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THE EVALUATION OF NEW GENERATION INFLAMMATORY MARKERS IN CHILDREN WITH MORBID OBESITY AND METABOLIC SYNDROME

Morbid Obez ve Metabolik Sendromlu Çocuklarda Yeni Nesil Enflamatuvar Belirteçlerin Değerlendirilmesi

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Tekirdag Namik Kemal University, Faculty of Medicine Non-interventional Clinical Research Ethical Committee approved the study protocol (date: 30.10.2019, protocol no: 2019.180.10.01).

Abstract

Aim: Technological advancements, unbalanced nutrition, sedentary life style, are important factors in obesity. Obesity-inflammation relationis beingexamined. In this study, the relationships among new generation inflammatory markers in children with normal body mass index (C) as well as obese (OB), morbid obese (MO) children and those with metabolic syndrome (MetS) were investigated.

Materials and Methods: A total of 172 children participated in the study.Group 1 comprised children with normal body-mass index (control group) (C). Obese (OB) children were in Group 2, MO children constituted Group 3 and Group 4 included MO children with MetS. The number of cases were 37, 34, 51 and 50 in groups 1, 2, 3 and 4, respectively. Anthropometric measurements were recorded. Serum spexin, adropin, adipolipin, fibroblast growth factor-21 and fetuin-A levels were determined. Statistical analyses were performed.

Result: Spexin and adipolin levels were significantly lower in obese groups than C group ($p<0.05$). Although adropin and FGF-21 levels did not differ significantly between groups, levels were lower in OB, MO, and MetS groups than C group.There were no significant differences among fetuin- A levels of the groups. Correlations between spexin and adipolin were the highest. These cytokines were negatively correlated with obesity parameters. The correlations between these cytokines were weakened from C group to MetS group.

Conclusion: Decreasing spexin and adipolin levels in accordance with increasing obesity degrees and weakening of the correlation between these cytokines in MO group compared to C group may be helpful during the further investigation of obesity.

Keywords: Adipolin, children, metabolic syndrome, obesity, spexin.

Öz

Amaç: Teknolojideki gelişmeler, dengesiz beslenme, sedanter hayat tarzı gibi yaşam değişiklikleri obezitenin gelişmesi için önemli faktörlerdir. Enflamasyon-obezite ilişkisi güncel bir konu olarak halen incelenmektedir. Bu çalışmada obez (OB), morbid obez (MO), metabolik sendromlu morbid obez (MetS) çocuklar ile sağlıklı, normal vücut kitle indeksi (K) olan çocuklarda yeni nesil enflamatuar belirteçler arasındaki ilişkiler araştırılmıştır.

Materyal ve Metot: Toplam 172 çocuk çalışma kapsamına alındı. Normal vücut kitle indeksine sahip çocuklar birinci grubu (kontrol grubu) (K) oluşturdu. Grup 2'de OB, Grup 3'te MO, Grup 4'te MetS'lu (MetS) çocuklar yer aldı. Olgu sayıları Grup 1,2, 3 ve 4 için sırasıyla 37, 34, 51 ve 50 olarak belirlendi. Antropometrik ölçümler alındı. Serum speksin, adropin, adipolin, fibroblast büyüme faktörü-21 ve fetuin-A düzeyleri ölçüldü. İstatistiksel analizlergerçekleştirildi.

Bulgular: Speksin ve adipolin düzeyleri obez gruplardaK grubuna göre anlamlı düzeyde düşük bulundu ($p<0.05$). Adropin ve FGF-21değerlerindegruplar arasında anlamlı bir fark bulunmamasına rağmendüzeylerin, K grubuna göre OB, MO and MetS gruplarında azalmış olduğu saptandı. Fetuin-A düzeylerinde gruplar arasında anlamlı bir farklılık bulunamadı.En yüksek korelasyonlar speksin ve adipolin düzeyleri arasında bulundu. Bu sitokinler obezite parametreleri ile negatif bir ilişki içindeydi. Aynı sitokinler arasındaki ilişki K grubundan MetS grubuna doğru zayıflamakta idi.

Sonuç: Artan obezite derecelerine paralel olarak speksin ve adipolin seviyelerindeki azalma ve bu iki parametre arasındaki korelasyonun K grubuna göre MO grupta zayıflaması, obezitenin ileri düzeyde araştırılmasında yardımcı olabileceği düşüncesini ortaya koymaktadır.

Anahtar Kelimeler: Adipolin, çocuk, metabolik sendrom, obezite, speksin.

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INTRODUCTION

Obesity is a common and widely investigated public health problem throughout the world.Studies on pediatric population is somewhat more important, because obesity in pediatric age range may lead to chronic health problems in future periods of their lives. Today, it is well-confirmed that obesity during childhood constitutes a background for diabetes mellitus, metabolic syndrome (MetS), cardiovascular diseases, non-alcoholic fatty liver disease and cancer during adulthood. Pediatric obesity has drawn great attention due to the elevations in the prevalence of children with morbid obesity and MetS in recent times.(1-6)

Its close association with severe chronic diseases has made the attention to be directed towards inflammation. Obesity is associated with insulin resistance (IR) and low-grade inflammation and this fact forced researchers to investigate both pro- and anti-inflammatory parameters. So far, serum concentrations of many adipokines, cytokines, chemokines were determined and interpreted among adult as well as pediatric obese individuals. Leptin, adiponectin, resistin, chemerin, vaspin, progranulin and many others in addition to their ratios were interpreted.(2,4,7,8) However, studies performed on some cytokines such as spexin, adipolin, adropin are relatively scarce. Fibroblast growth factor-21 (FGF-21) is still being investigated for its confusing pattern. (9,10) A somewhat older parameter, fetuin A, has recently been suggested for the evaluation of some obesity-related diseases. (11,12)

Spexin (SPX) is also called neuropeptide Q (NPQ). It is a novel biologically active neuropeptidewidely expressed in central nervous system and peripheral tissues. Spexin inhibits food intake and body weight.It exhibits an association with leptin, shows a negative correlation with body mass index (BMI) and IR and alleviates IR. It is also known as a regulatory adipokine in anxiety. It modulates depression, anxiety and blood pressure. (13-15)

Adipolin exhibits beneficial effects on insulin sensitivity like spexin. The other name of adipolin is C1q/TNF-related protein 12 (CTRP12). It is a newly discovered adipocytokine and introduced as a paralog of adiponectin. It exhibits anti-inflammatory effects. (16,17)

Adropin is introduced as a fat-burning hormone with multiple functions. It also exhibits positive correlation with adiponectin. It is negatively associated with the severity of coronary arterial diseases and is suggested as a potential marker predicting obesity and obesity-associated cancer. (18-20)

Fibroblast growth factor-21 is a member of FGF family. It is known as an atypical hormone, metabolic regulator and pro-longevity factor. It improves stress tolerance. Recombinant human FGF21 is introduced as a new therapeutic candidate for depression treatment.(21-23)

In recent reports, fetuin A is a hepatokine, which is suggested as an alternative marker for IR. It is also reported as an indicator for evaluating MetS and the severity of coronary artery disease.There are opposing findings related to functions of fetuin A. (11,12,24-26)

The aim of this study is to determine profiles of some new generation cytokines to make some possible contribution to studies performed in the field of obesity. For the purpose, serum levels of spexin, adipolin, adropin, FGF-21 and fetuin A were measured and their relations with anthropometric

measurements as well as with eachother were investigated in children with normal BMI, obesity, morbid obesity and MetS.

PATIENTS AND METHODS

Selection and Description of Patients

In this study, a total of 172 children [37 with normal body mass index (BMI) values (N-BMI; Group 1), 34 obese (OB; Group 2), 51 morbid obese (MO; Group 3) and 50 metabolic syndrome (MetS; Group 4)] were evaluated. All patients were morbid obese in the metabolic syndrome group. Out of 172 children, ninety-seven were girls and seventy-five were boys. The female-to-male ratio was 1,2. The mean ± SEM of age values of the study population was 11,0 ± 0,3 years. Both prepubertal and pubertal children were included in the study to be able to balance possible unforeseen alterations in the parameters studied.

A detailed history was taken from the parents prior to physical examination. Informed consent forms were filled out by the parents of children participated in the study. Tekirdag Namik Kemal University, Faculty of Medicine Non-interventional Clinical Research Ethical Committee approved the study protocol (date: 30.10.2019, protocol no: 2019.180.10.01). The children with acute or chronic inflammatory, hepatic, renal and malignant diseases were excluded from the scope of the study.

Anthropometric Measurements

Weight and height were measured and recorded.Barefooted children with thin clothing were measured for their weights by an electronic weighing instrument sensitive to 0.1 kg intervals. They were measured for their heights by a portable stadiometer designed in 0.1 cm intervals, in a position that child looks at completely in the horizontal plane and in a position that her occiput, back, hip and heels are in contact with the vertical posterior plane.

Body mass index values were calculated using weight and height measurements of the children.Waist circumference (C) (WC), hip C (HC), head C (HeC), neck C (NC) of each child were measured. Measurements were performed by a flexible, non-elastic tape. Each measurement was taken twice and the mean was recorded.

Waist C was identified as a horizontal line at the midpoint of the upper limit of the iliac crest and the lower rib followed by a normal expiration. Hip C was identified as a horizontal line passing through supra-pubically on the anterior aspect and the largest area of the gluteus on the posterior aspect. Head C was identified as a line passing through the glabella on the anterior aspect and the external occipital protuberance on the posterior aspect. Neck C was identified as the horizontal measurement passing through the most prominent part of the thyroid cartilage while the child is looking forward with neck in an upright position.

Obesity Classification

Obesity classification of the study groups was performed by using age and sex-adjusted BMI percentile tables prepared by World Health Organization. (27) Children with the values higher than 99th percentile were included into MO group. Obese group was composed of children,whose age- and

sex-based BMI percentile values were between 95 and 99. Those constituting the group with N- BMI comprised children, whose percentiles were between 15 and 85.

Metabolic Syndrome Criteria

Metabolic syndrome was diagnosed based upon the criteria suggested by International Diabetes Federation.(28) Two of the following criteria were expected to be present in children having ≥90 percentile for WC: Fasting blood glucose≥ 100 mg/dl, triacylglycerols≥ 150 mg/dl, high density lipoprotein cholesterol≤ 40 mg/dl, systolic blood pressure≥ 130 mm Hg, diastolic blood pressure≥ 85 mm Hg.

Laboratory Measurement of Cytokines

Blood was drawn and centrifuged. Serum samples were kept at -80°C till the analyses were performed. Analyses to determine spexin, adipolin, adropin, FGF-21 and fetuin A concentrations were conducted using enzyme-linked immunosorbent assays (Bioassay Technology Laboratory). Intra-assay and inter-assay coefficient of variation values were <%8 and <%10, respectively.

Statistical Evaluation

Data were evaluated statistically using SPSS Version 16.Descriptive statistics were performed. The normality of the distribution of the datawas tested using Kolmogorov-Smirnov test. Data were presented as mean ± standard deviation (SD). Standard error of mean (SEM) were calculated.Means of the groups were compared. Parametric one-way analysis of variance (ANOVA) and post hoc Tukey tests were used to determine the differences between groups for parameters with normal distribution. Median as well as median absolute deviation values were calculated where they are appropriate. Non-Parametric Mann-Whitney U and Kruskal Wallis Test statistics were performed for the statistical evaluation of the parameters exhibiting a distribution, which is not normal.Pearson's and Spearman's rho correlation analyses were performed based upon thetype of the data distribution. Correlation coefficients and degrees of significance were tabulated. Three dimensional scatterplot was drawnto visualize correlations for BMI-Spexin-Adipolin.p values ≤ 0.05 were accepted as the degree for statistical significance.

RESULTS

A total of 172 children participated in the study. Four groups were constituted. Children with N-BMI were in the first group (n=37). Obese children were divided into three groups. Groups 1, 2, and 3 comprised OB (n=34), MO (n=51) children and those with MetS (n=50), respectively.

Body mass index, waist circumference, hip circumference, head circumference and neck circumference values for groups of the study population were shown in Table I.

Table I. Anthropometric measurements of N-BMI, OB, MO and MetS groups.

Goups Parameters	Group 1 (N-BMI) x±SD(SE)	Group 2 (OB) x±SD(SE)	Group 3 (MO) x±SD(SE)	Group 4 h (MetS) x±SD(SE)	p
BMI (kg/m^2)	16.6±2.2(0.4)	25.0±3.5(0.6)	28.6±5.6 (0.8)	31.0±5.6 (0.8)	1-2,1-3,1-4 *
					2-3 ł, 2-4 *
Waist C (cm)	60.3±8.3(1.4)	83.1±12.3(2.1)	89.6±15.9(2.2)	95.0±14.8(2.1)	1-2,1-3,1-4,2-4 *
Hip C (cm)	72.0±12.5(2.1)	95.6±14.2(2.4)	98.6±16.6(2.3)	105.8±16.8(2.4)	1-2,1-3,1-4 * 2-4 #
Head C (cm)	51.8±2.1(0.4)	54.8±2.1(0.4)	54.9±2.5(0.4)	55.5±2.7(0.4)	1-2,1-3,1-4 *
Neck C (cm)	27.3±3.2(0.5)	32.5±2.9(0.5)	34.2±4.0(0.6)	36.0±4.2(0.6)	1-2,1-3,1-4 * 2-4 #

C=Circumference, N=Normal, OB=Obese, MO=Morbid Obese, MetS=Metabolic Syndrome, BMI=Body Mass Index, x=Mean, SD=StandardDeviation, SE=StandardError, * p<0.001, # p<0.05, ł p<0.01

There is no statistically difference between Group 3 (MO) and Group 4 (MetS) in terms of anthropometric measurements.

Table II showed blood pressurevalues of groups consisting of the study population.

Table II. Systolic and diastolic blood pressure values of N-BMI, OB, MO and MetS groups.

Groups Parameters	Group 1 (N-BMI) x±SD(SE)	Group 2 (OB) x±SD(SE)	Group 3 (MO) x±SD(SE)	Group 4 (MetS) x±SD(SE)	p
SBP (mm Hg)	97±12(2)	113±12(2)	113±13(2)	126±14(2)	1-2,1-3,1-4,2-4,3-4 *
DBP (mm Hg)	61±9(1)	74±12(2)	77±11(2)	84±14(2)	1-2,1-3,1-4,2-4 * 3-4 #

N=Normal, OB=Obese, MO=Morbid Obese, MetS=Metabolic Syndrome, BMI=Body Mass Index, SBP= Systolic Blood Pressure, DBP= DiastolicBlood Pressure, x=Mean, SD=Standard Deviation, SE=StandardError, * p<0.001, # p<0.05, ł p<0.01

Parameters related to the glucose metabolism of groups of the study population were shown in Table III.

Table III. Fasting blood glucose, insulin and HOMA-IR values of N-BMI, OB, MO, and MetS

Groups Parameters	Group 1 (N-BMI) x±SD(SE)	Group 2 (OB) x±SD(SE)	Group 3 (MO) x±SD(SE)	Group 4 (MetS) x±SD(SE)	P
Glucose (mg/dL)	90.2±9.0(1.5)	93.7±8.9(1.5)	90.7±6.8(1.0)	97.8±11.1 (1.6)	
					1-4, 3-4 *
m İnsulin (µIU/mL)	7.67	16.14	17.93	30.4	1-2,1-3,1-4 * 2-4,3-4 *
m HOMA	1.68	3.76	3.99	7.19	1-2,1-3,1-4 * 2-4,3-4 *

N=Normal, OB=Obese, MO=Morbid Obese, MetS=Metabolic Syndrome, BMI=Body Mass Index, HOMA-IR= Homeostatic Model Assesment for Insulin Resistance Index,
x= Mean, SD=StandardDeviation, SE=StandardError, m median, * p<0.001, # p<0.05, ł p<0.01

In Table IV, values related to lipid profiles for groupsof the study population were tabulated.

Table IV. Total cholesterol, triglyceride, low density lipoprotein cholesterol and high density lipoprotein cholesterol values for N-BMI, OB, MO and MetS groups.

Groups Parameters	Group 1 (N-BMI) x±SD(SE)	Group 2 (OB) x±SD(SE)	Group 3 (MO) x±SD(SE)	Group 4 (MetS) x±SD(SE)	p
TChol (mg/dL)	152.1±35.8(6.3)	160.4±25.0(4.4)	158.3±32.6(4.6)	167.3±37.0(5.2)	NS
TRG (mg/dL)	92.4±51.7(8.5)	100.2±56.7(9.7)	103.3±41.1(5.8)	174.5±95.0(13.4)	1-4, 2-4, 3-4 *
LDL-C (mg/dL)	82.0±21.3(3.8)	85.6±22.3(3.9)	88.4±26.1(3.7)	90.8±28.2(4.0)	NS
HDL-C (mg/dL)	56.0±12.0(2.0)	54.5±11.5(2.0)	49.5±12.3(1.7)	43.4±7.7(1.1)	1-4, 2-4 * 1-3, 3-4 #

N=Normal, OB=Obese, MO=Morbid Obese, MetS=Metabolic Syndrome, BMI=Body Mass Index, SBP= Systolic Blood Pressure, DBP= DiastolicBlood Pressure,
x=Mean, SD=Standard Deviation, SE=StandardError, * p<0.001, # p<0.05, ł p<0.01

Values of cytokines for groups in the study population were given in Table V.

Table V. Spexin, adipolin, FGF-21, adropin and fetuin A levels of N-BMI, OB, MOand MetS groups.

Groups Parameters	Group 1 (N-BMI) median	Group 2 (OB) median	Group 3 (MO) median	Group 4 (MetS) median	
Spexin (ng/L)	652.3	461.0	425.7	450.8	1-2,1-3,1-4 #
Adipolin	2.33	1.82	1.83	1.65	1-2,1-3,1-4 #
(ng/mL) FGF-	198.2	152.2	183.4	189.9	NS
21 (pg/mL)	140.0	96.9	102.0	114.9	NS
Adropin	444.8	324.9	366.4	451.1	NS

N=Normal, OB=Obese, MO=Morbid Obese, MetS=Metabolic Syndrome, BMI=Body Mass Index, FGF- 21=Fibroblast Growth Factor-21
* p<0.001, # p<0.05, ł p<0.01, NS=Not significant (p>0.05)

Spexin and adipolin levels inOB, MO and MetS groups were significantly lower than the values found in N-BMI group. Median absolute deviation values for spexin were 321.0, 164.4, 128.6, 86.3 in N-BMI, OB, MO and MetS groups, respectively. The corresponding values for adipolin were 1.11, 0.72, 0.61, 0.54.

Upon evaluation of the results of correlation analysis concerning cytokine values detected in each group, highest correlations were calculated for spexin-adipolin couple. The correlation coefficients were obtained as 0.918, 0.825 and 0.749 for children with N-BMI, OB and MO children including those with MetS, respectively. The correlation coefficient value calculated for this couple was 0.818;p<0.001 for the overall study population.

Significant correlations were obtained between adropin levels and head C (r= - 0.338; p=0.041) as well as neck C (r= - 0.361; p=0.028) values in N-BMI group.

HOMA-IR was correlated significantly with fetuin A (r= 0.495; p=0.000) in MO children.

Results of correlation analysis concerning the relations among anthropometric measurements and spexin as well as adipolin values for the overall study population were shown in Table VI.

Tablo VI. Correlation coefficients and degrees of significance describing the relations between anthropometric measurements and cytokine levels determined for the overall study population.

Groups Parameters	Spexin	Adipolin
BMI	- 0.209ł	- 0.266 *
Waist	- 0.187 #	- 0.243 #
C Hip	- 0.190 #	- 0.247ł
C	- 0.205 #	- 0.257 #
Head	- 0.220ł	- 0.274 #

C=Circumference, * p<0.001, ł p<0.01, # p<0.05

Negative correlations were calculated between anthropometric measurements and spexin as well as adipolin.

Correlations between BMI values of children and spexin as well as adipolin concentrations were shown in Figure 1.

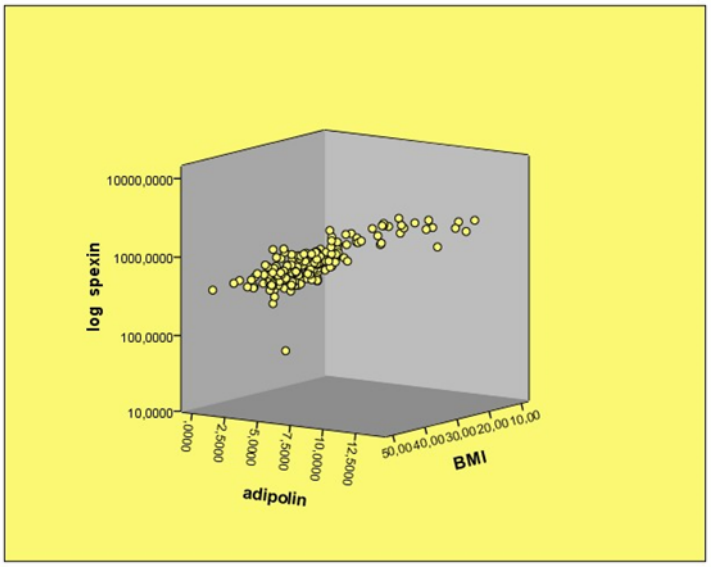

Figure 1. Three-dimensional scatterplot graphic drawn based upon correlations between BMI and spexin as well as adipolin.

DISCUSSION AND CONCLUSION

Obesity is an endocrine disease involving glands and hormone signallers. Such diseases have far-reaching consequences. (29-33) It is also important to integrate endocrine and cytokine systems and to detect whether inflammatory factors contribute to the development of obesity as well as MetS or not. The evaluation of some relatively new parameters, mostly derived from adipose tissue will handle the matter from another point of view.

Cytokines in clinical medicine participate in many fields extending from assisted reproduction techniques to life-threatening chronic diseases. (11,15,26,34,35) Within this context, some of new generation cytokines were investigated in obese children and those with MetS in this study.

Significantly lower spexin levels were reported in obese children. Spexin levels were lower also in MetS and type I as well as type 2 diabetes. An inverse correlation was found between reduced spexin

levels and hyperleptinemia. Spexin, a neuropeptide with regulatory function in obesity, is suggested to have a potential role in childhood obesity and its associated metabolic disorders. (13,36-40) In our study, medians of spexin levels were significantly lower in OB, MO and MetS groups vs N-BMI children.

In a study concerning hemodialysis, higher adipolin values were also reported in diabetes. Higher adipolin levels observed in diabetes group may be due to a compensatory elevation in the production of this parameter. In another study, adipolin levels were also significantly higher in MetS vs healthy controls. It has been reported that adipolin levels were lower in patients with type 2 diabetes.Decreased serum adipolin levels were also measured in patients with coronary artery disease. Adipolin was negatively associated with BMI and HOMA-IR, positively associated with adiponectin and HDL-C in these patients.(17,41,42) In our study, significantly decreased adipolin levels were observed in OB, MO and MetS groups in comparison to N-BMI group.

Obese patients had reduced levels of adropin. In type 2 diabetes, decreased serum adropin levels were observed. In patients with type 2 diabetes, increased adropin was associated with corresponding decreases in fat accumulation and inflammation. Adropin was correlated positively with adiponectin levels. It is suggested that adropin may be used as a biomarker for predicting the risk of obesity and inflammation in type 2 diabetes. Serum adropin was negatively correlated with BMI.Concentration of adropin differed between patients with and without cachexia. (18,19,43-45) In our study, a decreasing pattern in adropin levels were detected. However, decreases were not significant.

The negative correlations between adropin and head C as well as neck C in healthy individuals are valuable findings confirming the association of anthropometric parameters with numerous biological effects of adropin within normal ranges. As adropin concentrations are decreasing, some associations between this parameter and anthropometric measurements are lost.

An anti-inflammatory cytokine FGF-21 has been shown to elevate the production of another anti-inflammatory parameter, interleukin-10.FGF-21 levels are positively associated with MetS in patients with type 2 diabetes. Increases in FGF-21 in obese adolescents with type 2 diabetes suggest a resistance state because FGF-21 improves insulin sensitivity. FGF-21 is suggested to play a protective role against the development of IR over time in patients undergoing a continuous glucose load. Serum FGF-21 level is reported to be used as a tumor biomarker in early-stage breast cancer and for monitoring purposes. (9,46-49) In our study, there was no significant difference between groups in terms of FGF-21.

The increased fetuin-A levels in obese adolescents with type 2 diabetes supports the hypothesis that fetuin-A is involved in the pathogenesis of type 2 diabetes because this hepatokine leads to IR.An association between fetuin-A levels and diabetic retinopathy stage was noted. In diabetic patients, the risk of retinopathy development increases with higher fetuin-A levels. Fetuin-A may play an important role in the pathophysiology and progression of diabetic retinopathy. Fetuin-A levels increased in association with diabetes in subcutaneous adipose tissue but not in circulation in the obese subjects.

Fetuin-A induces cytokine expression and suppresses adiponectin production.(48, 50-52) We did not observe any statistically significant alteration among fetuin A levels of the groups.

The significant correlation between HOMA-IR and fetuin A in MO group contributed this parameter's identity as an alternative marker for insulin resistance.

It is concluded that adipolin and spexin were negatively correlated with obesity parameters. The highest correlations existed between adipolin and spexin in all groups. However, a decreasing tendency was noted going from N-BMI group (0.918) to OB (0.825) and toMO group including also the cases with MetS (0.749).This indicates that the strict association between these two parameters was significantly weakened in MO status in comparison with the healthy individuals. This decline in the correlation between spexin and adipolin calculated for MO children may be the effect of dysregulated glucose, lipid,and inflammatory metabolisms during the late stage of obesity and its possible consequence, MetS.

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Kaynaklar

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Tekirdag Namik Kemal University, Faculty of Medicine Non-interventional Clinical Research Ethical Committee approved the study protocol (date: 30.10.2019, protocol no: 2019.180.10.01).