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Original Research

Plasma Leptin, Nesfatin 1, NPY, and Zinc Levels in Obese and Metabolic Syndrome Children

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ABSTRACT

Objective: The aim of this study is to investigate the relationship between leptin, nesfatin 1 and NPY hormones and zinc in boys and girls diagnosed with metabolic syndrome and obesity.

Methods: This study included a total of 6 groups. Group 1 Boy Control, Group 2 Girl Control, Group 3 Obese Boys, Group 4 Obese Girls, Group 5 Boys with Metabolic Syndrome, Group 2 with Girls with Metabolic Syndrome. Plasma leptin, nesfatin-1, NPY (by ELISA method) and serum zinc (by AA method) levels were determined in blood samples obtained from the subjects.

Results: Leptin and zinc levels were significantly higher both in boy and girl patients with metabolic syndrome than in obese and control children. Nesfatin-1 and NPY levels were significantly lower both in girl and boy obese and metabolic syndrome children compared to their control groups.

Conclusion: In the current study a significant increase in plasma leptin and serum zinc levels and a significant decrease of plasma nesfatin-1 and NPY levels were observed in boys and girls with metabolic syndrome. The findings of our study show that leptin, nesfatin-1 and NPY levels may be important biomarkers in the assessment of metabolic syndrome risk in both girls and boys.

Keywords: Children, metabolic syndrome, obesity, leptin, nesfatin 1, NPY, zinc.

INTRODUCTION

Obesity is a disease which causes many diseases such as diabetes mellitus, heart disease, stroke, joint disorders, sleep disturbance, cancer, and hypertension, as well as increases the risk of mortality, and must be definitely treated [1]. Metabolic syndrome is a disease characterized by hyperinsulinemia, dyslipidemia, low high-density lipoprotein (HDL), and atherosclerosis in addition to obesity. Some patients are prediabetics, while the others have Type-2 diabetes [2]. Leptin is a protein hormone secreted mainly from white adipose tissue. Research on leptin, which is involved in the regulation of food intake, has proven the importance of this hormone in the regulation of body weight [3]. Nesfatin-1 is a hormone secreted from the hypothalamus and suppresses the hunger center. The suppression of food intake by nesfatin-1 occurs through a leptin-independent mechanism. [4]. Neuropeptide Y (NPY) is a hormone released by the hypothalamus which increases food intake. Whereas NPY injection to rats causes hyperphagia,

administration of NPY with repeating doses longer than 10 days leads to the development of obesity [5]. Zinc, which plays important roles in growth, development and immune systems, is also closely related to metabolism and the endocrine system. The roles of zinc in the regulation of fat and carbohydrate metabolism, insulin resistance and body weight are critical. Zinc is also involved in the regulation of nutrition. Symptoms of zinc deficiency are the same as those of anorexia nervosa. Therefore, zinc is considered to be involved in the pathogenesis of anorexia nervosa. Obese persons have low zinc and high leptin levels, indicating an important association between zinc and nutrition, thus between zinc and leptin [6]. There is also an important relationship between zinc and NPY regulation during anorexia which occurs in zinc insufficiency [6].

This decrease in nutrition, despite raised NPY levels in zinc insufficiency is defined as NPY resistance [7].

The aim of this study is to determine the relationship between leptin, nesfatin 1 and NPY hormones and zinc, which are effective in regulating food intake in boys and girls diagnosed with metabolic syndrome and obesity.

MATERIALS AND METHODS

Sixty children, 30 boys and 30 girls, who applied to the Pediatric Endocrinology outpatient clinic of Konya Training and Research Hospital were included in this study. Study protocol was approved by the Selcuk University Medical Faculty, Non-interventional Clinical Research ethic committee. The subjects included in the study were divided into 6 equal groups:

Groups for boys:

Group 1 Boy Control: This groups included boys aged 10-15 years and had no any health problem.

Main Points;

- The findings obtained in this study show that plasma leptin, nesfatin1 and NPY levels can be important biomarkers in the assessment of metabolic syndrome risk in both girls and boys.
- A second important finding of the present study is that the high serum zinc obtained in both girls and boys with metabolic syndrome suggests that zinc may play a role in the pathogenesis of the metabolic syndrome.

Group 2 Obese Boys: This groups included boys aged 10-15 years and diagnosed with obesity.

Group 3 Boys with Metabolic Syndrome: This group included boys aged 9-15 years and diagnosed with metabolic syndrome.

Groups for girls:

Group 1 Girl Control: This groups included girls aged 10-15 years and had no any health problem.

Group 2 Obese Girls: This groups included girls aged 10-15 years and diagnosed with obesity.

Group 3 Girls with Metabolic Syndrome: This group included girls aged 10-15 years and diagnosed with metabolic syndrome.

Inclusion and Exclusion Criteria, and Criteria of Exclusion After Beginning of the Study

International Diabetes Federation (IDF) criteria were used as metabolic syndrome criteria. Accordingly, a percentile of body mass index higher than 95th percentile was considered as obesity [8], and a waist circumference measuring higher than 95th according to age and gender was accepted as metabolic syndrome, considering reference values defined for Turkish children [9]. The exclusion criteria included chronic systemic diseases, syndromic obesity, hypercortisolism, hypothyroidism, gonadal dysfunction and drug usage. Any of the subjects in metabolic syndrome, obesity and control groups who rejected to participate was planned to be excluded. None of the subjects requested to be excluded during the study.

Collection of Blood Samples

Plasma and serum samples obtained from the blood samples that were collected from the subjects for routine laboratory investigations following at least 10-12 hours of fasting, were kept at -80°C. NPY (ng/mL), leptin (pg/mL) and nesfatin-1 (ng/mL) levels were determined with ELISA method, and serum zinc levels (µg/dL) with Atomic absorption method in the plasma samples.

Biochemical Analysis

Plasma leptin (Catalog No: ELH-Leptin-1), nesfatin 1 (Catalog No: EIH-NESF) and NPY (Catalog No: EIA-NPY) analyzes were determined as ng/ml by ELISA method.

Serum Zinc Analysis: The zinc levels were determined with Atomic absorption spectrophotometer. The values were

calculated as µg/dL.

Statistical Analysis

Statistical interpretation of the obtained data was done with a computer package program (SPSS 22.0). The arithmetic means and standard deviations (SD) of all parameters were calculated. By applying the "Shapiro-Wilk" test, it was determined that the data showed normal distribution. One-way analysis of variance (ANOVA) was used to determine the difference between the groups, while the Bonferroni test was used to find the group that caused the difference. P<0.05 values were considered significant.

RESULTS

Zinc, Leptin, Nesfatin-1 and NPY Results of Study Groups (girls and boys)

In our study, the highest zinc and leptin levels were obtained in boys and girls with metabolic syndrome (p<0.05, Tables 1 and 2). There was no significant difference between the zinc levels of obese children (girls and boys) and the control group. However, leptin levels of obese boys and girls were higher than the control groups (p<0.05, Tables 1 and 2). Nesfatin-1 levels of boys and girls with metabolic syndrome were significantly lower than all other study groups (p<0.01, Tables 1 and 2).

Nesfatin-1 levels of the obese (girls and boys) groups were lower than the control group (p<0.05) and higher than the metabolic syndrome groups (girls and boys) (p<0.05). The highest plasma NPY levels were obtained in the control groups (p<0.05, Tables 1 and 2).

Correlations of Male Groups Participating in the Study

The correlations between zinc, leptin, nesfatin-1 and NPY levels of the male groups were also examined in the study. Accordingly, it was determined that there was a high level of positive correlation between leptin and nesfatin 1 (r= 0.684 and p=0.029) and leptin and NPY (r= 0.877 and p= 0.001) only in the control group (p<0.05, Table 3). Again in the same group, a high level of positive correlation was observed between NPY and nesfatin 1 (r= 0.805 and p= 0.005) parameters. However, no significant correlation was found in any parameter in the other groups (p>0.05, Table 3).

Correlations of Female Groups Participating in the Study

In the study carried out, the correlations between Zinc, Leptin, Nesfatin-1 and NPY levels of the female groups were examined. Accordingly, there was a high level of positive correlation between NPY and nesfatin 1 (r= 0.730 and p= 0.016) parameters only in the control group (P<0.05, Table 4). In the other groups, no significant correlation was found in any parameter (p>0.05, Table 4).

Table 1. Comparison of Leptin. Nesfatin-1. NPY and Zinc Levels Between the Boys Included in the Study

Groups	Leptin (ng/ml)	Nesfatin-1 (ng/ml)	NPY (ng/ml)	Zinc (µg/dl)
Control	2.77±0.73^{c}	3.92±1.16^{a}	6.71±1.05^{a}	170.17±3.20^{b}
Obese Boys	18.71±5.89^{b}	2.19±0.77^{b}	2.96±0.42^{b}	170.69±3.86^{b}
Boys with Metabolic Syndrome	26.85±12.90^{a}	1.78±0.50^{c}	3.24±0.16^{b}	210.38±4.80^{a}

a.b.c: *Means with different superscripted letters in the same column are statistically significant (P<0.05).

Table 2. Comparison of Zinc. Leptin. Nesfatin-1 and NPY Levels Between the Girls Included in the Study

Groups	Leptin (ng/ml)	Nesfatin-1 (ng/ml)	NPY (ng/ml)	Zinc (µg/dl)
Control	2.78±1.48^{c}	4.16±0.71^{a}	8.78±3.70^{a}	140.24±2.75^{b}
Obese Girls	25.73±7.80^{b}	3.16±0.41^{b}	4.32±1.17^{b}	130.33±5.99^{b}
Girls with Metabolic Syndrome	35.90±12.30^{a}	2.25±0.41^{c}	4.62±1.54^{b}	200.92±6.27^{a}

a.b.c: *Means with different superscripted letters in the same column are statistically significant (P<0.05).

Table 3. Correlations of Male Groups Participating in the Study

Correlations						
Groups			**Zinc**	**Leptin**	**Nesfatin1**	**NPY**
1	Zinc	Pearson Correlation	1	0.358	0.029	0.313
		Sig. (2-tailed)		0.310	0.936	0.379
		N	10	10	10	10
	Leptin	Pearson Correlation	0.358	1	0.684*	0.877**
		Sig. (2-tailed)	0.310		0.029	0.001
		N	10	10	10	10
	Nesfatin1	Pearson Correlation	0.029	0.684*	1	0.805**
		Sig. (2-tailed)	0.936	0.029		0.005
		N	10	10	10	10
	NPY	Pearson Correlation	0.313	0.877**	0.805**	1
		Sig. (2-tailed)	0.379	0.001	0.005	
		N	10	10	10	10
2	Zinc	Pearson Correlation	1	-0.285	-0.095	0.376
		Sig. (2-tailed)		0.425	0.794	0.284
		N	10	10	10	10
	Leptin	Pearson Correlation	-0.285	1	0.434	-0.089
		Sig. (2-tailed)	0.425		0.210	0.808
		N	10	10	10	10
	Nesfatin1	Pearson Correlation	-0.095	0.434	1	-0.066
		Sig. (2-tailed)	0.794	0.210		0.857
		N	10	10	10	10
	NPY	Pearson Correlation	0.376	-0.089	-0.066	1
		Sig. (2-tailed)	0.284	0.808	0.857	
		N	10	10	10	10
3	Zinc	Pearson Correlation	1	0.381	0.345	0.473
		Sig. (2-tailed)		0.277	0.329	0.167
		N	10	10	10	10
	Leptin	Pearson Correlation	0.381	1	0.107	-0.134
		Sig. (2-tailed)	0.277		0.769	0.713
		N	10	10	10	10
	Nesfatin1	Pearson Correlation	0.345	0.107	1	0.497
		Sig. (2-tailed)	0.329	0.769		0.144
		N	10	10	10	10
	NPY	Pearson Correlation	0.473	-0.134	0.497	1
		Sig. (2-tailed)	0.167	0.713	0.144	
		N	10	10	10	10

*. Correlation is significant at the 0.05 level (2-tailed).

**. Correlation is significant at the 0.01 level (2-tailed).

Table 4. Correlations of Female Groups Participating in the Study

Correlations						
Groups			**Zinc**	**Leptin**	**Nesfatin1**	**NPY**
1	Zinc	Pearson Correlation	1	-0.033	-0.205	0.010
		Sig. (2-tailed)		0.927	0.569	0.979
		N	10	10	10	10
	Leptin	Pearson Correlation	-0.033	1	-0.151	0.085
		Sig. (2-tailed)	0.927		0.677	0.815
		N	10	10	10	10
	Nesfatin1	Pearson Correlation	-0.205	-0.151	1	0.730*
		Sig. (2-tailed)	0.569	0.677		0.016
		N	10	10	10	10
	NPY	Pearson Correlation	0.010	0.085	0.730*	1
		Sig. (2-tailed)	0.979	0.815	0.016	
		N	10	10	10	10
2	Zinc	Pearson Correlation	1	-0.544	-0.405	-0.202
		Sig. (2-tailed)		0.104	0.246	0.576
		N	10	10	10	10
	Leptin	Pearson Correlation	-0.544	1	0.364	-0.203
		Sig. (2-tailed)	0.104		0.302	0.574
		N	10	10	10	10
	Nesfatin1	Pearson Correlation	-0.405	0.364	1	0.020
		Sig. (2-tailed)	0.246	0.302		0.957
		N	10	10	10	10
	NPY	Pearson Correlation	-0.202	-0.203	0.020	1
		Sig. (2-tailed)	0.576	0.574	0.957	
		N	10	10	10	10
3	Zinc	Pearson Correlation	1	0.210	0.247	-0.298
		Sig. (2-tailed)		0.561	0.492	0.403
		N	10	10	10	10
	Leptin	Pearson Correlation	0.210	1	-0.319	0.086
		Sig. (2-tailed)	0.561		0.368	0.814
		N	10	10	10	10
	Nesfatin1	Pearson Correlation	0.247	-0.319	1	0.259
		Sig. (2-tailed)	0.492	0.368		0.470
		N	10	10	10	10
	NPY	Pearson Correlation	-0.298	0.086	0.259	1
		Sig. (2-tailed)	0.403	0.814	0.470	
		N	10	10	10	10
*. Correlation is significant at the 0.05 level (2-tailed).						

DISCUSSION

Discusssion of Leptin Results

In the current study, leptin levels in the metabolic syndrome groups (both girls and boys) were significantly higher than in all other study groups. Plasma leptin levels of the obesity group were lower than the metabolic syndrome group but higher than the control group.

High leptin concentration in obese children is defined as correlated with various variables of metabolic syndrome. Therefore, it is accepted that higher leptin levels may play an important role in the etiopathogenesis of metabolic syndrome [10]. Therefore, it is suggested that leptin levels may be a potential biomarker in determination of the risk for both cardiovascular diseases and metabolic syndrome in advance [11]. In a study performed for this purpose, leptin levels were determined in 65 healthy, 46 overweight, and 164 obese children (160 boys, 115 girls). At the end of the study, critical leptin level for metabolic syndrome was found as 13.4 ng/dL. It has been proposed that, each 1 ng/dL increase in leptin level may increase the risk of metabolic syndrome by about 3%. It was concluded in the mentioned study that leptin may be a biomarker in determination of the risk for development of metabolic syndrome in prepubertal children [11]. Similarly, it was demonstrated in a study by Obeidat et al. [12] on 630 persons (308 male and 322 female) that serum leptin levels may be an important biomarker in assessment of the risk for metabolic syndrome both in women and men, independently from obesity. In the present study, plasma leptin levels were higher in both boys and girls with metabolic syndrome than the other groups, without gender differences. In our study, the mean plasma leptin level was 35.90 ng/dL in girls with metabolic syndrome, and 26.85 ng/dL in boys with metabolic syndrome. Again in our study, plasma leptin levels of obesity group were lower than the metabolic syndrome, and higher than the controls both in girls and boys. Especially based on the critical leptin level of 13.4 ng/dL recommended by Madeira et al. [11], plasma leptin level of 25.83 ng/dL obtained in obese girls and 18.71 ng/dL obtained in obese boys indicate that both groups are potential candidates for metabolic syndrome. High plasma leptin levels we obtained both in girls and boys with metabolic syndrome are consistent with the results of above mentioned studies [10-13].

Discussion of Nesfatin-1 Results

In the present study, the lowest nesfatin-1 levels were obtained in the metabolic syndrome group. Nesfatin-1 levels of obesity group were higher than the metabolic syndrome group and lower than the control group.

Recently described Nesfatin-1 is a hormone synthesized in the hypothalamus and is effective on the regulation of nutritional behaviour [13]. It has been suggested that nesfatin-1 level found significantly lower in polycystic ovary syndrome (PCOS) patients compared to the control group may be associated with other metabolic markers including metabolic syndrome [13]. It has been reported that nesfatin-1 levels are significantly lower in patients with diabetes and metabolic syndrome compared to healthy persons, decreased level of nesfatin-1 is associated with insulin resistance which is seen in patients with metabolic syndrome [14]. Aksu et al. [15] found that Nesfatin-1 levels were found to be significantly lower in patients with metabolic syndrome compared to healthy controls. It has been suggested that Nesfatin-1, which is known to play a role in the pathophysiological mechanisms of insulin resistance, may be a useful factor for the development of new therapeutic targets in the treatment of obesity in the future [15]. In fact, Nakata et al. [16] proposed that regulatory processes of Nesfatin-1 and its precursor nucleobindin 2 (NUCB2) may provide new targets in the treatment of metabolic syndrome diseases. In this study, decreased Nesfatin-1 levels that we obtained both in the metabolic syndrome groups and obesity groups are consistent with results of above mentioned studies.

Discussion of NPY Results

In the present study, NPY levels were significantly lower both in the metabolic syndrome and obesity groups compared to the control subjects.

Polymorphism functions in the human neuropeptide Y gene (rs16139) is associated with metabolic disorders including metabolic syndrome and early-onset Type 2 diabetes (T2D) [17]. Rabaglino et al. [18] reported that oral administration of antibacterial Triclosan (TCS) to pregnant rats alters food intake in cub rats by increased NPY release, predisposing to metabolic syndrome in adolescence. In conclusion, disruptions in NPY release in metabolic syndrome and/or metabolic syndrome like events are critical [19]. Pathological increase in NPY release promotes energy storage via central and peripheral mechanisms, predisposing to metabolic syndrome [20]. In a study with both obese and non-obese PCOS patients, a significant increase was found compared to the healthy persons. It was concluded that insulin resistance observed in PCOS patients may be related to the differences in NPY release and effects of these differences on

metabolic pathways [21].

In our study, we found decreased NPY levels both in girl and boy metabolic syndrome and obesity groups compared to the control groups. Pathologic increase in NPY is known to promote energy storage via central and peripheral mechanisms, predisposing to metabolic syndrome [20]. Participants of our study consisted of girls and boys diagnosed with metabolic syndrome and obesity. Decreased NPY levels we obtained in these groups are likely to be resulted from increased leptin levels. Because the most prominent effect of leptin hormone is seen by suppressing NPY release at hypothalamus level [22].

Discussion of Zinc Results

There is a proven relationship between zinc and leptin. Zinc can either directly affect leptin gene expression or indirectly increase glucose utilization by adipose tissue, resulting in leptin production [23]. Studies on the relationship between zinc and nesfatin-1 are scarcely any. It has been reported that zinc supplementation has an increasing effect on decreased Nesfatin-1 levels in a high-fat diet-induced obese rat model. As a result, it was concluded in the mentioned study that oral zinc can prevent obesity-related metabolic diseases by improving energy balance [24]. Zinc interferes with the activity of NPY, a potent stimulant of nutrition. Zinc is required for the synthesis of Galanin, a molecule critical for NPY's receptor activity. When zinc is deficient, galanin cannot be synthesized, and in this case, NPY resistance occurs [23]. As a result, there is a critical and complex relationship between zinc, an important trace element, and the hormones leptin, nesfatin-1 and NPY.

In the present study, the highest serum zinc levels were obtained in the metabolic syndrome group. It was questioned that zinc which is an important trace element may play a critical role in metabolic syndrome disease which incidence is rapidly increasing worldwide [25]. Based on this point, in a study conducted on South Korean adult persons, serum zinc levels were determined in 1926 participants. Serum zinc levels were tended to decrease especially among female participants. In the same study, an association between zinc levels and metabolic syndrome disease was underlined, and it was reported that zinc levels should be examined also in terms of gender [25]. There are data indicating that gene variations of ZNT8 gene which is one of the zinc carrier proteins play a role in metabolic syndrome disease [26]. There are also evidence of that zinc also plays a role in insulin resistance seen in patients with polycystic ovary syndrome (PCOS) [25]. PCOS patients have lower zinc levels compared to healthy controls [27]. Torkanlou et al. [28] reported significantly lower serum zinc levels in 706 obese subjects compared to the controls.

Results of the above mentioned authors indicate decreased zinc levels in metabolic syndrome and/or related metabolic disorders. Whereas in the present study we obtained higher zinc levels in the metabolic syndrome group compared to the control subjects. From this aspect, our result is not in parallel with the above reports. Here, the critical issue may be that; all pediatric metabolic syndrome patients are under an increased risk for diabetes [29]. Therefore, attention is drawn to the need for a pediatric Mets definition in children with metabolic syndrome [29]. In the present study, high serum zinc levels we obtained in children with metabolic syndrome may be important for diabetes risk. In diabetes, serum zinc levels vary depending on the type of Diabetes (30). Whereas Type 2 diabetes is in general associated with decreased plasma or serum zinc levels, these levels mostly increase in Type 1 diabetes [30]. Increase of zinc levels in Type 1 diabetes is caused by rapid breakdown of pancreatic beta cells, and passage of zinc stored in beta cells to the extracellular fluid [30, 31]. This event occurs in the beginning of Type 1 diabetes, and later increased urinary excretion zinc results in a decrease in serum zinc levels [30, 31]. In our study, we did not plan follow-up of the girls and boys with metabolic syndrome after the study in terms of the development of diabetes. However, high serum zinc levels can be said to be a marker for diabetes risk, and may be important fro this aspect.

In a study from China, serum zinc levels were determined in 52 patients with metabolic syndrome and 149 healthy control subjects. Patients with metabolic syndrome were found to have higher zinc levels compared to the controls [32]. Higher zinc levels we obtained in girls and boys with metabolic syndrome are consistent with the results of Yu et al. [32].

When results of this study were evaluated as a whole; significant increases were found in plasma leptin and zinc levels of girls and boys with metabolic syndrome, and significant suppression in plasma nesfatin-1 and NPY levels. Whereas leptin levels of the obese girls and boys were lower than the metabolic syndrome groups and higher than the control groups, nesfatin-1 and NPY levels of the obese groups were higher than the metabolic syndrome groups and lower than the control groups.

Based on the results of this study, it can be said that determination of plasma leptin levels may be an important biomarker in evaluation of the risk for metabolic syndrome both in girls and boys. Again, high plasma leptin zinc levels obtained both in girls and boys with metabolic syndrome support the opinion that zinc may play a role in the pathogenesis of metabolic syndrome.

In conclusion; it can be said that high serum zinc levels obtained in girls and boys with metabolic syndrome may be a marker for the risk of diabetes. When results of this study were evaluated as a whole; metabolic syndrome and obesity lead yo change in the levels of leptin, nesfatin-1 and NPY hormones that are effective in the regulation of food intake. These changes may be associated especially with the increased zinc levels in metabolic syndrome.

Limitations

The limiting factor in the current study is the inability to molecularly examine the relationship between metabolic syndrome and zinc.

In future studies, revealing the possible roles of zinc transport proteins in metabolic syndrome may provide important information.

CONCLUSION

When the results of our study are evaluated as a whole;

1. A significant increase in plasma leptin and zinc levels, and a significant reduction of plasma nesfatin-1 and NPY levels were observed in boys and girls with metabolic syndrome.

2.The findings of our study show that leptin, Nesfatin-1 and NPY levels may be important biomarkers in the assessment of metabolic syndrome risk in both girls and boys.

3. High serum zinc obtained in both girls and boys with metabolic syndrome supports the idea that zinc may play a role in the pathogenesis of metabolic syndrome.

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Informed Consent: The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Conflict of Interest: The authors declare that they have no potential conficts of interest to disclose.

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Ethical Approval: This study was conducted in accordance with the Declaration of Helsinki. The study protocol was approved by the Experimental Animals Ethics Board of Selcuk University Experimental Medicine Research and Application Center (2015-1). This research was performed on the animals (rat).

Author Contributions: Conception: Condept:RM;AKB – Design:RM; AKB - Supervision:RM; AKB- Fundings: -Materials:AA, OU, SBB, EM, SSE, MB - Data Collection and/or Processing: AA, OU, SBB, EM, SSE, MB - Analysis and/or Interpretation: AA, OU, SBB, EM, - Literature: AA, OU, SBB, EM, - Writing:OU, SBB- Critical Review:RM;AKB.

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