMI). Participants enrolled for the patient group are subjects with a diagnosis of iron deficiency (serum ferritin levels <30ng/ml, transferrin saturation <20%), vitamin D deficiency (vitamin D levels of <20ng/ml), vitamin B12 deficiency (vitamin B12 levels of <200pg/ml) and no have comorbidities. Subjects with vitamin D deficiency were supplemented with oral vitamin D at 50000 IU/week for 2 months. Participants with vitamin D levels >30 ng/ml after vitamin D supplementation were included in the study. As a rule of exclusion from the study, under the age of 18, having a pregnancy, comorbidities and additional

complaints, using additional medication were taken into consideration. Every volunteer provided written informed consent before participating in the research. The study has been approved by Local Ethical Committee Necmettin Erbakan University, Konya, Turkey (2021/3152).

Clinical and Biochemical Assessment

Detailed medical history and anthropometric measurements such as height, weight were taken from all cases and controls. BMI values were acquired by dividing their weight in kilograms by their height in meters squared. Venous blood specimens of the participants were taken after an overnight fasting for at least 10 hours. Biochemical parameter measurements were performed with commercially available kits by computerized analyzer (Roche Cobas c501, Mannheim Germany). Vitamin D, B12, and ferritin concentrations were determined by Electrochemiluminescence İmmunoassay (ECLIA) on the fully automated analyzer (Roche Cobas e601, Mannheim Germany). Samples of venous blood were centrifuged and serum were stored at -80°C for batch analysis. The assays of serum PNX-14 and nesfatin-1 concentrations were performed using Enzyme-Linked ImmunoSorbent Assay (ELISA) method by way of commercial kits (BT Lab Bioassay Technology Laboratory Human Elisa Kits, Shanghai Korain Biotech, China). PNX-14 catalog number: E7481Hu, standard curve range: 20-3800ng/L, sensitivity: 8.19ng/L, intra-assay: CV<8%, inter-assay: CV<10%. Nesfatin 1 catalog number: E3063Hu, standard curve range: 0.3-90 ng/ml, sensitivity: 0.15 ng/ml, intra-assay: CV<8%, inter-assay: CV<10%. Optical density was measured at 450 nm on an ELx800 Absorbance Microplate Reader (Biotek, Winooski, VT, USA).

Statistical Analysis

All statistical analyses were done by way of IBM®SPSS® (version 22). We used the chi-squared test to compare the proportion of categorical variables such as gender. The normality of the variables was analyzed with the one-sample Kolmogorov-Smirnov test. We applied Student's t test to compare normally distributed variables. We compared variables that were not normally distributed using the Mann-Whitney U test. The correlations between variables were calculated by Spearman's Correlation analysis. *P* values <0.05 were taken to be evidence of statistical significance. G*Power 3.1 for Windows software was applied for power analysis. The sample size analysis revealed that there should be 15 patients for each group with a power ratio of 80% and an alpha margin of error of 0.05 to compare the six groups. The effect size used for this calculation is 0.500 based on similar studies, and the actual power is calculated as 0.962. As a result of the analysis, considering the dropout rate, it was planned to take 25 patients for each group.

RESULTS

Baseline characteristics of the participants are presented in Table 1. Iron and ferritin concentrations of the iron deficiency patients and combined deficiency patients were significantly lower than those of controls (p<0.001). Unsaturated iron binding capacity concentrations of the iron deficiency patients and combined deficiency patients were significantly higher than those of controls (p<0.001). Vitamin B12 concentrations of the vitamin B12 deficiency patients and combined deficiency patients were significantly lower than those of controls (p<0.001). Vitamin D concentrations of the vitamin D deficiency patients and combined deficiency patients were significantly lower than those of controls (p<0.001).

Table 1 – Clinical and demographic characteristics of the patients groups and controls.

Variables	Control (n=32)	Combined deficiency (n=32)	Iron deficiency (n=33)	Vitamin B12 deficiency (n=30)	After treatment of Vitamin D (n=24)	Vitamin D deficiency (n=33)	*p*
Female/Male	17/15	18/14	20/13	18/12	13/11	18/15	0.077
Age (years)	45.4±16.5	46.5±17.2	38.9±11.3	44.9±14.9	43.9±14.4	41.6±14.2	0.333
BMI, kg/m^2	24.4±2.6	24.9±3.8	24.2±3.7	24.8±3.5	25.1±3.7	25.2±3.7	0.863
Glucose, mg/dL	95.1±6.9	95.2±6.3	92.5±6.3	93.6±7.9	91.1±8.5	94.8±7.6	0.573
Urea, mg/dL	29.8±7.7	26.6±10.1	24.5±7.7	27.1±5.0	24.8±5.9	24.4±6.9	<0.05
Creatinine, mg/dL	0.8±0.2	0.7±0.2	0.7±0.1	0.7±0.2	0.8±0.2	0.8±0.2	0.233
AST, U/L	17.1±4.1	15.3±4.7	15.7±4.3	16.9±5.4	16.2±4.0	15.8±3.8	0.540
ALT, U/L	19.1±8.8	15.9±5.8	15.9±6.2	15.6±7.2	18.1±8.1	18.3± 8.5	0.286
Triglyceride, mg/dL	118 (43-227)	175 (50-398)	100 (42-168)	155 (43-227)	133 (70-307)	126 (60-293)	0.092
HDL-C, mg/dL	55.3±9.9	48.9±8.8	56.4±12.4	48.7±10.2	53.2±9.7	52.3±9.3	<0.05
LDL-C, mg/dL	126 (88-216)	117 (59-173)	116 (91-177)	119 (86-170)	135 (74-216)	127 (63-214)	0.108
Cholesterol, mg/dL	206 (155-293)	199 (125-250)	196 (156-276)	199 (142-284)	217 (157-296)	206 (127-298)	0.282
Iron, mcg/dL	95.9 (48-159)	25.0 (15-36)	23.4 (13-35)	65.6 (38-215)	89.0 (33-180)	82.7 (34-165)	<0.001
Unsaturated iron binding capacity mcg/dL	229 (120-225)	367 (232-476)	372 (287-512)	271 (111-352)	247 (158-328)	252 (135-386)	<0.001
Ferritin, ng/mL	78.3 (17-232)	13.2 (2-40)	5.9 (2-13)	59.5 (20-301)	83.9 (29-314)	72.6 (13-275)	<0.001
Vitamin B12, pg/mL	432 (222-677)	193 (91-425)	364 (233-805)	170 (131-199)	426 (213-672)	400 (206-711)	<0.001
Vitamin D, ng/mL	35.2±7.6	10.9±4.2	31.7±3.6	31.5±1.8	35.1±3.8	13.7±4.4	<0.001

Note: ALT: Alanine Aminotransferase; AST: Aspartate Aminotransferase; BMI: Body Mass Index; HDL-C: High Density Lipoprotein-Cholesterol; LDL-C: Low Density Lipoprotein-Cholesterol.

Serum PNX-14 concentrations were significantly lower in patients with iron deficiency and combined deficiency compared with the control group (p<0.005). Similarly, low PNX-14 levels were found in patients with vitamin B12 deficiency and patients with vitamin D deficiency with respect to controls (p<0.05). Serum nesfatin-1 concentrations were significantly lower in patients with iron deficiency, vitamin B12 deficiency and combined deficiency compared with the control group (p<0.05). There was no difference in the values of nesfatin-1 before and after treatment in the vitamin D deficiency group compared to the control (Table 2).

Spearman's Rho correlation test was performed. There was a positive correlation between PNX-14 and nesfatin-1 in the iron deficient group (Table 3). In the group with vitamin B12 deficiency, PNX-14 values showed a positive correlation with high-density llipoprotein cholesterol and a negative correlation with Body Mass Index (BMI). Additionally nesfatin-1 values showed a positive correlation with low-density llipoprotein cholesterol (Table 4).

Table 2 – Serum biomarkers of patients and control individuals.

Analytes	Control (n=32)	Combined deficiency (n=32)	Iron deficiency (n=33)	Vitamin B12 deficiency (n=30)	After treatment of Vitamin D (n=24)	Vitamin D deficiency (n=33)	*p*
Phoenixin-14, ng/L	2538.7 (190-7358)	835.5 (228-6606)*	882.1 (167-3533)*	1161.6 (153-5651)**	1589.8 (370-4299)	1246.4 (253-4266)**	<0.001
Nesfatin-1, ng/mL	259.5 (7-1384)	74.1 (10-534)**	83.1 (10-704)**	87.7 (4-692)**	179.9 (8-828)	156.5 (10-789)	<0.05

Note: *p<0.005, compared with control group; **p<0.05, compared with control group.

Table 3 – Spearman's correlation analyses were performed to investigate the association of biomarkers levels in Iron deficiency.

Phoenixin-14	Phoenixin-14	Nesfatin-1
r	1.0	0.833
p	–	**<0.001**

Note: Bold value indicates statistically significant.

Table 4 – Spearman's correlation analyses were performed to investigate the association of biomarkers levels in Vitamin B12 deficiency.

Analytes	Phoenixin-14	Nesfatin-1	HDL	BMI	LDL	Vitamin B12
Phoenixin-14						
r	1.0	-0.092	0.392	-0.376	-0.228	-0.197
p	–	0.627	**<0.05**	**<0.05**	0.225	0.296
Nesfatin-1	–					
r	-0.092	1.0	-0.076	0.142	0.459	0.146
p	0.627	–	0.691	0.456	<0.05	0.443

Note: Bold value indicates statistically significant. HDL: High Density Lipoprotein ; BMI: Body Mass Index; LDL: Low Density Lipoprotein.

DISCUSSION

PNX-14 and nesfatin-1 recently described multifunctional neuropeptides which have been associated with reproduction, food intake, energy metabolism and cardiovascular regulation [13]. Although the interest in these proteins has increased in recent years, there are limited studies on the role of nesfatin-1 and PNX-14 in MNDs.

Nesfatin-1 is an anorexigenic neuropeptide known for its role in appetite regulation and energy homeostasis [16]. Nesfatin-1 has also been associated with the development of anorexia nervosa [17]. Centrally given nesfatin-1 reproducibly causes reductions in food intake in rodents [18]. Weibert et al. [19] reported that peripheral NUCB2/nesfatin-1 was positively associated with disordered eating in women with obesity. Lower nesfatin-1 concentrations were observed in blood samples of obese children compared to healthy children [20,21]. Serum nesfatin-1 values have been shown to be increased in chronically malnourished children [22]. Increased serum nesfatin-1 levels in underweight individuals found in another study by Kaba et al. [23]. They suggest that nesfatin-1 may be associated with the regulation of food intake and decreased appetite in children. In another study by Ustabaş Kahraman et al. found lower nesfatin-1 and vitamin B12 levels in acute malnourished children compared to the healthy controls. They suggested that nesfatin-1 plays a significant role in the maintenance of nutritional status and regulating food intake [24]. In our study nesfatin-1 concentrations were significantly lower in cases with iron deficiency, vitamin B12 deficiency and combined deficiency compared with the control group. There was no difference in the values of nesfatin-1 in vitamin D deficiency group compared to control group. Şahin et al. [25] showed lower vitamin D levels in women with polycystic ovary syndrome compared to the controls and there was no correlation between vitamin D and nesfatin-1 levels, consistent with our study. Contrary to our findings, Aşkar et al. [26] found higher nesfatin levels in cases with iron deficiency and vitamin B12 deficiency, compared with the control group. These varying results may be due to differences in the populations of the studies. In addition, neuropeptide levels have the potential to be affected by many different factors such as stress, fasting state and duration. Based on our research results, nesfatin 1 might be related to MNDs such as iron and vitamin B12 deficiency.

The co-expression of PNX-14 and nesfatin-1 takes place at a high range. PNX-14 and nesfatin-1 show counterbalancing interaction in various cellular processes [13]. Intracerebroventricular administration of PNX is associated with increased food intake and activation of nesfatin-1 immunoreactive neurons in rats [27]. PNX is connected with weight and its expression is linked to feeding status, fatty acids and glucose [28]. PNX level is closely related to some eating disorder symptoms. In malnourished adolescent in patients with anorexia nervosa, serum PNX concentrations was decreased [29]. Therefore, we also investigated the relationship of PNX-14 with vitamin B12,

vitamin D and iron deficiency in our study. We showed that PNX-14 concentrations were significantly lower in patients with iron, vitamin D, vitamin B12 and combined deficiency compared with the control group. The decrease in nesfatin-1 and PNX-14 levels may have led to inadequate regulation of appetite and food intake functions in people with iron deficiency. In participants with vitamin B12 deficiency, PNX-14 measurement results showed a positive correlation with high-density lipoprotein cholesterol and a negative correlation with BMI.

Vitamin D deficiency is correlated with the risk of metabolic diseases, including T2DM (3-5). Furthermore ıron deficiency has been associated with obesity and related metabolic disorders [30]. Research thus far has shown that PNX was involved in the development of obesity, IR, pathogenesis of inflammatory reactions of the body, and increased food intake [31]. In this study, serum PNX-14 concentrations were significantly lower in patients with iron and vitamin D deficiency compared with the control group. Low PNX-14 levels may be a risk for vitamin D deficiency due to inadequate food intake or malabsorption.

Vitamin B12 deficiency is much more common than thought and causes a wide variety of diseases. In our study serum PNX-14 and nesfatin-1 values were significantly lower in participants with vitamin B12 deficiency. The gut-brain axis is a bidirectional hormonal and neural signaling pathway that connects the gut and the brain. Several studies reported that PNX-14 and nesfatin-1 might have possible roles in the gut-brain axis [31,32]. Vitamin B12 treatment exerts a protective effect on the intestinal epithelium in various models of gastrointestinal disease [33]. Moreover, vitamin D are accepted to participate in intestinal microbiota modulations in health and diseases [34]. Iron deficiency and iron treatment have been associated with changes to gut microbiota [35]. Iron homeostasis is closely related with the inflammatory disorders. The inflammation associated with obesity and overweight decreases iron absorption [36]. The inhibitory effects of PNX-14 and nesfatin-1 on inflammation and oxidative stress have recently been widely reported [11,15]. According to these results PNX-14 and nesfatin-1 may exerts a possıble beneficial effects against pathophysiological conditions such as inflammation and oxidative stress, in iron, vitamin D and Vitamin B12 deficiencies. The decrease in PNX-14 and nesfatin-1 levels may have contributed to iron and vitamin B12 deficiency by decreasing their protective effects in the gastrointestinal system.

This study has limitations such as being a single-center study and the possibility that participants' verbal statements regarding their fasting status or duration may be inaccurate, which may affect the results. Differences in study methodologies also lead to differences in literature. The strength of our study is that, to our knowledge, very few studies have been conducted investigating serum PNX-14 and nesfatin-1 in people with micronutrient deficiencies.

CONCLUSION

In our study, we observed that PNX-14 levels in people with iron, vitamin D, vitamin B12 and combined deficiencies were lower than in healthy people. Nesfatin-1 levels were lower in people with iron, vitamin B12 and combined deficiencies than in healthy controls. We did not find a relationship between Vitamin D deficiency and nesfatin-1 concentrations. There was an increase in PNX-14 levels after vitamin D supplementation. These results show that PNX-14 and nesfatin-1 levels are associated with micronutrient deficiencies. Regulation of the levels of these neuropeptides may be beneficial fort he morbidity risks in micronutrient deficiencies. New studies that will investigate the role of nesfatin-1 and PNX-14 in micronutrient deficiencies will provide more information about the mechanisms of action of the mentioned neuropeptides.

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