CORRELATION OF PLASMA LEPTIN AND ADIPONECTIN IN NON-OBESE MALE SAUDI UNIVERSITY STUDENTS

Abdulhalim S. Serafi[*1], Mohammed A. Bafail[1], Sumera Sohail[2] and Zahir Hussain[1]

[1]*Department of Physiology, Faculty of Medicine, Umm Al-Qura University, Makkah, Saudi Arabia*
[2]*Department of Physiology, University of Karachi, Karachi, Pakistan*
***Corresponding author email:** asserafi@uqu.edu.sa

ABSTRACT

Leptin and adiponectin serum or plasma levels vary in various disorders. The present report comprised non-obese male university students (n: 75; age: 18-20 years) for studying the effect of BMI of normal range on plasma leptin and adiponectin levels, as well as the association of plasma leptin and adiponectin in these subjects, using Human ELISA (enzyme-linked immunosorbent assay) kit methods. Significant positive linear correlation for the plot of body mass index (BMI) against plasma leptin (ng/mL), and significant negative linear correlation for the plot of BMI against plasma adiponectin, and leptin against adiponectin were obtained. The present report provides interesting and potential information for the relationship among BMI, plasma leptin and plasma adiponectin that is helpful for future studies for exploring the use of this information for the management of disorders with altered/ abnormal levels of leptin and adiponectin in obese and non-obese people.

Keywords: Plasma leptin, adiponectin, adipokines, BMI (body mass index), non-obese university students

INTRODUCTION

Adipocytokines or adipokines are those cytokines that are secreted by adipose tissue. There are a variety of these cytokines. Leptin and adiponectin are two important adipokines (Waki *et al*., 2003). The serum/ plasma leptin and adiponectin may be used as important clinical markers to determine the role of various levels of body mass index (BMI) in obese and non-obese subjects (Blüher and Mantzoros, 2015).

Advent of recombinant leptin/ leptin analog metreleptin are used for the treatment of congenital leptin deficiency and lipodystrophy. One of the prestigious Prize in Saudi Arabia- 'King Faisal International Prize' was awarded on the recognition of research on leptin (KFF – KFIP – Winners, 2013) beside several other prizes (News-Medical, 2009; The Lasker Foundation, 2010; BBVA Foundation, 2012). Other adipokines and their involvements/ functions suggest that adipokines have the potential to be used as biomarkers in a variety of diseases (Blüher and Mantzoros, 2015).

Leptin is a 16-kDa protein and an adipocytokine produced mainly in white adipose tissues though also produced in the brown adipose tissues and in a variety of body organs (Margetic *et al*., 2002). It is 167-amino acid protein present in our body in free form and bound with proteins (Sinha *et al*., 1996). It regulates food intake and energy expenditure (Bełtowski, 2006) and fat stores and performs several other functions (Maffei *et al*., 1995). Plasma leptin level is proportional to the amount of adipose tissue and it is increased markedly in obese people (Bełtowski, 2006). Due to contradictory results on the association of leptin with dyslipidemia, a study comprising serum leptin, body height, weight, BMI waist circumference, and hip circumference, showed leptin positively correlating with BMI, and waist circumference (Mirrakhimov *et al*., 2014).

Involvement of leptin in various diseases and disease conditions has been studied and reviewed previously (Hussain, 1991; Redon, 2001; Aneja *et al*., 2004; Hussain *et al*., 2007; Sattar *et al*., 2009; Sohail *et al*., 2013; Sohail and Hussain, 2013; Taylor *et al*., 2014; Ayeser *et al*., 2016; Serafi *et al*., 2016). The role of leptin in BMI variations has been revealed (Kazumi *et al*., 1999; Sattar *et al*., 2009; Kerimkulova *et al*., 2014). Most of the studies show positive relationship of leptin plasma or serum levels with BMI (Kazumi *et al*., 1999; Hirose *et al*., 2001; Adami *et al*., 2002; Al-Sultan and Al-Elq, 2006; Antunes *et al*. 2009), and even indicate independent significant association of BMI with leptin levels (Antunes *et al*. 2009; Nakamura *et al*., 2009). However, there are controversies about the precise relationship of leptin with BMI, as it was suggested that the change in leptin levels related to BMI might also be due to age, race, type of obesity and other factors (Redon, 2001).

Adiponectin, a 244-amino-acid polypeptide was discovered first in 1995 and characterized in various cells (Scherer *et al*., 1995; Matsuzawa *et al*., 2004; Lara-Castro *et al*., 2007). It is secreted from adipose tissues and also from placenta in pregnancy (Chen *et al*., 2006) into blood and modulates glucose regulation and fatty acid

Professor Dr. Abdulhalim Salim Serafi, MBChB, MSc, PhD, FESC
Chairman Saleh Hamza Serafi Chair for Research in Coronary Heart Disease (SCRCHD)
Deanship for Scientific Research (DSR), Umm Al-Qura University (UQU), Makkah, Saudi Arabia Consultant Cardiologist & Chairman
Department of Physiology, Faculty of Medicine, Umm Al-Qura University (UQU), Makkah, Saudi Arabia

breakdown (Díez and Iglesias, 2003) and is involved in a number of other metabolic processes. Adiponectin is a collagen-like protein expressed in adipose tissue (Díez and Iglesias, 2010).

Adiponectin's weight reducing effect through brain is similar in action of leptin (Nedvídková *et al*., 2005), though both can have synergistic actions. Two of its receptors (adiponectin receptor 1 – ADIPOR1 and adiponectin receptor 2 – ADIPOR2) and another receptor of cadherin family (T-cadherin - CDH13) (Yamauchi *et al*., 2003; Hug *et al*., 2004) have tissue specificities. Adiponectin levels are decreased in obesity, and are regulated by post-translational cellular mechanisms though the exact mechanism of regulation is unknown yet (Liu and Liu, 2012).

Adiponectin is produced in inverse proportion to fat mass in contrast to the secretion of leptin and other adipokines that are produced in direct proportion to fat mass, or as a pro-inflammatory or have adverse actions i.e., circulating adiponectin highest in lean individuals as inversely correlating with fat mass (Ding *et al*., 2012). This shows that the low levels of serum adiponectin might be considered as a risk factor in a variety of diseases (Ding *et al*., 2012). Functions of adiponectin had been unclear, though it has been clinically shown that serum adiponectin is inversely associated with body weight, particularly abdominal visceral fat accumulation (Nishida *et al*., 2007).

In regard to Saudi population, and especially in young students, it is needed to determine the association of leptin, and adiponectin with BMI, and relationship existing for leptin against adiponectin levels. Hence, we proposed the present study in young male university students to investigate the mentioned associations.

METHODS AND MATERIALS

The present report comprised non-obese male university students (age: 18-20 years) for studying the effect of BMI of normal range on plasma leptin and adiponectin levels, as well as the association of plasma leptin and adiponectin in these subjects. Total number of subjects in this study were 75. The information (mainly age of the subjects, ethnicity/ race, education level/ skills, year of education/ certificates or degrees, body temperature, blood pressure, nutrition, personal habits, smoking and other information) from the subjects was recorded in a questionnaire.

Plasma levels of leptin were measured in ng/mL, whereas plasma adiponectin in µg/mL. The BMI was represented in body weight in kgs / body height in squared meters (m^2). Criteria for exclusion and inclusions of the conditions was decided. All subjects were unmarried and non-smokers, and without any complicated disorder. The subjects were fully informed about the purpose of the present research and collection of required data. They filled specific forms as volunteers for participating in the present study with their own willingness. No any subject was forced to provide data for the present study. Plasma levels of leptin and adiponectin were measured employing ELISA (enzyme-linked immunosorbent assay) kit (Human ELISA Kit) methods. Inter-assay and intra-assay variations were determined to be satisfactory.

The data entry and analysis were done using SPSS software version 24. General principles were considered following a previous article (Zahir *et al*., 2014). Regression was used to find the cause-and-effect relation between two variables by applying the relevant equation. The scatterplot of points indicated the strength of correlation, and analysis of the coefficient of determination (R^2) was employed to determine the correlation between two variables. The mean ± SEM and BMI (17-20 kg/m^2) were determined. For the comparison of two variables, student's t-test was employed. For regression lines, the values of the slope, intercept, df (degree of freedom), coefficient of determination (R^2) and p were determined.

RESULTS

The mean ± SD value for BMI (kg/m^2) in the subjects was 18.83 ±0.76. Plasma levels of leptin (ng/mL) and adiponectin (µg/mL) were respectively as 6.66 ± 2.99 and 5.62 ± 2.03.

The results for the regression and correlation are given in equation form (Table 1). Association of BMI and plasma leptin in male non-obese Saudi university students showed highly significant positive linear correlation ($p < .001$). This was further confirmed from the regression line for the values of slope (3.26), intercept (-54.77) and R^2 (0.69) (Table 1).

The relationship between BMI and plasma adiponectin showed highly significant negative association (($p < 0.001$). The regression plot showed the values of slope, intercept and R^2 respectively as -1.69, 37.40 and 0.40 (Table 1).

The plot of leptin against adiponectin also gave highly significant negative linear correlation ($p < 0.001$). It is evident further from the values for slope (-0.47), intercept (8.72) and R^2 (0.47) (Table 1).

Table 1. Association of plasma leptin and adiponectin in non-obese male Saudi students.

Correlations	Equation	Value of slope	Intercept	$R^{2\#}$	p-value*
BMI & plasma leptin	Y= 3.2616x -54.766; R^2 = 0.688)	3.26	-54.77	0.69	<0.001
BMI & plasma adiponectin	Y = -1.6881x + 37.405; R^2 = 0.3992	-1.69	37.40	0.40	<0.001
Plasma leptin & adiponectin	Y = -0.4671+8.7228; R^2 = 0.4726	-0.47	8.72	0.47	<0.001

BMI: body mass index, #: coefficient of determination, * df (degree of freedom): 73

DISCUSSION

Present report reveals positive linear correlation of BMI against plasma leptin, and negative linear correlation for BMI against adiponectin, and leptin against adiponectin, in young male university students age 18-20 years. Although the association of BMI with serum/ plasma leptin has been suggested as mainly due to age, type of obesity and other factors, and not merely due to obesity (Redon, 2001), the positive and significant relationship for BMI against plasma leptin in the current report is quite similar to previous reports (Antunes *et al*. 2009; Nakamura *et al*., 2009). There are other reports that agree with our present findings (Kazumi *et al*., 1999; Sattar *et al*., 2009; Kerimkulova *et al*., 2014). The present results for the association of leptin with BMI were found resembling in the work of various other workers (Hirose *et al*., 2001; Adami *et al*., 2002; Al-Sultan and Al-Elq, 2006; Antunes *et al*. 2009).

There are reports wherein positive relation of adiponectin with BMI was investigated (Cesari *et al*., 2007; Ciroma *et al*., 2017), or no relationship between BMI and adiponectin levels was found (Pádua *et al*., 2021). These reports contradict our present results since the type of their data was quite different. However, inverse relationship of adiponectin with BMI was found in several previous reports (Stefan *et al*., 2002; Meilleur *et al*., 2010; Klünder-Klünder *et al*., 2013; Ramzan *et al*., 2014; Adaja, 2018) providing evidence for our present results. Furthermore, adiponectin levels were found varying with age, sex and BMI (Nri-Ezedi *et al*., 2021) that suggests to carry out further studies in both sexes with different age groups and BMI levels / categories.

The present report provides interesting and potential information about the relationship existing among BMI, plasma leptin and plasma adiponectin that is helpful for future studies for exploring the use of this information for the management of disorders with altered/ abnormal levels of leptin and adiponectin in obese and non-obese people.

ACKNOWLEDGEMENTS

The authors would like to thank the Deanship of Scientific Research at Umm Al-Qura University for the continuous support. This work was supported financially by the Deanship of Scientific Research at Umm Al-Qura University to Prof. Dr. Abdulhalim Salim Hamza Serafi (Grant Code: 19-MED-1-01-0018).

REFERENCES

Adaja, T.M. (2018). Atherogenic triad in overweight and obese adults in Benin-City, South-South Nigeria. *Int. J. Trop. Dis. Heal.*, 32:1-9.

Adami, G.F., D. Civalleri, F. Cella, G. Marinari, G. Camerini, F. Papadia and N. Scopinaro (2002). Relationships of serum leptin to clinical and anthropometric findings in obese patients. *Obes. Surg*., 12(5):623-7.

Al-Sultan, A.I. and A.H. Al-Elq (2006). Leptin levels in normal weight and obese Saudi adults. *J. Family Community Med*., 13(3):97-102.

Aneja, A., F. El-Atat, S.I. McFarlan and J.R. Sowers (2004). Hypertension and obesity. *Recent Prog. Horm. Res.*, 59:169-205.

Antunes, H., C. Santos and S. Carvalho (2009). Serum leptin levels in overweight children and adolescents. *Br. J. Nutr.*, 101(8):1262-6.

Ayeser, T., M. Basak, K. Arslan and I. Sayan (2016). Investigating the correlation of the number of diagnostic criteria to serum adiponectin, leptin, resistin, TNF-alpha, EGFR levels and abdominal adipose tissue. *Diabetes Metab. Syndr* 10(2 Suppl 1):S165-9.

Bełtowski, J. (2006). Role of leptin in blood pressure regulation and arterial hypertension. *J. Hypertens.,* 24(5):789-801.

BBVA Foundation Frontiers of Knowledge Awards. BBVA Foundation. 2012.

Blüher, M. and C.S. Mantzoros (2015). From leptin to other adipokines in health and disease: Facts and expectations at the beginning of the 21st century. *Metabolism,* 64(1):131-145.

Cesari, M., K. Narkiewicz, R. De Toni, E. Aldighieri, C.J. Williams, and G.P. Rossi (2007). Heritability of plasma adiponectin levels and body mass index in twins. *J.Clin. Endocrinol. Metab.* 92:3082-8.

Chen, J., B. Tan, E. Karteris, S. Zervou, J. Digby, E.W. Hillhouse, M. Vatish, and H.S. Randeva (2006). Secretion of adiponectin by human placenta: differential modulation of adiponectin and its receptors by cytokines. *Diabetalogica*, 49 (6): 1292–302.

Ciroma, F.L., J.O. Ayo, A. Mohammed, M.B. Akor-Dewu, M.A. Kana, S.N. Kase (2017). Association between Adiponectin, Serum Lipids and Obesity in a University Setting in Nigeria. *Niger J. Physiol. Sci*., 32(1):69-74.

Díez, J.J. and P. Iglesias (2003). The role of the novel adipocyte-derived hormone adiponectin in human disease. Eur *J. Endocrinol.* 148 (3): 293–300.

Díez, J.J. and P. Iglesias (2010). The role of the novel adipocyte-derived protein adiponectin in human disease: an update. *Mini Re.v Med. Chem.,* 10(9):856-69.

Ding, M., E.M. Rzucidlo, J.C. Davey, Y. Xie, R. Liu, Y. Jin, L. Stavola and K.A. Martin (2012). Adiponectin in the heart and vascular system. *Vitam. Horm.,* 90:289-319.

Hirose, H., I. Saito, T. Kawai, M. Tsujioka, H. Kawabe and T. Saruta (2001). Relationships between baseline serum leptin levels and 2-year changes in body mass index, blood pressure and metabolic parameters in Japanese male adolescents and middle-aged men. *Clin. Sci*. (Lond), 100(2):145-50.

Hug, C., J. Wang, N.S. Ahmad, J.S. Bogan, T.S. Tsao and H.F. Lodish (2004). T-cadherin is a receptor for hexameric and high-molecular-weight forms of Acrp30/adiponectin. *Proc Natl Acad Sci U S A,* 101 (28): 10308–13.

Hussain, Z. (1991). Clinicobiological study of coronary artery disease. Pak Med J, 14 (5): 35-38.

Hussain, Z., S. Sohail and A. Ashraf (2007). Endothelial dysfunction, cytokines and diabetes mellitus. *Human Health,* 3 (7-8): 3-4.

Kazumi, T., A. Kawaguchi, J. Katoh, M. Iwahashi and G. Yoshino (1999).Fasting insulin and leptin serum levels are associated with systolic blood pressure independent of percentage body fat and body mass index. *J Hypertens.,* 17(10):1451-5.

Kerimkulova, A.S., O.S. Lunegova, A.E. Mirrakhimov, N.T. Alibaeva, K.V. Neronova, A.A. Baĭramukova and E.M. *Mirrakhimov (2014). Association of leptin with obesity and hypertension in an ethnic Kyrgyz group. Ter Arkh,* 86(1):49-53.

KFF – KFIP – Winners 2013 – Medicine. King Faisal Foundation. 2013.

Klünder-Klünder, M., S. Flores-Huerta, R. García-Macedo, J. Peralta-Romeroa and M. Cruz (2013). Adiponectin in eutrophic and obese children as a biomarker to predict metabolic syndrome and each of its components. *BMC Public Health*, 13:88.

Lara-Castro, C., Y. Fu, B.H. Chung and W.T. Garvey (2007). Adiponectin and the metabolic syndrome: mechanisms mediating risk for metabolic and cardiovascular disease. *Curr. Opin. Lipidol*, 18 (3): 263–70.

Liu, M. and F. Liu (2012). Up- and down-regulation of adiponectin expression and multimerization: Mechanisms and therapeutic implication. *Biochimie,* 94 (10): 2126–30.

Maffei, M., J. Halaas, E. Ravussin, R.E. Pratley, G.H. Lee, Y. Zhang, H. Fei, S. Kim, R. Lallone and S. Ranganathan (1995). Leptin levels in human and rodent: measurement of plasma leptin and ob RNA in obese and weight-reduced subjects. *Nat. Med.,* 1 (11): 1155–61.

Margetic, S., C. Gazzola, G.G. Pegg and R.A. Hill (2002). Leptin: a review of its peripheral actions and interactions. *Int. J. Obes. Relat. Metab. Disord*. 26 (11): 1407–1433.

Matsuzawa, Y., T. Funahashi, S. Kihara and I, Shimomura (2004). Adiponectin and metabolic syndrome. *Arterioscler. Thromb. Vasc. Biol.,* 24 (1): 29–33.

Meilleur, K.G., A. Doumatey, H. Huang, B. Charles, G. Chen, J. Zhou, D. Shriner, A. Adeyemo, and C. Rotimi (2010). Circulating adiponectin is associated with obesity and serum lipids in West Africans. *J. Clin. Endocrinol. Metab.* 95:3517-21.

Mirrakhimov, E., A. Kerimkulova, O. Lunegova, A. Mirrakhimov, N. Alibaeva and M. Nabiev (2014). Lipids and leptin level in natives of Kyrgyzstan. *Turk. Kardiyol. Dern. Ars*. 42(3):253-8.

Nakamura, Y., H. Ueshima, N. Okuda, Y. Murakami, K. Miura, Y. Kita, T. Okamura, T.C. Turin, B. Rodriguez, J.D. Curb and J. Stamler (2009). International Study of Macro/Micronutrients and Blood Pressure, Japan and Hawaii Research Group. Relation of serum leptin to blood pressure of Japanese in Japan and Japanese-Americans in Hawaii. *Hypertension*, 54(6):1416-22.

Nedvídková, J., K. Smitka, V. Kopský and V. Hainer (2005). Adiponectin, an adipocyte-derived protein. *Physiol. Res*, 54 (2): 133–40.

News-Medical (2009). Jeffrey Friedman receives Shaw Prize for discovery of leptin. *News-Medical.net.* 2009.

Nishida, M., T. Funahashi and I. Shimomura (2007). Pathophysiological significance of adiponectin. *Med. Mol. Morphol*., 40(2):55-67.

Nri-Ezedi, C. A., T. Ulasi, J. Chukwuka, H. Okpara, O. Ofiaeli, E. Nwaneli and A. Ulasi (2021). Serum total adiponectin in healthy pre-pubertal nigerian school children. *Niger J Clin. Pract.*, 24(6):821-827.

Pádua, E.C.R., S. Daher, I.P.C. Sampaio, E. Araujo Júnior and C.F. Guazzelli (2021). Evaluation of the Blood Level of Adiponectin in Pregnant Adolescents. *Rev. Bras. Ginecol. Obstet.*, 43.(6):429-435.

Ramzan, M., I, Ali, M.H. Ramzan, F. Ramzan and F. Ramzan (2014). A profile of plasma concentration of adiponectin in primary school children in Dera Ismail Khan. *J. Postgrad Med. Inst*, 28:33-6.

Redon, J. (2001). Hypertension in obesity. *Nutr. Metab. Cardiovascular. Dis.*, 11(5):344-53.

Sattar, N., G. Wannamethee, N. Sarwar, J. Chernova, D.A. Lawlor, A. Kelly, A.M. Wallace, J. Danesh and P.H. Whincup (2009). Leptin and coronary heart disease: prospective study and systematic review. *J. Am. Coll. Cardiol.*, 53(2):167-75.

Scherer, P.E., S. Williams, M. Fogliano, G. Baldini and H.F. Lodish (1995). A novel serum protein similar to C1q, produced exclusively in adipocytes. *J. Biol. Chem.*, 270(45):26746-9.

Serafi, A.S., M.A. Bafail and Z. Hussain (2016). Role of leptin in hypertension: A short review. *Int. J. Biol. Biotech.*, 13 (3): 453-458.

Sinha, M.K., I. Opentanova, J.P. Ohannesian, J.W. Kolaczynski, M.L. Heiman, J. Hale, G.W. Becker, R.R. Bowsher, T.W. Stephens and I.F. Caro (1996). Evidence of free and bound leptin in human circulation. Studies in lean and obese subjects and during short-term fasting. *J. Clin. Invest*, 98 (6): 1277–82.

Sohail, S. and Z. Hussain (2013). Pathophysiology of ischemic disorders - Ischemia, adipocytokines and diabetes mellitus. *Int. J. Biol. Biotech.*, 10 (2) 155-166.

Sohail, S., Z. Hussain, Quratul ain and S.J. Ashraf (2013). Blood cholesterol and leptin levels in male smoking and non-smoking patients with diabetes mellitus. *Int. J. Biol. Res*., 1 (1):15-18.

Stefan, N., J.C. Bunt, A.D. Salbe, T. Funahashi, Y. Matsuzawa and P.A. Tataranni (2002). Plasma adiponectin concentrations in children: relationships with obesity and insulinemia. J Clin Endocrinol Metab, 87(10):4652-6.

Taylor, P.D., A.M. Samuelsson and L. Poston (2014). Maternal obesity and the developmental programming of hypertension: a role for leptin. *Acta Physiol*. (Oxf), 210(3):508-23.

The Lasker Foundation (2010). 2010 Awards. Lasker Foundation.

Wada, K., H. Yatsuya, K. Tamakoshi, R. Otsukai, C. Fujii, K. Matsushita, K. Sugiura and H. Toyoshima (2006). A positive association between leptin and blood pressure of normal range in Japanese men. *Hypertens. Res*, 29(7):485-92.

Yamauchi, T., J. Kamon, Y. Ito, A. Tsuchida, T. Yokomizo, S. Kita, T. Sugiyama, M. Miyagishi, K. Hara, M. Tsunoda, K. Murakami, T. Ohteki, S. Uchida, S. Takekawa, H. Waki, N.H. Tsuno, Y. Shibata, Y. Terauchi, P. Froguel, K. Tobe, S. Koyasu, K. Taira, T. Kitamura, T. Shimizu, R. Nagai and T. Kadowaki (2003). Cloning of adiponectin receptors that mediate antidiabetic metabolic effects. *Nature*, 423 (6941): 762–9.

Zahir, H., A. Javaid, R. Rehman and Z. Hussain (2014). Statistical concepts in biology and health sciences. *Journal of Ayub Medical College Abbottabad*, 26 (1): 95-7.

Waki, H., T. Yamauchi, J. Kamon, Y. Ito, S. Uchida, S. Kita, K. Hara, Y. Hada, F. Vasseur, P. Froguel, S. Kimura, R. Nagai and T. Kadowaki (2003). Impaired multimerization of human adiponectin mutants associated with diabetes. Molecular structure and multimer formation of adiponectin. *J. Biol. Chem*, 278(41):40352-63.

(*Accepted for publication December 2021*)