**International Journal of Biology, Pharmacy
and Allied Sciences (IJBPAS)**

'A Bridge Between Laboratory and Reader'

www.ijbpas.com

IDENTIFICATION OF OBESITY IN YOUNG INDIAN SCHOOL-GOING CHILDREN USING ADIPOKINES AS BIOMARKERS

ABHANG SA^{1*}, THAKRE RR² AND NAIK SS³

1: Professor of Biochemistry, Symbiosis Medical College for Women, Symbiosis International (Deemed) University Lavale, Pune, Maharashtra, India

2: Research Scholar, B. J. Medical College, Pune

3: Head of Biochemistry and Endocrinology, K.E.M. Hospital, Pune

*Corresponding Author: Dr. S. A. Abhang: E Mail: prof.biochemistry1@smcw.siu.edu.in

Received 30th Sept. 2020; Revised 26th Oct. 2020; Accepted 18th Nov. 2020; Available online 1st Sept. 2021

<https://doi.org/10.31032/IJBPAS/2021/10.9.5613>

ABSTRACT

Background: Adipokines (adiponectin and leptin), as biomarkers can help to identify the onset of obesity. We observed a direct association between leptin and obesity and an inverse relation between adiponectin and obesity in school going children. With no defined cut-offs in Indian children for leptin and adiponectin to identify obesity, we aimed to find cut-off values of serum adiponectin, leptin concentrations.

Methods: A cross sectional study involved a total of 200 school going children in age group of 10 – 20 years. Biochemical parameters, adiponectin and leptin were measured.

Results: Optimal cut-off for identification of obesity (based on ROC curve analysis) of adiponectin was 2.5 µg/mL. Optimal cut-off value in females was 0.41 µg/mL. The analysis demonstrated similar AUC at leptin concentration of 9.76 ng/mL and 17.76 ng/mL with BMI as variable. Optimal cut-off for identification of obesity of leptin was 9.76 ng/mL, resulting in highest sensitivity of 63.4 and specificity of 89.1 in males. In females, optimal cut-off value of 17.76 ng/mL resulted in highest sensitivity of 70.0 and specificity of 73.4.

Conclusion: Adipokines could be useful biomarkers for insulin resistance in clinical practice. In obese children, lower values of adiponectin and higher values of leptin were responsible for obesity. The combination of adiponectin and leptin improves diagnostic accuracy at these

cut-offs. We suggest for children, cut-off for plasma adiponectin and leptin 2.5 µg/mL and 0.41 µg/mL and 9.76 ng/mL and 17.76 ng/mL in males and females respectively.

Keywords: Insulin resistance, Adiponectin, Leptin, Obesity, Adipokines

INTRODUCTION

Obesity is the most common factor influencing insulin resistance. While adiposity and insulin resistance are interrelated, they are not necessarily the same. Over weight is an alarming risk factor in most of the chronic diseases, such as diabetes, coronary artery diseases as well as cancer. Earlier obesity was thought to be a problem of only high income and more developed countries, but recently, there is an alarming rise in obesity in developing countries in the low as well as middle economic groups, urban area [1].

India is the capital of escalating epidemic of insulin resistance syndrome. There are various factors contributing to this growing epidemic including environment, genetics, micronutrients, and adipokines, and of course maternal nutrition is under debate [2].

The predisposition of most Indians towards a higher level of body fat and central adiposity as opposed with other nationalities may be existing in utero [3, 4]. The adipose tissue releases pro-inflammatory cytokines as well as fatty acids which eventually lead to endothelial dysfunction by increasing insulin resistance [3].

Insulin resistance and insulin sensitivity are not dependent on obesity. Heterogeneity is observed in subcategories of IR phenotype in obese patients. As stated by World Health Organization (WHO), the individuals having more than 25 Kg/m² or 35–40 Kg/m² are at high-risk with respect to adiposity-related morbidity.

Additionally, estimates given as per the Health Report by the World Health Organization (WHO) are also predicting a severe deterioration in mean life expectancy, resulting from comorbidities arising due to obesity, which include diabetes, atherosclerosis and cancer in 2020.

Obesity including visceral adiposity and insulin resistance are the main factors in type 2 diabetes and coronary artery diseases [5]. The obesity pandemic spread across the entire globe has a major impact on the prevalence of metabolic syndrome and coronary artery disease [6].

In obese subjects, plasma adiponectin levels are found to decrease while lean subjects tend to have higher adiponectin levels [7]. Similarly, pro-inflammatory factors, such as TNFα and IL-6 cause a reduction in adiponectin levels [8, 9].

Functional adipocytes present in lean organisms express adiponectin at very high levels whereas obesity-linked dysfunctional adipocytes downregulate adiponectin. This makes adiponectin unique in pro-inflammatory adipokines. Various studies have observed the correlation between metabolic dysfunction linked to obesity and adiponectin levels. Primarily, built-up of visceral fat and plasma adiponectin correlate negatively [7]. In subjects with type 2 diabetes, plasma adiponectin levels are found to be decreased while levels of high adiponectin reduce the risk of type 2 diabetes [10]. Hypoadiponectinaemia (low plasma adiponectin level) may cause many types of disorders like diabetes mellitus, hypertension and dyslipidaemia, which eventually results in atherosclerosis. Hypoadiponectinaemia is caused by visceral fat accumulation induced by several environmental factors, such as over nutrition and physical inactivity. Genetic factors like I164T SNP, are also related with hypoadiponectinemia. Moreover, atherosclerosis is also caused by hypoadiponectinaemia by reducing the preventive interaction between arteries and adiponectin. Low adiponectin levels are linked with conditions such as diabetes, obesity or coronary artery diseases, which occur during insulin-resistance. Anti-atherogenic, anti-inflammatory and anti-diabetic (potent insulin-sensitizing)

properties of adiponectin are also well-known [11]. It was suggested as a good marker for conditions such as coronary artery disease and increased insulin levels. The onset and progression of diabetes in adults can also be determined by levels of adiponectin in subjects.

Several detailed studies have been carried out to establish the connection between adiponectin and insulin resistance in adults and adolescents of different races and socio-economic strata. It was also noted that low levels of adiponectin can be a predictor of diabetes mellitus type II. Adiponectin levels vary between different ethnic groups due to disparate genetic and environmental factors. Adipocytes play an essential role representing the insulin responsive tissue. A significant relation has been shown between insulin resistance of adipose tissue and a pro-inflammatory adipocytokine profile, suggesting that the two may be interlinked mechanistically. It is clear that strong inflammatory component, that is associated with obesity contribute to developing MetS and vascular disease [9]. In the normal healthy adults adiponectin is linked with the dreaded risk of diabetes [12].

It is observed that in an urban south Indian population there is association between low adiponectin levels and the metabolic syndrome such as diabetes, insulin resistance, and dyslipidemia [14]. Adipose-

related metabolic syndrome, insulin resistance and inflammation observed in lean and obese subjects may be reduced by high levels of adiponectin present in circulation. Thus the circulating adiponectin level is a risk predictor for metabolic syndrome, and self-reliant markers of inflammation adiposity and insulin resistance [6].

Leptin (meaning *thin*) originates from the word **leptose**. Its primary function is to play the role of an anti-obesity hormone. The serum concentrations of leptin in healthy individuals correlate positively with the content of body fat, but on reduction of high calorie food intake and reduction in fat depot, the correlation turns negative. Leptin is expressed in adipose tissue and placenta. It is a peptide hormone, and it sensitive towards the fat depot of the body, thus influencing food intake. In the hypothalamus specific centres are activated by leptin in order to reduce food intake, by increasing energy expenditure, enhancing glucose and fat metabolism. In addition, leptin can perform all these actions directly also. Leptin levels are directly related to the fat depot and the degree of energy imbalance in an individual. These levels are high in a majority of obese subjects.

Though very few cases are reported where deficiency of leptin is related with severe obesity in humans, many researchers are engaged in studying the relation between

leptin deficiency and human obesity. If we consider leptin to be an adipostat hormone, then correspondingly low leptin levels may serve as a precursor for possible weight gain in the future. Leptin expression in adipocytes is reduced by troglitazone without any decline in fat mass [15]. Troglitazone also blocks leptin secretion induced by glucocorticoid in non-diabetic and obese subjects. This might be due to reduction in insulin resistance and a decrease in plasma insulin levels after troglitazone therapy. Thus, leptin regulates adipose tissue mass and distribution. Females may have higher leptin levels than males after adjusting BMI [18-20].

In Japanese type 2 diabetic subjects, serum levels of leptin were correlated with the subcutaneous fat [21]. Insulin was found to mediate the control of leptin expression partially by nutrition. After peak insulin secretion, leptin expression was found to increase during the feeding cycle [22]. On the other hand, leptin was found to be decreased in subjects with decrease in insulin levels, during experimental diabetes, while an increase was detected post insulin treatment [23]. Leptin expression is dependent on insulin and leptin levels remain elevated for several days after insulin dose [24, 25]. Segal *et al.* [27] observed the correlation between serum leptin concentration and insulin sensitivity in different patients from

different groups. The lean patients were divided into insulin-sensitive insulin-resistant, while a third group was obese insulin-resistant. They concluded from their observations that elevated plasma leptin levels and insulin resistance is associated but does not depend on body fat mass.

Wauters *et al.* studied the role of gender and fat mass in prediction of leptin concentration in type 2 diabetic patients. They also observed the significance of degree of insulin resistance and insulin secretion on leptin levels [28]. In Mauritius a study on a multi-ethnic group, on controlling for central and overall adiposity, found the association between insulin resistance and leptin concentration [29]. High concentration of serum leptin was noted across quartiles of fasting insulin, independent of body mass index (BMI) or gender. In case of lipodystrophic patients, improvement observed in glycemic control and insulin stimulation of glucose metabolism due to leptin therapy. More studies have found the association between adult obesity and relatively high circulating leptin concentrations. Further, some studies also found that leptin resistance may be a factor in obesity in some populations which are non-obese and have high basal leptin concentrations [32, 33].

The present study was undertaken to find out the optimal cut-off values of serum

adiponectin, leptin concentrations in Indian school-going children from Pune (in the age group of 10 – 20 years) to identify obesity and also to find gender wise difference which will help in preventing the risk of developing metabolic syndrome.

MATERIALS AND METHODS

Subjects: This study involves a total of 200 school going children between the age group of 10 – 20 yrs. The children participating in this study mostly came from educated families who lived in an urban setting with relatively middle socio-economic background.

Design: A cross-sectional study and total students were categorized into two groups, based on their BMI: group I (120 subjects) as non-obese subjects with a BMI <25 kg/m², group II (80 subjects) as obese subjects with BMI ≥ 25 kg/m² respectively. Obesity was defined as BMI ≥ 25 kg/m² (34–36). All the participants have given their informed consent and the study was approved by the ethics committee of B. J. Govt. Medical College & Sassoon General Hospital, Pune (Ref letter no. BJMC/IEC/Pharmac/D1210156-58).

Inclusion criteria: All the willing school going subjects in the age group of 10-20 years children not suffering from any major illness.

Exclusion criteria: It consists of subjects not knowing the birth weight, those with diabetes mellitus or other chronic diseases,

and individuals under treatment at the time of the study.

Participants: The participants were boys and girls who represent the middle socio-economic population of Pune School.

Indexes: The BMI was calculated as body weight (kg) / height (m)². The homeostatic index of insulin resistance (HOMA-IR) was calculated as follows:

HOMA-IR= Fasting glucose (mg/dL) × Fasting insulin (uU/mL) / 405(37).

Methods: 10 ml of venous blood of was collected in the morning after overnight fast (08 – 12hours) and analysed after serum separation to measure the concentration of: serum insulin, adiponectin, leptin, CRP-hs concentration were measured using kit (ELISA; Calbiotech, Biovendor, and Diagnostics Biochem).

Glucose was measured by GOD-POD method.

Statistical Method: Data analysis was done using SPSS, (version 12) software. Mean, Medians and Coefficient of Variation (CV) were calculated for all parameters. Independent Student's t test was used to perform gender comparisons as well as between obese and non-obese children, used for the correlation analysis was done using Pearson correlation coefficient (r). A p value ≤ 0.05 was taken as significant and (p<0.001) highly significant. Area under Receiver Operating Characteristic (ROC) Curve: is an effective method to evaluate

the sensitivity or specificity of diagnostic tests against a specific Gold standard. This technique is used to find the optimal cut-off based on ROC.

RESULTS AND DISCUSSION

The ROC curve analysis shows (Table 1, Figure 1-2) that the distribution of area under the curve (AUC) differs significantly for adiponectin for the identification of obesity from the reference value of 0.500 (P-value<0.05).

The distribution of area under the curve (AUC) is relatively higher for adiponectin for the identification of obesity in male as well as the female groups.

In males, with reference to ROC analysis, the optimal cut-offs of adiponectin for the identification of obesity in males is 2.50 with area under the curves being 0.890.

In females, with reference to ROC analysis, the optimal cut-offs of adiponectin for the identification of obesity in males is 0.41 with area under the curves being 0.837.

The diagnostic efficacy indices such as sensitivity, specificity, PPV, NPV and accuracy of Adiponectin in males were 90.2%, 85.4%, 82.2%, 92.2% and 87.5% respectively.

The diagnostic efficacy indices such as sensitivity, specificity, PPV, NPV and accuracy of Adiponectin in females were 62.5% 81.2%, 67.6%, 77.6% and 74.0% respectively (Table 2).

The ROC curve analysis shows (Table 3, Figure 3-4) that the distribution of area under the curve (AUC) differs significantly for leptin for the identification of obesity from the reference value of 0.500 (P-value<0.05).

The distribution of area under the curve (AUC) is relatively higher for leptin levels for the identification of obesity in male as well as female groups.

In males, with reference to ROC analysis, the optimal cut-offs of leptin for the identification of obesity in males is 9.76 with area under the curves being 0.679.

In females, with reference to ROC analysis, the optimal cut-offs of leptin for the identification of obesity in females is 17.76 with area under the curves being 0.712.

The diagnostic efficacy indices such as sensitivity, specificity, PPV, NPV and accuracy of leptin in males were 63.4%, 89.1%, 81.2%, 76.6% and 78.1% respectively.

The diagnostic efficacy indices such as sensitivity, specificity, PPV, NPV and accuracy of leptin in females were 70.0%, 73.4%, 62.2%, 79.7% and 72.1% respectively (Table 4).

Table 1: Distribution of area under the ROC curves (AUC) for adiponectin in the study group

Group	Parameter	Optimal cut-off based on ROC	AUC $\pm$ SE	95% CI of AUC	P-value
Males	Adiponectin	2.50	0.890 $\pm$ 0.036	0.819 – 0.960	0.001***
Females	Adiponectin	0.41	0.837 $\pm$ 0.039	0.760 – 0.914	0.001***

***P-value<0.001 (Statistically significant), Reference value = 0.500. SE – Standard Error.

Table 2: Distribution of diagnostic efficacy indices of adiponectin in the study group, based on ROC curve analysis

Group	Sensitivity	Specificity	PPV	NPV	Accuracy
Males	90.2	85.4	82.2	92.2	87.5
Females	62.5	81.2	67.6	77.6	74.0

Table 3: Distribution of area under the ROC curves (AUC) for leptin in the study group

Group	Parameter	Optimal cut-off based on ROC	AUC $\pm$ SE	95% CI of AUC	P-value
Males	Leptin	9.76	0.679 $\pm$ 0.066	0.550 – 0.808	0.003**
Females	Leptin	17.76	0.712 $\pm$ 0.061	0.593 – 0.832	0.001***

***P-value<0.001 (Statistically significant), Reference value = 0.500. SE – Standard Error.

Table 4: Distribution of diagnostic efficacy indices of leptin for the in the study group, based on ROC curve analysis

Group	Sensitivity	Specificity	PPV	NPV	Accuracy
Males	63.4	89.1	81.2	76.6	78.1
Females	70.0	73.4	62.2	79.7	72.1

DISCUSSION

We investigated the relationship between plasma adiponectin concentration, leptin and their effects on insulin resistance in the school-going children of the age group (10 – 20 years). It was observed that female children had a higher leptin (13.56 ng/mL) than that of the males (4.52ng/mL),

whereas lower adiponectin levels (41.56ng/mL) than that of male children (48.44 ng/mL).

As per a WHO Meeting report published in 2013, it is pertinent from the Life-course model that non-communicable diseases, especially obesity be detected at an early age (preferably during childhood or

adolescence) for ensuring proper corrective actions and thus reducing the detrimental effects of the resulting comorbidities. Later detections and interventions of obesity and related diseases have markedly reduced effects [38].

Rapid increases in the rates of childhood and adolescent obesity, irrespective of how it is defined, underscore the critical aspects of measuring the conditions early in life. The WHO criteria (BMI-based definitions) for overweight and obese cut offs are 25 Kg/m² and 30 Kg/m². Experts suggest lower cut offs for BMI in Asian populations, especially Indians, who tend to show an increased susceptibility to the related comorbidities as they possess fats in higher percentages and thus are more vulnerable to its metabolic consequences(39).Cut off value of 25 Kg/m² has been defined in the current study for obese subjects, urban Indian children and adolescents [34-36].

Assessment of obesity is complicated in children and adolescents. Similarly, in case of adults, the correlations between BMI, fat levels and associated morbidities vary in different ethnic groups. These parameters also differ according to age, gender and maturity. Consequently, attempts have been made to assess obesity according to various parameters. These include waist circumference, percentage body fat and normally BMI, as a ratio of weight to

height. Various studies tend to define obesity in diverse ways [40]. Attempts to evaluate body fat and enumerate population standards against which individuals could be compared must be improved [41]. This would involve optimizing cut off values for various parameters.

Adiponectin and leptin are the adipose tissue derived adipokines, representing the essential connection between metabolic syndrome and adiposity [42].

This makes it essential to identify obesity in children and adolescents so that the comorbidities arising from this condition can be curtailed. Optimal cut off values for adiponectin and leptin in children and adolescents can definitely help in identifying conditions such as obesity, which would further avert the onset and development of metabolic syndrome and other comorbidities.

Obese children with reduced adiponectin levels were closely associated with insulin resistance. Obese children had significantly low levels of adiponectin ($p < 0.003$), these results are in accordance with the data presented by Arita *et al.*, Garg *et al.* and Kuo *et al.* who also found a lower adiponectin concentration in obese subjects than in non-obese subjects [43-45].

Yamauchi *et al.* observed that adiponectin is a protecting hormone because it improves insulin resistance [46].

Females (22.67 Kg/m^2) had significantly higher BMI ($p < 0.045$) than males (21.66 Kg/m^2), supported by significantly lower levels of adiponectin ($p < 0.007$) in females ($41.56 \text{ } \mu\text{g/mL}$) than males ($48.44 \text{ } \mu\text{g/mL}$). Change in adiponectin and leptin may be related with physical activity during puberty especially in males. Similar outcomes were conveyed by Hannon *et al.*, signify a decline in adiponectin levels as youngsters progressed to puberty [47]. Sirico *et al.* confirmed that physical activity or exercise without any dietary or life style changes leads to significant increased adiponectin and decreased leptin levels in obese children [48]. The decline in plasma adiponectin levels might be due to an increase in plasma androgen levels [49]. Some authors have further suggested that in insulin resistance and obesity adiponectin supplementation could be a standard treatment in humans [46].

As leptin can regulate blood sugar by controlling appetite and storage fat, it can provide a missing relation between obesity and diabetes [50-52].

According to Considine *et al.* in normal the levels of leptin were 7.5 ng/mL and 31.3 ng/mL in obese. Any increase in fat mass resulted in an exponential increase in leptin [16, 50]. The content of ob mRNA in the adipocytes of obese individuals was double than that of the normal-weight individuals which implies that obese individuals are not

sensitive to endogenously synthesise leptin. This might point towards a leptin resistant state.

The serum concentrations of leptin in healthy individuals correlate positively with the content of body fat, but on the reduction of energy intake and a decline of energy stores in fat, the correlation turns negative. Adami *et al.* reported a positive correlation between serum leptin levels and BMI [16, 53, 54]. Higher leptin levels are found in a majority of obese subjects and are correlated with body fat percentage and the BMI.

Heymsfield *et al.* [55] administered different levels of leptin to obese individuals. They found a continuous weight reduction up to (7 Kg) with glycemic control or insulin action over six months remaining the same in subjects receiving a high amount of leptin. Average serum leptin concentration in such group increased to 667 ng/mL , which is 30–40 times higher than the baseline. Thus, they concluded that a very high dose of leptin is required to control leptin resistance.

Leptin levels were significantly increased with the rise in BMI ($p < 0.001$) as it is related to fat mass. Hence it is clear that higher plasma leptin levels (19.02 ng/mL) were directly proportional to BMI. These findings were supported by Park *et al.* and Abdullah *et al.* [56, 57]. Hyperleptinemia or ‘leptin resistance’ might contribute to

decreased in adiponectin production in adipose tissue. Maskari *et al.* and Jornayvaz *et al.* reported that leptin and BMI are positively correlated very strongly, which is similar to our findings [58, 59]. Aaron R *et al.* studied the relation between BMI leptin and found that adiposity determines leptin levels but deficiency of leptin is not important in obesity [60].

We also observed that leptin concentration was directly related to obesity whereas adiponectin was inversely related, indicating the negative feedback of each other to maintain BMI. We found lower adiponectin levels (32.9 µg/mL) in obese children as compared to non-obese (53.8 µg/mL) which was supported by the work of Pea *et al.* [61]. Leptin concentration plays a strong role in developing obesity than adiponectin.

CONCLUSION

The cut-off values of adiponectin and leptin could potentially improve the identification of obesity in the young Indian school children. Adipokines could be useful biomarkers for insulin resistance in clinical practice. Obese children had lower adiponectin and higher leptin levels suggestive of an inverse association with adipokines.

ACKNOWLEDGEMENTS

The authors acknowledge the sincere efforts of Dr. Ajay Chandanwale, Dean, Dr. Sameer Joshi, Deputy Dean and Dr.

Kadam, Head of Department Medicine, B. J. Govt. Medical College and Sassoon General Hospital, Pune for providing permission for the study. I also appreciate the support extended by Dr. Abhay Jagtap, Dr. Nitin Gurav and Mr. Rahul Girmé from Department of Biochemistry, B. J. Govt. Medical College, Pune. A special mention I would like to make is of Dr. Anand Pandit, Head of Department, Pediatrics, KEM hospital, Pune for his immense support during the course of research. I would also like to express my special thanks of gratitude to Dr. Bavdekar, Mr. Mahendra Hoge for their extensive help.

REFERENCES

- [1] World Health Organization. Overweight and Obesity Quick facts South-east Asia Region. Dep Sustain Dev Heal Environ. 2011;2.
- [2] Yajnik CS *et al.* Fetal Growth and Glucose and Insulin Four-year-old indian Metabolism Children. Diabet Med. 1995; 12(4): 330–6.
- [3] Jung UJ, Choi MS. Obesity and its metabolic complications: The role of adipokines and the relationship between obesity, inflammation, insulin resistance, dyslipidemia and nonalcoholic fatty liver disease. Int J Mol Sci. 2014; 15(4): 6184–223.
- [4] Yajnik CS. The Insulin Resistance Epidemic in India: Fetal Origins,

- Later Lifestyle, or Both? *Nutr Rev.* 2009; 59(1): 1–9.
- [5] Third report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III) final report. NIH Public Access. 2002; 106: 3143–3421.
- [6] Hung J, McQuillan BM, Thompson PL, Beilby JP. Circulating adiponectin levels associate with inflammatory markers, insulin resistance and metabolic syndrome independent of obesity. *Int J Obes.* 2008; 32: 772–9.
- [7] Miwa Ryo, MD; Tadashi Nakamura, MD; Shinji Kihara, MD; Masahiro Kumada, MD; Satomi Shibazaki, MD; Mihoko Takahashi, PhD; Masaki Nagai, MD; Yuji Matsuzawa, MD; Tohru Funahashi M. Adiponectin as a biomarker of the metabolic syndrome. *Eur J Med Res.* 2010; 15(2): 147–51.
- [8] Ouchi N, Kihara S, Funahashi T, Matsuzawa Y, Walsh K. Obesity, adiponectin and vascular inflammatory disease. *Curr Opin Lipidol.* 2003; 14(6).
- [9] Berg AH, Scherer PE. Adipose tissue, inflammation, and cardiovascular disease. *Circ Res.* 2005; 96(9): 939–49.
- [10] Li S, Shin HJ, Ding EL, van Dam RM. Adiponectin Levels and Risk of Type 2 Diabetes. *Jama.* 2009; 302(2): 179.
- [11] Ohashi K, Ouchi N, Matsuzawa Y. Anti-inflammatory and anti-atherogenic properties of adiponectin. *Biochimie.* 2012; 94(10): 2137–42.
- [12] Spranger, Joachim; Kroke, Anja; Möhlig, Matthias; Bergmann, Manuela M; Ristow, Michael; Boeing, Heiner; Pfeiffer AFH. Adiponectin and protection against type 2 diabetes mellitus.
- [13] Cruz M, Garcia-Macedo R, Garcia-Valerio Y, Gutierrez M, Medina-Navarro R, Duran G, *et al.* Low adiponectin levels predict type 2 diabetes in Mexican children. *Diabetes Care.* 2004; 27(6): 1451–3.
- [14] Mohan V, Deepa R, Pradeepa R, Vimalaswaran KS, Mohan A, Velmurugan K, *et al.* Association of low adiponectin levels with the metabolic syndrome - The Chennai Urban Rural Epidemiology Study (CURES-4). *Metabolism.* 2005; 54(4): 476–81.
- [15] Okuno A, Tamemoto H, Tobe K,

- Ueki K, Mori Y, Iwamoto K, *et al*. Troglitazone increases the number of small adipocytes without the change of white adipose tissue mass in obese Zucker rats. *J Clin Invest*. 1998; 101(6): 1354–61.
- [16] Lonnqvist, F., Arner, P., Nordfors, L., Schalling M. Overexpression of the obese (ob) gene in adipose tissue of human obese subjects. *Nat Med*. 1995; 1(6): 546–51.
- [17] Montague CT, Prins JB, Sanders L, Digby JE, O’Rahilly S. Depot- and sex-specific differences in human leptin mRNA expression: Implications for the control of regional fat distribution. *Diabetes*. 1997; 46(3): 342–7.
- [18] Ostlund E, Yang W, Research L. Relation between plasma leptin concentration and body fat, gender, diet, age, and metabolic covariates. *Endocrinol Metab*. 1996; (12): 21–5.
- [19] Saad MF, Damani S, Gingerich RL, Riad-Gabriel MG, Khan A, Boyadjian R, *et al*. Sexual dimorphism in plasma leptin concentration. *J Clin Endocrinol Metab*. 1997; 82(2): 579–84.
- [20] Hickey MS, Houmard JA, Considine R V., Tyndall GL, Midgette JB, Gavigan KE, *et al*. Gender-dependent effects of exercise training on serum leptin levels in humans. *Am J Physiol Metab*. 2017; 272(4): E562–6.
- [21] Taniguchi A, Nakai Y, Sakai M, Yoshii S, Hayashi M, Nishitani K, *et al*. Relationship of Regional Adiposity to Insulin Resistance in Nonobese Japanese Type 2 Diabetic Patients. *Diabetes Care*. 2001; 24(5): 966–8.
- [22] Saladin R, De Vos P, Guerre-Millot M, Leturque A, Girard J, Staels B, *et al*. Transient increase in obese gene expression after food intake or insulin administration. *Nature*. 1995; 377(6549): 527–8.
- [23] Macdougald OA, Hwang C-S, Fan H, Lane MD. Regulated expression of the obese gene product (leptin) in white adipose tissue and 3T3-L1 adipocytes (obesity/protein secretion/ob locus/CCAAT/enhancer-binding protein/preadipocyte differentiation). *Biochemistry*. 1995;92(September): 9034–7.
- [24] Kolaczynski JW, Nyce MR, Considine R V., Boden G, Nolan JJ, Henry R, *et al*. Acute and chronic effect of insulin on leptin production in humans: Studies in vivo and in vitro. *Diabetes*. 1996; 45(5): 699–701.

- [25] Boden G, Chen X, Kolaczynski JW, Polansky M. Effects of prolonged hyperinsulinemia on serum leptin in normal human subjects. *J Clin Invest.* 1997; 100(5): 1107–13.
- [26] Fischer S, Hanefeld M, Haffner SM, Fusch C, Schwanebeck U, Köhler C, et al. Insulin-resistant patients with type 2 diabetes mellitus have higher serum leptin levels independently of body fat mass. *Acta Diabetol.* 2002;
- [27] Segal KR, M L, S K. Relationship between insulin sensitive and plasma leptin concentration in lean and obese men. *Diabetes.* 1996; 45(July): 988–91.
- [28] Wauters M, Considine R V., Yudkin JS, Peiffer F, De Leeuw I, Van Gaal LF. Leptin levels in type 2 diabetes: Associations with measures of insulin resistance and insulin secretion. *Horm Metab Res.* 2003; 35(2): 92–6.
- [29] Zimmet PZ, Collins VR, De Courten MP, Hodge AM, Collier GR, Dowse GK, *et al.* Is there a relationship between leptin and insulin sensitivity independent of obesity? A population-based study in the Indian Ocean nation of Mauritius. *Int J Obes.* 1998; 22(2): 171–7.
- [30] Petersen KF, Oral EA, Dufour S, Befroy D, Ariyan C, Yu C, *et al.* Leptin reverses insulin resistance and hepatic steatosis in patients with severe lipodystrophy. *J Clin Invest.* 2002; 109(10): 1345–50.
- [31] Nyholm B. Increased circulating leptin concentration in insulin-resistant first-degree relatives of patients with non-insulin dependent diabetes mellitus relationship to body composition and insulin sensitivity but not to family history of NIDDM. *Eur J Endocrinol.* 1997; 136(i): 16–9.
- [32] Chessler SD, Fujimoto WY, Shofer JB, Boyko EJ, Weigle DS. Increased plasma leptin levels are associated with fat accumulation in Japanese Americans. *Diabetes.* 1998; 47(2): 239–43.
- [33] Lindroos AK, Lissner L, Carlsson B, Carlsson LMS, Torgerson J, Karlsson C, et al. Familial predisposition for obesity may modify the predictive value of serum leptin concentrations for long-term weight change in obese women. *Am J Clin Nutr.* 1998; 67(6): 1119–23.
- [34] Singhal A, Jamieson N, Fewtrell M, Deanfield J, Lucas A, Sattar N. Adiponectin predicts insulin resistance but not endothelial

- function in young, healthy adolescents. *J Clin Endocrinol Metab.* 2005; 90(8): 4615–21.
- [35] WHO Expert Consultation. Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. *Lancet.* 2004 Jan 10; 363(9403): 157–63.
- [36] McKeigue P M, Shah B MMG. Relation of central obesity and insulin resistance with high diabetes prevalence and cardiovascular risk in South Asians. *Lancet.* 1987; 337: 382–6.
- [37] Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and β -cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia.* 1985; 28(7): 412–9.
- [38] Switzerland WG. Consideration of the evidence on childhood obesity for the Commission on Ending Childhood Obesity Report of the Ad hoc Working Group on Science and Evidence for Ending Childhood Obesity. WHO 2016.
- [39] James PT, Leach R, Kalamara E, Shayeghi M. The worldwide obesity epidemic. *Obes Res.* 2001; 9 Suppl 4(February 2015).
- [40] Flegal KM, Ogden CL, Wei R, Kuczmarski RL, Johnson CL. Prevalence of overweight in US children: Comparison of US growth charts from the Centers for Disease Control and Prevention with other reference values for body mass index. *Am J Clin Nutr.* 2001; 73(6): 1086–93.
- [41] Prentice AM, Jebb SA. Beyond body mass index. *Obes Rev.* 2001; 2(3): 141–7.
- [42] Fasshauer M, Bluher M. Adipokines in health and disease. *Trends Pharmacol Sci.* 2015; 36(7): 461–70.
- [43] Arita Y, Kihara S, Ouchi N, Takahashi M, Maeda K, Miyagawa J, et al. Paradoxical Decrease of an Adipose-Specific Protein, Adiponectin, in Obesity. *Biochem Biophys Res Commun.* 1999 Apr; 257(1): 79–83.
- [44] Garg MK, Dutta MK, Mahalle N. Adipokines (adiponectin and plasminogen activator inhibitor-1) in metabolic syndrome. *Indian J Endocrinol Metab* [Internet]. 2012; 16(1): 116–23. Available from: <http://www.ijem.in>
- [45] Kuo SM, Halpern MM. Lack of association between body mass index and plasma adiponectin

- levels in healthy adults. *Int J Obes.* 2011; 35: 1487–94.
- [46] Yamauchi T, Amon JK, Aki HW, Erauchi YT, Ubota NK, Ara KH, *et al.* The fat-derived hormone adiponectin reverses insulin resistance associated with both lipoatrophy and obesity. *Nat Med.* 2001; 7: 941–6.
- [47] Hannon TS, Janosky J, Arslanian SA. Longitudinal study of physiologic insulin resistance and metabolic changes of puberty. *Pediatr Res.* 2006; 60(6): 759–63.
- [48] Sirico F, Bianco A, D'Alicandro G, Castaldo C, Montagnani S, Spera R, *et al.* Effects of Physical Exercise on Adiponectin, Leptin, and Inflammatory Markers in Childhood Obesity: Systematic Review and Meta-Analysis. *Child Obes.* 2018; 14(4): 207–17.
- [49] Bottner A, Kratzsch J, Muller G, Kapellen TM, Bluher S, Keller E, *et al.* Gender differences of adiponectin levels develop during the progression of puberty and are related to serum androgen levels. *J Clin Endocrinol Metab.* 2004; 89(8): 4053–61.
- [50] Considine R. V., Sinha M. K. HML *et al.* Serum Immunoreactive-Leptin Concentrations in Normal-Weight and Obese Humans. *Endocrinologist.* 1996;6(4):349.
- [51] Considine R V. Leptin and obesity in humans. *Eat Weight Disord - Stud Anorexia, Bulim Obes.* 2014; 2(2): 61–6.
- [52] Weigle DS, Ganter SL, Kuijper JL, Leonetti DL, Boyko EJ, Fujimoto WY. Effect of regional fat distribution and Prader-Willi syndrome on plasma leptin levels. *J Clin Endocrinol Metab.* 1997; 82(2): 566–70.
- [53] Adami GF, Civalleri D, Cella F, Marinari G, Camerini G, Papadia F, *et al.* Relationships of serum leptin to clinical and anthropometric findings in obese patients. *Obes Surg.* 2002;
- [54] Hamilton BS, Paglia D KA. Increased obese mRNA expression in omental fat cells from massively obese humans. *Nat Med.* 1995; 1(6): 546–51.
- [55] Heymsfield SB, Greenberg AS, Fujioka K, Dixon RM, Kushner R, Hunt T, *et al.* Recombinant leptin for weight loss in obese and lean adults: A randomized, controlled, dose-escalation trial. *J Am Med Assoc.* 1999; 282(16): 1568–75.
- [56] Abdullah AR, Hasan HA, Raigangar VL. Analysis of the Relationship of Leptin, High-

- Sensitivity C-Reactive Protein, Adiponectin, Insulin, and Uric Acid to Metabolic Syndrome in Lean, Overweight, and Obese Young Females. *Metab Syndr Relat Disord*. 2009; 7(1): 17–22.
- [57] Park JE, Choi HJ, Kim IK, Lee HJ, Kang JH, Song J. Influence of serum leptin levels on future overweight risk in Korean children. *Nutr Metab Cardiovasc Dis*. 2012; 22(3): 260–8.
- [58] Al Maskari MY, Alnaqdy AA. Correlation between serum leptin levels, body mass index and obesity in Omanis. *Sultan Qaboos Univ Med J*. 2006; 6(2): 27–31.
- [59] Jornayvaz FR, Vollenweider P, Bochud M, Mooser V, Waeber G, Marques-Vidal P. Low birth weight leads to obesity, diabetes and increased leptin levels in adults: The CoLaus study. *Cardiovasc Diabetol*. 2016; 15(1): 1–10.
- [60] Folsom AR, Jensen MD, Jacobs DR, Hilner JE, Tsai AW, Schreiner PJ. Serum leptin and weight gain over 8 years in African American and Caucasian young adults. *Obes Res*. 1998;
- [61] Pea AS, Belobrajdic DP, Wiltshire E, Gent R, Hirte C, Couper J. Adiponectin relates to smooth muscle function and folate in obese children. *Int J Pediatr Obes*. 2010; 5(2): 185–91.