ORIGINAL ARTICLE

SEX-DISCORDANT ASSOCIATION OF ADIPONECTIN IN OBESE AND NON-OBESE PRIMARY SCHOOL CHILDREN

Muhammad Ramzan[1], Irshad Ali[2], Muhammad Haris Ramzan[3], Faiqah Ramzan[4]

[1]Department of Biochemistry, Peshawar Medical College, Peshawar, [2]Department of Chemistry, and [4]GCBB, Gomal University, D.I. Khan, and [3]Department of Physiology, KMU Institute of Medical Sciences, Kohat, Pakistan

ABSTRACT

Background: Adiponectin is an adipocytokine with antidiabetic and antiatherogenic effects. The objective of this study was to determine plasma adiponectin concentration in children and to evaluate association of adiponectin with gender, obesity and lipid profile.

Material & Methods: This cross-sectional study was carried out in Department of Chemistry, Gomal University, D.I. Khan, from June 2007 to August 2010. Eighty-three school children (6-11 years age) were randomly selected among 1336 children. Height, weight and BMI of each child was calculated. Fasting blood sample was taken for plasma adiponectin by ELISA.

Results: Out of 83 children 23(27.71%) were normal weight and 60 (72.28%) obese children. Gender-wise 48(57.83%) were boys and 35(42.16%) girls. Plasma adiponectin in normal weight children was within laboratory range. It was 21.50μg/ml and 20.89μg/ml in boys and girls respectively reflecting non-significant gender difference. In obese children it was 20.38 μg/ml and 25.56 μg/ml in boys and girls respectively, showing significant gender difference ($p<0.01$). There was no significant difference between adiponectin concentration of normal weight and obese boys ($p>0.05$), however, obese girls had significantly higher levels compared to normal weight girls ($p<0.05$).

Conclusion: Significant difference in plasma adiponectin level was noted in obese and normal weight girls. Sex-discordant association with adiponectin was observed mostly in obese boys and girls and expressed favorable lipoprotein levels.

Key Words: School children; Adiponectin; Lipids; Lipoproteins; Obesity.

This article may be cited as: Ramzan M, Ali I, Ramzan MH, Ramzan F. Sex-discordant associations of adiponectin in obese and non-obese primary school children. Gomal J Med Sci 2015; 13: 41-5.

INTRODUCTION

Adiponectin is an adipokine produced exclusively by white adipose tissue (WAT) and plays an important role in obesity related morbidities like metabolic syndrome and cardiovascular disease (CVD). It is known to play an important role in the pathogenesis of obesity, type 2 diabetes mellitus and coronary artery disease (CAD).[1,2]

WAT is now regarded as an endocrine organ, secreting a number of hormones called the adipokines. Its role as a hormone secreting organ was established in 1994 with the discovery of leptin as a secreted protein of adipocytes.[3] Approximately 20-30% of all genes in WAT encode secretary proteins.[4] WAT has a number of cells including preadipocytes, adipocytes and stroma vascular cells. Bone derived macrophages are also present in WAT and contribute to the development of systemic inflammation and insulin resistance.[5,6]

Massive increase in the fat mass in obesity leads to dysregulation of circulating adipokines that may be responsible for obesity related complications. Adiponectin is the only adipokine that is down regulated in obesity. Plasma adiponectin levels are negatively correlated with the body mass index.[7] Plasma adiponectin levels show strong negative relationship with the visceral (not subcutaneous) intra-abdominal fat mass.[8,9]

Circulating concentration of adiponectin is affected by a number of physiological factors like age, gender and puberty.[10,11] Adiponectin levels

Corresponding Author:
Dr. Muhammad Ramzan
Department of Biochemistry
Peshawar Medical College,
Peshawar, Pakistan
E-mail: dr.ramzan49@gmail.com

are twofold higher in the newborn babies reflecting positive association with birth weight and BMI.[12,13] Adiponectin level increases with gestational age showing positive association with fetal obesity.[14,15] Adiponectin levels decrease during early childhood and this is related to postnatal weight gain.[16] A reversal of the positive to negative association usually occurs at some time during childhood.[12] Plasma adiponectin levels are significantly higher in female subjects than males indicating the effect of sex hormones on circulating adiponectin.[17,18] Girls have larger visceral fat mass despite similar waist circumference; this could explain the relative insulin resistance in girls than boys.[19] Adiponectin levels tend to decrease in puberty which is usually associated with the development of insulin resistance.[20]

Elevated adiponectin levels are observed in certain physiological conditions like weight loss in obese subjects.[21] Higher adiponectin levels are observed in pathological conditions associated with inflammation like pregnant women with preeclampsia,[22] arthritis[23] and end stage renal disease.[24]

Reduction in the circulating adiponectin levels are expressed in pathological conditions as in obesity,[21] cardiovascular disease[25] and type 2 DM.[26]

Plasma adiponectin concentration may be unrelated to the current body size of both the boys and girls and in opposite direction, expressed as sex-discordant associations with adiponectin. This positive relationship between body size and adiponectin may be due to: the complex hormonal regulation of adiponectin secretion, degradation and clearance.[27] The inhibitory effects of androgens and stimulatory effects of estrogens on adiponectin secretion would explain the higher adiponectin level in girls than boys. Increased adipocyte arometase activity could also possibly explain the higher adiponectin levels in obese boys but not the lower adiponectin levels in obese girls and obese adults.

Plasma adiponectin level is inversely related to biochemical cardiovascular risk factors like total cholesterol (TC), low density lipoproteins (LDL) cholesterol and triglycerides (TG),[28] and positively associated with high density lipoprotein (HDL) cholesterol.[8,28] A number of studies suggest that high adiponectin levels may be associated with lower risk of CVD.[29,30]

The objective of this study was to determine the plasma adiponectin concentration in primary school children and to evaluate the association of adiponectin to obesity, gender and lipid profile in children.

MATERIAL AND METHODS

This cross-sectional study was carried out from June 2007 to August 2010 in the primary schools located in the municipality area of Dera Ismail Khan, KPK, Pakistan.

A total number of 1336 school children (6-11 years age) were examined for this purpose. Thorough clinical examination excluded those suffering from chronic health problems. The study was approved by the Gomal University Board of Advanced Studies and Research and carried out according to the Guide lines of the Ethical Committee. Written informed consent was obtained from school children, their legal guardians and heads of the institutions.

Height and weight of each child was taken according to the standard anthropometric parameters. Body Mass Index (BMI) was calculated according to Quatelet's Index. BMI number was plotted on the CDCs Growth Charts 2-20 years for boys and girl to get BMI for age percentile. Body mass status was calculated according to World Health Organization, 1995 criteria (WHO, 1995). A child was declared underweight, if his BMI-for-age percentile was <5th percentile and normal weight if it remained between 5th and <85th, overweight between 85th and <95th percentile and obese ≥95th percentile.

Fasting blood samples were collected using disposable sterile syringes. Serum was separated by centrifugation at 1600×g and stored at -80°C for subsequent hormonal analysis. Serum adiponectin levels were determined by enzyme linked Immunosorbant assay (ELISA) using highly sensitive Human Adiponectin ELISA, GenWay Biotech, Inc, San Diego, CA.

RESULTS

The body mass status and gender distribution of the sample is given in Table 1.

The mean adiponectin plasma concentration in normal weight children was noted as 21.50 μg/ml and 20.89 μg/ml in boys and girls respectively reflecting non-significant gender difference. Plasma adiponectin concentration in normal weight children was within laboratory range (5-30 μg/ml) except a boy with 37.65 μg/ml. (Table 2)

The mean plasma concentration of adiponectin in obese children was noted as 20.38 μg/ml and 25.56 μg/ml in boys and girls respectively, showing significant gender difference ($p<0.01$). (Table 3) There was no significant difference between the plasma adiponectin concentration of normal weight and obese boys ($p>0.05$). However, obese girls had significantly higher adiponectin level compared with normal weight girls ($p<0.05$).

It is important to note that 11/83 children (one normal weight and 10 obese children), had higher concentration of adiponectin compared to normal concentration (5-30 μg/ml). This finding is in contrast

Table 1: Sample distribution of school children (6-11 years)

Body Mass Status	Normal Weight				Obese			
Gender	Boys		Girls		Boys		Girls	
	N	%	N	%	N	%	N	%
Number of Children	14	16.86	9	10.84	34	40.96	26	31.32
Total	23 (29.06%)				60 (70.94%)			

Table 2: Adiponectin profile of normal weight school boys (n=14) and girls (n=9).

Variable	Mean ± SD	Min	Max
Adiponectin (μg/ml) levels in Boys	21.50±5.94	11.60	37.65
Adiponectin (μg/ml) levels in Girls	20.89±3.11	15.60	27.17

Table 3: Adiponectin profile of obese school boys (n=34) and girls (n=26).

Variable	Mean ± SD	Min	Max
Adiponectin (μg/ml) levels in Boys	20.38±9.71	12.69	59.45
Adiponectin (μg/ml) levels in Girls	25.56±10.31	12.31	55.24

with the usual finding that obese children have lower plasma adiponectin concentration as compared to the normal subjects. Adiponectin concentration in these cases with altered plasma level, ranged from 37.00 μg/ml in normal weight children to 59.45 μg/ml in obese boys, and 40.13 μg/ml in obese girls; referred to as sex-discordant associations with adiponectin and is seen both in boys and girls separately and in opposite direction.

A significant increase ($p<0.01$) in adiponectin concentration was noticed in obese as compared to normal weight children. No significant difference ($p>0.05$) was observed in adiponectin levels in obese boys as compared to normal weight boys while the levels increased significantly ($p<0.05$) in obese girls as compared to normal weight girls.

DISCUSSION

The goal of the present study was to evaluate the association of obesity, age and gender with plasma adiponectin, and lipid profile in children. Circulating adiponectin levels in the normal weight children were observed within laboratory range (5-30 μg/ml) with no significant gender difference. Plasma adiponectin level in obese children was not reduced, instead, it was observed to be higher in a number of cases (10) to the tune of 59.45 μg/ml. The altered plasma concentration of adiponectin was observed, both in obese and normal weight boys and in opposite direction i.e. sex-discordant association with adiponectin.

Assessment of plasma adiponectin concentration has been carried out by a number of researchers from neonates to adults, some have observed the gender difference to exist while others has not. The findings of Bottner et al[20] are not in agreement with the findings of the present study. They reported gender differences to exist in both normal weight and obese children. They investigated 200 normal weight children aged 7.9-17.9 years and noted a tendency towards lower adiponectin levels in boys as compared to girls. In boys, there was a remarkable decline in adiponectin levels with the progression of puberty compared to girls. Their study also included 135 obese children aged 3.4-17.6 years. Adiponectin levels were significantly lower in obese as compared to normal weight children. These differences were more pronounced in adolescents than pre-pubertal children.

Chu et al[31] evaluated 1248 children in Taipei, Taiwan, for association of plasma adiponectin level with metabolic risk profiles and insulin resistance. Boys had lower adiponectin levels than girls. Circulating levels of adiponectin were positively correlated with HDL-C in both boys and girls, but negatively correlated with BMI, leptin and insulin resistance. Boys had higher cholesterol, TG and systolic blood pressure (BP).

Hassan et al[32] assessed adiponectin and its association with BP and anthropometric markers in obese Egyptian children, aged 7-11 years. Their cross-sectional survey involved 2083 children. The sample included 124 obese children. Reduction in the adiponectin level was noted in obese children.

Reduction in the circulating adiponectin levels among obese children can be explained further by the changes in BMI in a pediatric population based cohort by Nishimura et al.[33] They carried out a 3 year prospective cohort of 268 boys and 251 girls aged 9-10 in Inasaitama, Japan. Median BMI significantly

increased from baseline to follow-up in boys from 17.1 to 18.3 kg/m2 ($p<0.001$) and in girls from 16.5 to 18.5 kg/m2 ($p<0.001$), respectively. Adiponectin values significantly decreased from baseline to follow up in boys (13.5 to 8.9 µg/ml, respectively) ($p<0.001$) and in girls (12.4 to 9.5 µg/ml, respectively) ($p<0.001$).

The present study also revealed sex-discordant association with adiponectin both in normal weight and obese children. Circulating adiponectin level was largely unrelated to their body size. Significant associations were seen in boys and girls separately and in opposite directions. Sex-discordant association with adiponectin was also been observed by Ong et al.[10]

Kern et al[34] noted that plasma adiponectin and adiponectin mRNA were highly correlated with each other ($r=080$, $p<0.001$) and obese subjects expressed significantly lower levels of adiponectin. However, a significant sex difference in adiponectin expression was observed, especially in lean subjects. On comparison of women and men of the same BMI, the women has a twofold higher percent body fat, yet their plasma adiponectin was 65% higher than men. Subjects, who were insulin sensitive, demonstrated 2 fold higher adiponectin than Insulin resistant cases. Discordant subjects expressed the lowest level of TNF-α from their adipose tissues.

Various reasons are given for the discordant associations with adiponectin including; complexity in the hormonal regulation of the adiponectin secretion, degradation and clearance. Visceral adipose tissue mostly secrete adiponectin, girls have larger central mass than boys, despite similar waist circumference.[19,35] Stimulatory effect of estrogen and inhibitory effect of androgen would explain the higher concentration of adiponectin in girls than boys.[27] Insulin may stimulate adiponectin or mRNA expression in adipocytes in these children.[36]

CONCLUSION

Adiponectin is an adipokine dysregulated in obesity and is important biomarker in obesity related complications. Sex-discordant association with adiponectin was seen mainly in obese children and is reported to protect the subjects from type 2 diabetes mellitus and cardiovascular disease. This was reflected in the lipid profiles of obese children with elevated level of adiponectin.

Measurement of plasma adiponectin level in obese children and improving its level by weight reduction and life style changes will help in preventing obesity related complications in future as adults.

Acknowledgments

Authors are thankful to Dr. Muhammad Aslam Khan and Mr. Fazal Mehmood for providing technical assistance in lipid profile assessment.

REFERENCES

1. Chandran M, Phillips SA, Ciaraldi T, Henry RR. Adiponectin: more than just another fat cell hormone? Diabetes Care 2003; 26: 2442-50.
2. Koerner A, Kratzsch J, Kiess W. Adipocytokines: leptin-the classical, resistin-the controversical, adiponectin-the promising, and more to come. Best Prac Res Clin Endocrinol Metabol 2005; 19: 525-46.
3. Zhang Y, Proenca R, Maffei M, Barone M, Leopold L, Friedman JM. Positional cloning of the mouse obese gene and its human homologue. Nature 1994; 372: 425-32.
4. Maeda K, Okubo K, Shimomura I, Funahashi T, Matsuzawa Y, Matsubara K. cDNA cloning and expression of a novel adipose specific collagen-like factor, apM1 (AdiPose Most abundant Gene transcript 1). Biochem Biophys Res Com 1996; 221: 286-9.
5. Weisberg SP, McCann D, Desai M, Rosenbaum M, Leibel RL, Ferrante AW, Jr. Obesity is associated with macrophage accumulation in adipose tissue. J Clin Invest 2003; 112: 1796-1808.
6. Xu H, Barnes GT, Yang Q, Tan G, Yang D, Chou CJ, et al. Chronic inflammation in fat plays a crucial role in the development of obesity-related insulin resistance. J Clinic Inves 2003; 112: 1821-30.
7. 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 Com 1999; 257: 79-83.
8. Cnop M, Havel PJ, Utzschneider KM, Carr DB, Sinha MK, Boyko EJ, et al. Relationship of adiponectin to body fat distribution, insulin sensitivity and plasma lipoproteins: evidence for independent roles of age and sex. Diabetologia 2003; 46: 459-69.
9. Kwon K, Jung SH, Choi C, Park SH. Reciprocal association between visceral obesity and adiponectin: in healthy premenopausal women. Int J Card 2005; 101: 385-90.
10. Ong KK, Frystyk J, Flyvbjerg A, Petry CJ, Ness A, Dunger DB. Sex-discordant associations with adiponectin levels and lipid profiles in children. Diabetes 2006; 55: 1337-41.
11. Butte NF, Comuzzie AG, Cai G, Cole SA, Mehta NR, Bacino CA. Genetic and environmental factors influencing fasting serum adiponectin in Hispanic children. J Clin Endocrinol Metabol 2005; 90: 4170-6.
12. Dunger D, Ong K. Abundance of adiponectin in the newborn. Clin Endocrinol 2004; 61: 416-7.
13. Sivan E, Mazaki-Tovi S, Pariente C, Efraty Y, Schiff E, Hemi R, et al. Adiponectin in human cord blood: relation to fetal birth weight and gender. J Clin Endocriol Metabol 2003; 88: 5656-60.
14. Kotani M, Detheux M, Vandenbogaerde A, Communi D, Vanderwinden JM, Le Poul E, et al. The metastasis suppressor gene KiSS-1 encodes kisspeptins, the natural ligands of the orphan G

protein-coupled receptor GPR54. J Biol Chem 2001; 276: 34631-6.

15. Kajantie E, Hytinantti T, Hovi P, Andersson S. Cord plasma adiponectin: a 20-fold rise between 24 weeks gestation and term. J Clin Endocrinol Metabol 2004; 89: 4031-6.
16. Iniguez G, Soto N, Avila A, Salazar T, Ong K, Dunger D, et al. Adiponectin levels in the first two years of life in a prospective cohort: relations with weight gain, leptin levels and insulin sensitivity. J Clin Endocrinol Metabol 2004; 89: 5500-3.
17. Dekker JM, Funahashi T, Nijpels G, Pilz S, Stehouwer CD, Snijder MB, et al. Prognostic value of adiponectin for cardiovascular disease and mortality. J Clin Endocrinol Metabol 2008; 93: 1489-96.
18. Aso Y, Yamamoto R, Wakabayashi S, Uchida T, Takayanagi K, Takebayashi K, et al. Comparison of serum high-molecular weight (HMW) adiponectin with total adiponectin concentrations in type 2 diabetic patients with coronary artery disease using a novel enzyme-linked immunosorbent assay to detect HMW adiponectin. Diabetes 2006; 55: 1954-60.
19. Caprio S. Relationship between abdominal visceral fat and metabolic risk factors in obese adolescents. Am J Hum Biol 1999; 11: 259-66.
20. 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 Metabol 2004; 89: 4053-61.
21. Yang WS, Lee WJ, Funahashi T, Tanaka S, Matsuzawa Y, Chao CL, et al. Weight reduction increases plasma levels of an adipose-derived anti-inflammatory protein, adiponectin. J Clin Endocrinol Metabol 2001; 86: 3815-9.
22. Haugen F, Ranheim T, Harsem NK, Lips E, Staff AC, Drevon CA. Increased plasma levels of adipokines in preeclampsia: relationship to placenta and adipose tissue gene expression. Am J Phys Endocrinol Metabol 2006; 290: E326-333.
23. Senolt L, Pavelka K, Housa D, Haluzik M. Increased adiponectin is negatively linked to the local inflammatory process in patients with rheumatoid arthritis. Cytokine 2006; 35: 247-52.
24. Shoji T, Shinohara K, Hatsuda S, Kimoto E, Fukumoto S, Emoto M, et al. Altered relationship between body fat and plasma adiponectin in end-stage renal disease. Metabol Clin Exp 2005; 54: 330-4.
25. Ouchi N, Kihara S, Arita Y, Maeda K, Kuriyama H, Okamoto Y, et al. Novel modulator for endothelial adhesion molecules: adipocyte-derived plasma protein adiponectin. Circulation 1999; 100: 2473-6.
26. Hotta K, Funahashi T, Arita Y, Takahashi M, Matsuda M, Okamoto Y, et al. Plasma concentrations of a novel, adipose-specific protein, adiponectin, in type 2 diabetic patients. Arterioscler Thromb Vasc Biol 2000; 20: 1595-9.
27. Fasshauer M, Paschke R. Regulation of adipocytokines and insulin resistance. Diabetologia 2003; 46: 1594-1603.
28. Matsubara M, Maruoka S, Katayose S. Decreased plasma adiponectin concentrations in women with dyslipidemia. J Clinic Endocrinol Metab 2002; 87: 2764-9.
29. Kubota N, Terauchi Y, Yamauchi T, Kubota T, Moroi M, Matsui J, et al. Disruption of adiponectin causes insulin resistance and neointimal formation. J Biological Chem 2002; 277: 25863-6.
30. Arita Y, Kihara S, Ouchi N, Maeda K, Kuriyama H, Okamoto Y, et al. Adipocyte-derived plasma protein adiponectin acts as a platelet-derived growth factor-BB-binding protein and regulates growth factor-induced common postreceptor signal in vascular smooth muscle cell. Circulation 2002; 105: 2893-8.
31. Chu NF, Shen MH, Wu DM, Lai CJ. Relationship between plasma adiponectin levels and metabolic risk profiles in Taiwanese children. Obesity Res 2005; 13: 2014-20.
32. Hassan NE, EL-Ashry HH, Awad AH, El-Masry SA, Youssef MM, Sallam MM, et al. Adiponectin in obese children and its association with blood pressure and anthropometric markers. Med Res J 2011; 10: 1-4.
33. Nishimura R, Sano H, Matsudaira T, Morimoto A, Miyashita Y, Shirasawa T, et al. Changes in body mass index, leptin and adiponectin in Japanese children during a three-year follow-up period: a population-based cohort study. Cardiovasc Diabetol 2009; 8: 30.
34. Kern PA, Di Gregorio GB, Lu T, Rassouli N, Ranganathan G. Adiponectin expression from human adipose tissue: relation to obesity, insulin resistance, and tumor necrosis factor-alpha expression. Diabetes 2003; 52: 1779-85.
35. Motoshima H, Wu X, Sinha MK, Hardy VE, Rosato EL, Barbot DJ, et al. Differential regulation of adiponectin secretion from cultured human omental and subcutaneous adipocytes: effects of insulin and rosiglitazone. J Clinical Endocrinol Metab 2002; 87: 5662-7.
36. Viengchareun S, Zennaro MC, Pascual-Le Tallec L, Lombes M. Brown adipocytes are novel sites of expression and regulation of adiponectin and resistin. FEBS Letters 2002; 532: 345-50.

CONFLICT OF INTEREST
Authors declare no conflict of interest.
GRANT SUPPORT AND FINANCIAL DISCLOSURE
None declared.