The Valuable Triad of Adipokine Indices to Differentiate Pediatric Obesity from Metabolic Syndrome: Chemerin, Progranulin, Vaspin

Mustafa M. Donma, Orkide Donma

Abstract—Obesity is associated with cardiovascular disease risk factors and metabolic syndrome (MetS). In this study, associations between adipokines and adipokine as well as obesity indices were evaluated. Plasma adipokine levels may exhibit variations according to body adipose tissue mass. Besides, upon consideration of obesity as an inflammatory disease, adipokines may play some roles in this process. The ratios of proinflammatory adipokines to adiponectin may act as highly sensitive indicators of body adipokine status. The aim of the study is to present some adipokine indices, which are thought to be helpful for the evaluation of childhood obesity and also to determine the best discriminators in the diagnosis of MetS. 80 prepubertal children (aged between 6-9.5 years) included in the study were divided into three groups; 30 children with normal weight (NW), 25 morbid obese (MO) children and 25 MO children with MetS. Physical examinations were performed. Written informed consent forms were obtained from the parents. The study protocol was approved by Ethics Committee of Namik Kemal University Medical Faculty. Anthropometric measurements, such as weight, height, waist circumference (C), hip C, head C, neck C were recorded. Values for body mass index (BMI), diagnostic obesity notation model assessment Index-II (D2 index) as well as waist-to-hip, head-to-neck ratios were calculated. Adiponectin, resistin, leptin, chemerin, vaspin, progranulin assays were performed by ELISA. Adipokine-to-adiponectin ratios were obtained. SPSS Version 20 was used for the evaluation of data. p values ≤ 0.05 were accepted as statistically significant. Values of BMI and D2 index, waist-to-hip, head-to-neck ratios did not differ between MO and MetS groups (p ≥ 0.05). Except progranulin (p ≤ 0.01), similar patterns were observed for plasma levels of each adipokine. There was not any difference in vaspin as well as resistin levels between NW and MO groups. Significantly increased leptin-to-adiponectin, chemerin-to-adiponectin and vaspin-to-adiponectin values were noted in MO in comparison with those of NW. The most valuable adipokine index was progranulin-to-adiponectin (p ≤ 0.01). This index was strongly correlated with vaspin-to-adiponectin ratio in all groups (p ≤ 0.05). There was no correlation between vaspin-to-adiponectin and chemerin-to--adiponectin in NW group. However, a correlation existed in MO group (r = 0.486; p ≤ 0.05). Much stronger correlation (r = 0.609; p ≤ 0.01) was observed in MetS group between these two adipokine indices. No correlations were detected between vaspin and progranulin as well as vaspin and chemerin levels. Correlation analyses showed a unique profile confined to MetS children. Adiponectin was found to be correlated with waist-to-hip (r = -0.435; p ≤ 0.05) as well as head-to-neck (r = 0.541; p ≤ 0.05) ratios only in MetS children. In this study, it has been investigated if adipokine indices have priority over adipokine levels. In conclusion, vaspin-to-adiponectin, progranulin-to-adiponectin, chemerin-to-adiponectin along with waist-to-hip and head-to-neck ratios were the optimal combinations. Adiponectin, waist-to-hip, head-to-neck, vaspin-to-adiponectin, chemerin-to-adiponectin ratios had appropriate discriminatory capability for MetS children.

Keywords—Adipokine indices, metabolic syndrome, obesity indices, pediatric obesity.

I. INTRODUCTION

CHILDHOOD obesity is associated with MetS and cardiovascular diseases (CVDs). Adipokines make a considerable contribution to insulin resistance (IR) and obesity [1]. Leptin as well as resistin both are positively correlated whereas adiponectin is negatively correlated with BMI suggesting that the concentrations of these biomarkers may change from lean to obesity [2].

In a study performed on adolescents, positive associations between serum chemerin levels and potentially life threatening members of the lipid profile family including triglycerides and cholesterol levels were reported. Adiponectin levels were in positive correlation with high density lipoprotein cholesterol concentrations [3].

Some adipokines participate in atherosclerotic plaque rupture and cardiovascular events. Leptin, chemerin and resistin are essentially known for their proinflammatory nature. Chemerin and resistin may act as potential markers for plaque instability and stroke risk [4]. Elevated leptin-to-adiponectin ratio is suggested as potentially useful prognostic biomarker of atherothrombotic acute ischemic stroke [5].

It is reported that chemerin is an adipokine with inflammatory and metabolic actions related to chronic disease development. It is correlated with essential hypertension, type 2 diabetes (T2D), and coronary heart diseases. Chemerin elevated in obesity and MetS is associated with endothelial dysfunction and plays a crucial role in early and advanced atherosclerosis [6]-[9].

Changes in chemerin may also be positively correlated with changes in adiponectin levels. This finding might be related to the chemerin's dual inflammatory and anti-inflammatory effects. It may also be due to IR and insulin sensitivity enhancing effects of this parameter, depending on the metabolic conditions [10].

Progranulin has recently been introduced as a novel marker of chronic inflammatory response in obesity and T2D capable of directly affecting the insulin signaling pathway. Serum

M. M. D., Prof. Dr., is with the Namik Kemal University, Faculty of Medicine, Department of Pediatrics, Tekirdag, Turkey (corresponding author to provide phone: 00-90-532-371-72-07; fax: 00-90-282—250-99-28; e-mail: mdonma@ gmail.com).

O. D., Prof. Dr., is with the Istanbul University, Cerrahpasa Medical Faculty, Department of Medical Biochemistry, Istanbul, Turkey (e-mail: odonma@gmail.com).

World Academy of Science, Engineering and Technology
International Journal of Medical and Health Sciences
Vol:12, No:5, 2018

levels of this parameter might be closely associated with microvascular complications in T2D [11].

Vaspin is also a recently identified adipokine related to obesity and insulin sensitivity. Vaspin is correlated with coronary artery disease in T2D [12], [13].

Plasma adipokine levels may vary depending upon body adipose tissue mass. Since obesity is considered as an inflammatory disease, adipokines may play some roles in this process. The ratios developed from antiinflammatory and proinflammatory adipokines may be much more informative to express adipokine status of the body.

This study was conducted to investigate the relationship between adipokines and the indices derived from these adipokines. Their associations with obesity indices have also been reviewed. The aim of this study is to calculate and introduce a number of adipokine indices, which may help the evaluation of obesity and MetS during childhood.

II. PATIENTS AND METHODS

A. Patients

This study comprised 80 children, whose ages were between 6.0 and 9.5 years. The study population was composed of prepubertal children. Three individual groups (30 children with normal BMI (NW), 25 children with MO and 25 children with MetS) were composed. The detailed anamnesis was taken during the physical examination. Informed consent forms were filled out by the parents of children participated in the study. Namik Kemal University, Faculty of Medicine Ethical Committee approved the study protocol. The children with acute or chronic inflammatory, hepatic, renal and malignant diseases were excluded from the scope of the study.

B. Anthropometric Measurements

Weight, height, waist circumference (C), hip C, head C, neck C measurements were taken and recorded.

C. Obesity Classification

Obesity classification of the study groups was performed by using age and sex-adjusted BMI percentile tables prepared by World Health Organization [14]. Children with the values higher than 99th percentile were included into MO group. Those constituting the group with normal BMI comprised children, whose percentiles were between 15th and 85th.

D. MetS Criteria

MetS was diagnosed based upon the criteria suggested by International Diabetes Federation [15]. Two of the following criteria were expected to be present in children having ≥90 percentile for waist C: Fasting blood glucose (FBG) ≥ 100 mg/dl, triacylglycerols (TRG) ≥ 150 mg/dl, high density lipoprotein cholesterol (HDL-C) ≤ 40 mg/dl , systolic blood pressure (SBP) ≥ 130 mm Hg, diastolic blood pressure (DBP) ≥ 85 mm Hg.

E. Laboratory Measurement of Adipokines

Analyses to determine adiponectin, resistin, leptin, chemerin, vaspin, and progranulin concentrations were conducted using enzyme-linked immunosorbent assays.

F. Ratio Calculations

The calculations for BMI, diagnostic obesity notation model assessment Index-II (D2 index) [16], waist-to-hip and head-to-neck ratios were performed. Adipokine-to-adiponectin ratios (such as resistin-to-adiponectin, leptin-to-adiponectin, chemerin-to-adiponectin, vaspin-to-adiponectin, and progranulin-to-adiponectin) were calculated.

G. Statistical Evaluation

Data were evaluated statistically using SPSS Version 20. p values ≤ 0.05 were accepted as the degree for statistical significance.
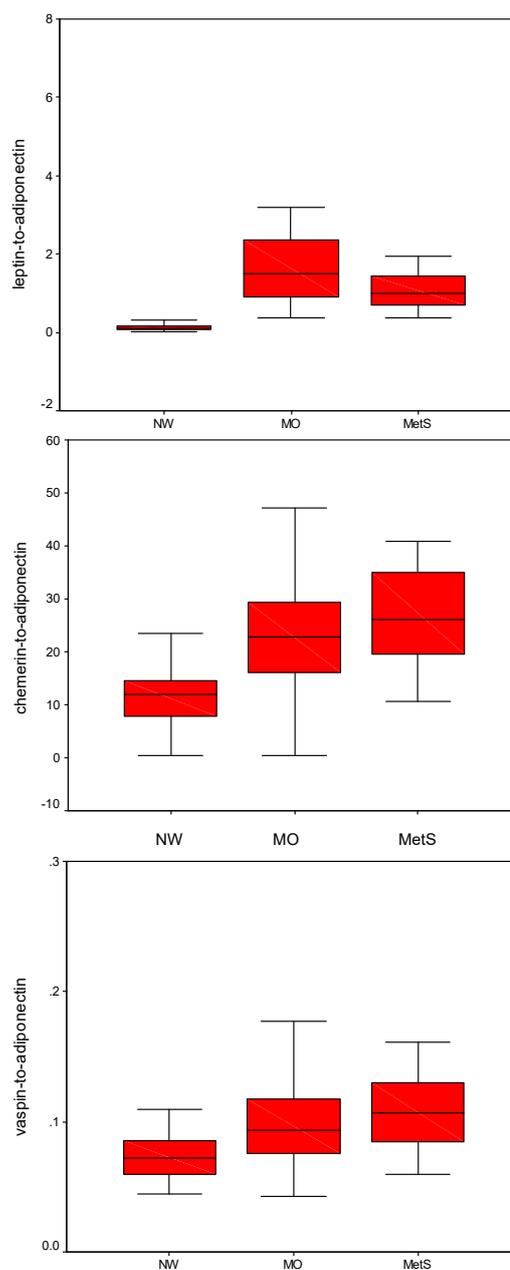

Fig. 1 Ratios of leptin, chemerin and vaspin to adiponectin in three groups

World Academy of Science, Engineering and Technology
International Journal of Medical and Health Sciences
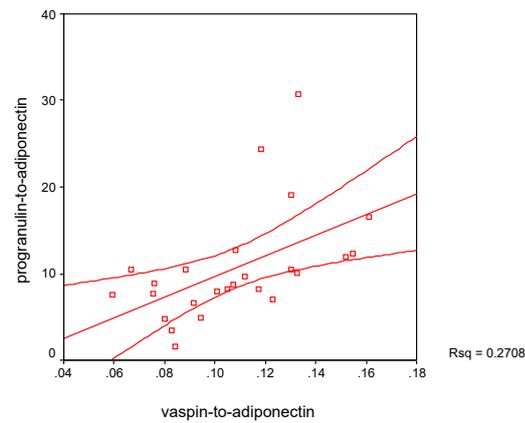Vol:12, No:5, 2018

III. RESULTS

A total of 80 prepubertal children were included into the scope of this study. Fig. 1 shows box plot diagrams of leptin-to-adiponectin, chemerin-to-adiponectin and vaspin-to-adiponectin in NW, MO and MetS groups.
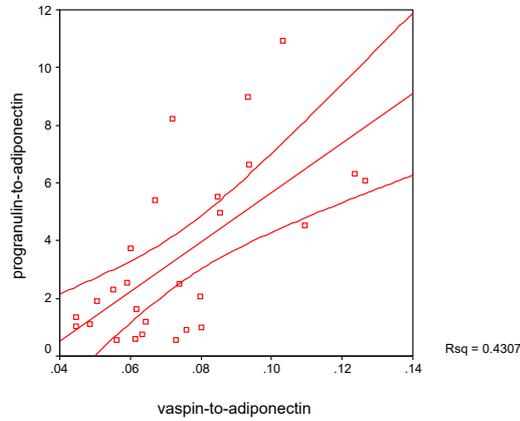
(a)
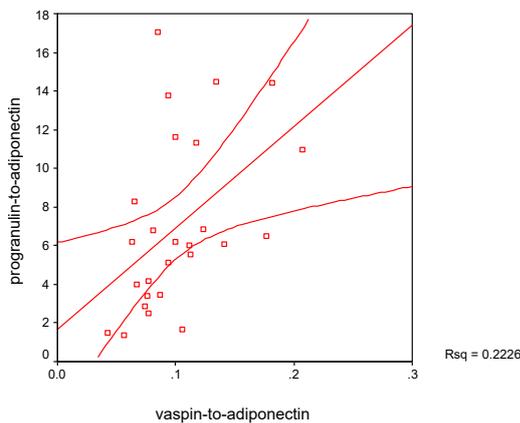
(b)

(c)

Fig. 2 Correlations between progranulin-to-adiponectin and vaspin-to-adiponectin in three groups (a) NW, (b) MO, (c) MetS

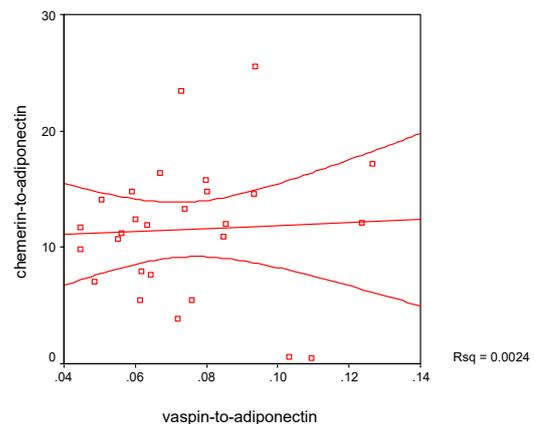No statistically significant difference was noted between

BMI and D2 indices, waist-to-hip, head-to-neck ratios observed in MO and MetS groups ($p \geq 0.05$). Among all adipokines studied, progranulin was the only parameter, which exhibited statistically significant differences between the groups ($p \leq 0.01$). Vaspin and resistin did not differ between NW and MO groups. In MO group, the ratios of leptin, chemerin and vaspin to adiponectin were found to be statistically higher than those calculated for NW.

In Fig. 2, the correlations between progranulin-to-adiponectin and vaspin-to-adiponectin in children with NW (a), MO (b) and MetS (c) groups were shown.
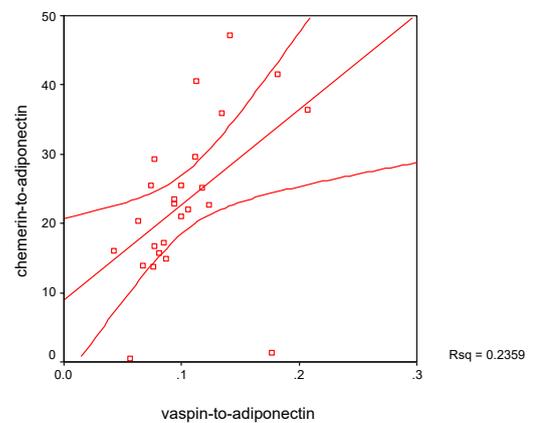
The correlations between vaspin-to-adiponectin and progranulin-to-adiponectin were significant ($p \leq 0.05$) in all groups.

Fig. 3 shows graphs drawn for the correlations between chemerin-to-adiponectin and vaspin-to-adiponectin in three groups ((a) NW, (b) MO, (c) MetS)
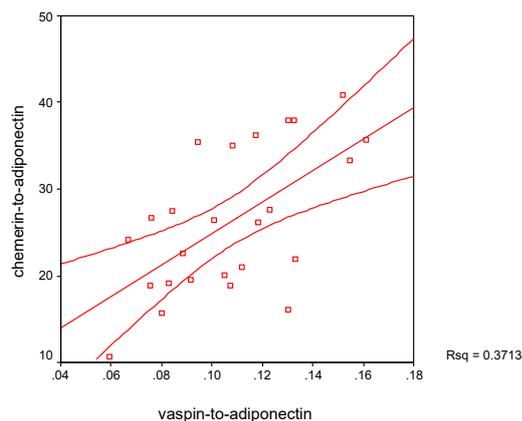
The ratios of vaspin-to-adiponectin as well as chemerin-to-adiponectin were not correlated in NW group, whereas they are correlated in MO group ($r = 0.486$; $p \leq 0.05$). A strong positive correlation between vaspin-to-adiponectin and chemerin-to-adiponectin was calculated in MetS group ($r = 0.609$; $p \leq 0.01$). Any correlation could not be found between vaspin and progranulin as well as chemerin levels.

(a)

(b)

World Academy of Science, Engineering and Technology
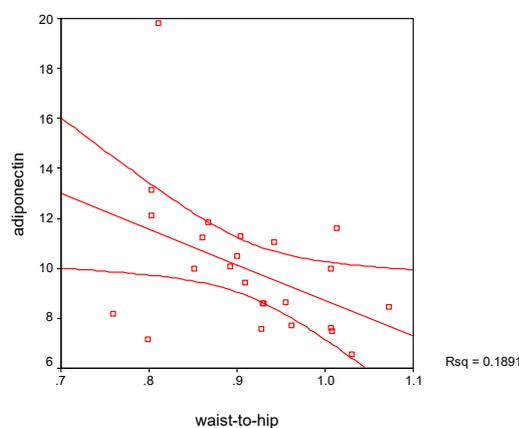International Journal of Medical and Health Sciences
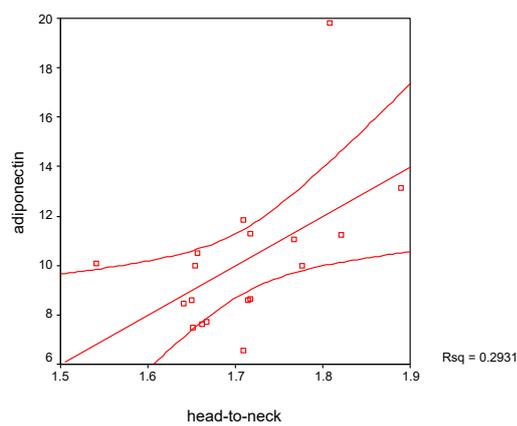Vol:12, No:5, 2018

(c)

Fig. 3 Correlations between chemerin-to-adiponectin and vaspin-to-adiponectin in three groups (a) NW, (b) MO, (c) MetS

(a)

(b)

Fig. 4 Correlations of adiponectin with waist-to-hip (a) as well as head-to-neck (b) ratios in MetS group

In Fig. 4, adiponectin was found to be correlated both with waist-to-hip (a) and with head-to-neck (b) ratios in MetS group.

Correlations between adiponectin and waist-to-hip ratio as well as adiponectin and head-to-neck ratio were found to be as

r=-0.435; p≤0.05 and r= 0.541; p≤0.05, respectively.

IV. Discussion

Proinflammatory and anti-inflammatory cytokines are known to participate in clinical disorders. There are many studies reporting the cytokine ratios such as TNF-α/IL-10, IL-10/IL-6, IFN-γ/IL-4 [17]-[20]. However, adipokine ratios are not mentioned so frequently.

The most frequently reported adipokine ratio is leptin-to-adiponectin ratio (LAR). This ratio has been introduced as a biomarker of systemic insulin sensitivity in normoglycemic women [21]. In a study performed on adolescents, LAR was found to be related to insulin sensitivity also in children [22]. In another study, LAR, which could be used as a marker for IR was investigated in adults with MetS. It was concluded that low LAR is a predictor for the regression of MetS. It is suggested that this ratio could be a useful clinical marker for the management of high risk individuals with MetS [23].

In our study this ratio was found to be significantly increased both in MO as well as MetS groups compared to that of children with normal BMI (p≤0.001). There was not any difference between the values calculated in MO and MetS groups.

Gumanova et al [24] reported that ratios of leptin-to-insulin and adiponectin-to-endothelin are sex-dependently associated with the extent of coronary atherosclerosis. These ratios are suggested as useful biomarkers for noninvasive diagnosis of initial stages of coronary lesions in patients with coronary artery disease. It is also reported that adiponectin-to-resistin index was found to be strongly associated with acute coronary syndrome [25]. Utility of adiponectin-to-leptin and adiponectin-to-resistin ratios as potential biomarkers of polycystic ovary syndrome (PCOS) were also examined. These ratios were negatively correlated with BMI, homeostatic model assessment-IR and free insulin [26]. In a similar manner, the ratios of resistin-to-adiponectin were reduced in obese women with PCOS [27]. We have calculated resistin-to-adiponectin ratios in all of three groups; however, no statistically significant difference was noted between the groups (p≥0.05).

In our study, we have calculated adipokine ratios. These ratios were chemerin-to-adiponectin, vaspin-to-adiponectin and progranulin-to-adiponectin. First two ratios exhibited similar patterns, as in the case of leptin-to-adiponectin. The values obtained in MO and MetS groups did not differ statistically from one another. However, they were significantly higher than the values detected for children with normal BMI (p≤0.001).

Progranulin-to-adiponectin ratio, which was correlated with vaspin-to-adiponectin ratio in all groups, was the highly recommended adipokine index (p≤0.01).

Lack of correlation in NW group, however, existence of a correlation in MO group and the finding of a much stronger correlation observed in MetS group between vaspin-to-adiponectin and chemerin-to-adiponectin are quite important from the evaluation of the clinical utility of adipokine ratios point of view, because vaspin levels were not correlated with

World Academy of Science, Engineering and Technology
International Journal of Medical and Health Sciences
Vol:12, No:5, 2018

progranulin as well as chemerin levels.

Children with MetS exhibited interesting correlations, which were confined to this group only. In this group, adiponectin was correlated negatively with waist-to-hip and positively with head-to-neck ratios.

Interpretation of progranulin-to-adiponectin ratios, correlations between vaspin-to-adiponectin and chemerin-to-adiponectin ratios, correlations between adiponectin and waist-to-hip as well as head-to-neck ratios will be helpful during the evaluation of MetS in MO children.

ACKNOWLEDGMENT

REFERENCES

[1] J. Daxer, T. Herttrich, Y. Y. Zhao, M. Vogel, A. Hiemisch, K. Scheuermann, et al., "Nocturnal levels of chemerin and progranulin in adolescents: influence of sex, body mass index, glucose metabolism and sleep," *J. Pediatr. Endocrinol. Metab.,* vol. 30, no. 1, pp. 57-61, Jan 2017.

[2] R. M. Mantovani, N. P. Rocha, D. M. Magalhães, I. G. Barbosa, A. L. Teixeira, E. Simões, et al., "Early changes in adipokines from overweight to obesity in children and adolescents," *J. Pediatr. (Rio J.),* vol. 92, no. 6, pp. 624-630, Nov–Dec. 2016.

[3] Z. Maghsoudi, R. Kelishadi, and M. J. Hosseinzadeh-Attar, "The comparison of chemerin, adiponectin and lipid profile indices in obese and non-obese adolescents," *Diabetes Metab. Syndr.,* vol. 10, no. 2 (Suppl 1), pp. S43-S46, Apr-Jun. 2016.

[4] K. Gasbarrino, C. Mantzoros, J. Gorgui, J. P. Veinot, C. Lai, and S. S. Daskalopoulou, "Circulating chemerin is associated with carotid plaque instability, whereas resistin is related to cerebrovascular symptomatology," *Arterioscler. Thromb. Vasc. Biol.,* vol. 36, no. 8, pp.1670-1678, Aug. 2016.

[5] F. Carbone, F. Burger, G. Roversi, C. Tamborino, I. Casetta, S. Seraceni, et al., "Leptin/adiponectin ratio predicts poststroke neurological outcome," *Eur. J. Clin. Invest.,* vol. 45, no. 11, pp. 1184-1191, Nov. 2015.

[6] F. Eichelmann, C. Weikert, R. di Giuseppe, R. Biemann, B. Isermann, M. B. Schulze, et al., "Methodological utility of chemerin as a novel biomarker of immunity and metabolism," *Endocr. Connect.,* vol. 6, no. 5, pp. 340-347, Jul. 2017.

[7] G. Zhang, M. Xiao, L. Zhang, Y. Zhao, and Q. Yang Q, "Association of serum chemerin concentrations with the presence of atrial fibrillation," *Ann. Clin. Biochem.,* vol. 54, no. 3, pp. 342-347, May 2017.

[8] B. Lu, M. Zhao, W. Jiang, J. Ma, C. Yang, J. Shao, et al., "Independent association of circulating level of chemerin with functional and early morphological vascular changes in newly diagnosed type 2 diabetic patients," *Medicine (Baltimore).,* vol. 94, no. 47, pp. e1990, Nov. 2015.

[9] P. Gu, M. Cheng, X Hui, B. Lu, W. Jiang, and Z. Shi, "Elevating circulation chemerin level is associated with endothelial dysfunction and early atherosclerotic changes in essential hypertensive patients," *J. Hypertens.,* vol. 33, no. 8, pp. 1624-1632, Aug. 2015.

[10] H. Y. Shin, S. Park, and J. W. Lee, "Positive association between the changes in chemerin and adiponectin levels after weight reduction," *Endocr. Res.,* vol. 42, no. 4, pp. 287-295, Nov. 2017.

[11] L. Xu, B. Zhou, H. Li, J Liu, J. Du, W. Zang, et al., "Serum levels of progranulin are closely associated with microvascular complication in type 2 diabetes," *Dis. Markers.,* vol. 2015, pp. 357279, 2015.

[12] S. Moradi, K. Mirzaei, A. A. Abdurahman, S. A. Keshavarz, and A. Hossein-Nezhad, "Mediatory effect of circulating vaspin on resting metabolic rate in obese individuals," *Eur. J. Nutr.,* vol. 55, no. 3, pp. 1297-1305, Apr. 2016.

[13] F. Hao, H. Zhang, J. Zhu, H. Kuang, Q Yu, M. Bai,et al., "Association between vaspin level and coronary artery disease in patients with type 2 diabetes," *Diabetes Res. Clin. Pract.,* vol. 113, pp. 26-32, Mar. 2016.

[14] World Health Organization (WHO). The WHO Child Growth Standarts. Available at: http:// www.who.int /childgrowth/en/. Accessed on June 10, 2016.

[15] P. Zimmet, K. G. Alberti, F. Kaufman, N. Tajima, M. Silink, S. Arslanian, G. Wong, P. Bennett, J. Shaw, S. Caprio, and IDF consensus group, "The metabolic syndrome in children and adolescents-an IDF consensus report", *Pediatr. Diabetes,* vol: 8, no.5, pp. 299-306, Oct. 2007.

[16] O. Donma, M. M. Donma, M. Demirkol, M. Aydın, T. Gokkus, B. Nalbanoglu, A. Nalbantoglu, and B. Topcu, "Laboratory indices in late childhood obesity: The importance of DONMA indices," *Int J Med Health Biomed Bioeng Pharmaceutical Eng,* vol. 10, no. 5, pp. 280-286, May 2016.

[17] R. Hou, M. Garner, C. Holmes, C. Osmond, J. Teeling, L. Lau, et al., "Peripheral inflammatory cytokines and immune balance in Generalised Anxiety Disorder: Case-controlled study," *Brain Behav. Immun.,* vol. 62, pp. 212-218, May 2017.

[18] A. B. Acharya, S. Thakur, M. V. Muddapur, and R. D. Kulkarni, "Cytokine ratios in chronic periodontitis and type 2 diabetes mellitus," *Diabetes Metab. Syndr.,* vol. 11, no. 4, pp. 277-278, Oct – Dec. 2017.

[19] H. C. Lin, and J. Y. Lin, "Immune cell-conditioned media suppress prostate cancer PC-3 cell growth correlating with decreased proinflammatory/anti-inflammatory cytokine ratios in the media using 5 selected crude polysaccharides," *Integr. Cancer Ther.,* vol. 15, no. 4, pp. NP13-NP25, Dec. 2016.

[20] S. Biswas, P. K. Ghoshal, S. C. Mandal, and N. Mandal, "Relation of anti- to pro-inflammatory cytokine ratios with acute myocardial infarction," *Korean J. Intern. Med.,* vol. 25, no. 1, pp. 44-50, Mar. 2010.

[21] C. Bravo, L. R. Cataldo, J. Galgani, J. Parada, and J. L. Santos, "Leptin/adiponectin ratios using either total or high-molecular-weight adiponectin as biomarkers of systemic insulin sensitivity in normoglycemic women," *J. Diabetes Res.,* vol. 2017, pp. 9031079, 2017.

[22] I. Aldhood-Hainerova, H. Zamrazilova, Hill M, and Hainer V, "Insulin sensitivity and its relation to hormones in adolescent boys and girls," *Metabolism,* vol. 67, pp. 90-98, 2017.

[23] D. R. Kang, D. Yadav, S. B. Koh, J. Y. Kim, and S. V. Ahn, "Impact of serum leptin to adiponectin ratio on regression of metabolic syndrome in high-risk individuals: The ARIRANG Study," *Yonsei Med. J.,* vol. 58, no. 2, pp. 339-346, Mar. 2017.

[24] N. G. Gumanova, N. E. Gavrilova, O. I. Chernushevich, A. Y. Kots, and V. A. Metelskaya, "Ratios of leptin to insulin and adiponectin to endothelin are sex-dependently associated with extent of coronary atherosclerosis," *Biomarkers,* vol. 22, no. 3-4, pp. 239-245, May-Jun. 2017.

[25] P. Singh, M. G. Sridhar, M. Rajappa, J. Balachander, and T. Kadhiravan, "Adiponectin-resistin index and its strong association with acute coronary syndrome in South Indian men," *Inflamm. Res.,* vol.63, pp. 961-968, 2014.

[26] S. Sarray, S. Madan, L. R. Saleh, N. Mahmoud, and W. Y. Almawi, "Validity of adiponectin-to-leptin and adiponectin-to-resistin ratios as predictors of polycystic ovary syndrome," *Fertil. Steril.,* vol. 104, no. 2, pp. 460-466, Aug. 2015.

[27] B. Pangaribuan, I. Yusuf, M. Mansyur, and A. Wijaya, "Serum adiponectin and resistin in relation to insulin resistance and markers of hyperandrogenism in lean and obese women with polycystic ovary syndrome," *Ther. Adv. Endocrinol. Metab.,* vol. 2, no. 6, pp. 235-245, 2011.