Diet Induced Acidosis is Associated with Lower Circulating Adiponectin Levels regardless of Body Weight Status

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ABSTRACT

Low circulating Adiponectin level have been observed to significantly increase the risk of developing type 2 Diabetes mellitus, cardiovascular diseases and several malignancies. A number of potential determinants of the circulating Adiponectin levels have been investigated in order to develop newer preventive strategies for such diseases. The possible role of diet induced acidosis in decreasing the circulating level of Adiponectin in healthy population has been proposed. However, findings from previous studies are not consistent. It is likely that the association is affected by genetic and environmental factors that differ among different populations. We investigated the impact of diet induced acidosis on the circulating level of Adiponectin in a group of apparently healthy adult Nigerians. Food frequency questionnaire and the Nigerian Food Composition Table were used for the assessment of dietary intake. Acid forming potential of our local diets were estimated as Potential Renal Acid Load (PRAL) scores. Plasma total Adiponectin was measured. Across the quartiles of the PRAL scores, there was a statistically significant trend with higher intake of dietary acid associated with significant decreased circulating Adiponectin level (p for trend < 0.05). Study participants in the highest quartile of the PRAL scores have a statistically significant lower Adiponectin level compared with participants in the lowest quartile (12.6 ± 2.2µg/mL vs. 6.1 ± 2.5µg/mL, p < 0.05). We conclude that among the subjects in this study lower intake of dietary acid is associated with significant increase in circulating Adiponectin level.

Keywords: Dietary acid load, Adiponectin, Adults, Nigeria

INTRODUCTION

Adiponectin is an adipocytokine that is predominantly produced by adipocytes and plays a significant role in metabolic and cardiovascular homeostasis through its insulin-sensitizing actions and anti-inflammatory and antiatherogenic properties.[1,2] More recently, it has been observed that, among the general population, lower circulating levels of Adiponectin can substantially increase the risk of developing type 2 Diabetes mellitus, cardiovascular diseases and several malignancies.[3-10] This has led to studies on the investigation of potential determinants of the circulating Adiponectin levels in order to develop newer preventive approaches for diseases such as type 2 Diabetes mellitus and cardiovascular diseases, and a number of potential determinants of circulating Adiponectin level have been investigated.[11]

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Report from an experimental study suggests that cellular acidosis down-regulates Adiponectin gene expression and therefore decreases circulating Adiponectin level; and a number of reports from interventional studies, mainly done among Caucasians, suggest that consumption of foods with high acid forming potential, such as processed foods, is associated with a decrease in circulating level of Adiponectin, while consumption of diets with base forming potential result in increased Adiponectin circulating level.[12-26] However, some reports from other investigators do not confirm these findings.[20,27,28] There is a recent increase in the prevalence of habitual consumption of high acid forming diets in our setting, and the effect of that on the circulating level of Adiponectin, in the general population, has not been investigated.[29]

Therefore, using the potential renal acid load (PRAL) score to estimate the acid-forming potential of our local diets, we tested whether diet-induced acidosis is associated with low circulating level of Adiponectin among a group of apparently healthy adult Nigerians.

MATERIALS AND METHODS

Study Participants

We conducted this cross-sectional analytical hospital-based study among two hundred and thirty-two (232) apparently healthy adult Nigerians (128 males and 104 females) aged above 18 years. The subjects were recruited into the study at the State Specialist Hospital, Gombe, Nigeria, from among individuals who presented to the hospital for routine medical check-up, pre-marital screening and blood donors. All study subjects are Nigerians of African descent and living in Gombe State. Subjects with diagnosed diabetes mellitus or any other illness, smokers, alcoholics, pregnant and lactating women, under-reporters or over-reporters of dietary intake ($\leq$ 800kcal/day or > 4,200kcal/day respectively) and individuals on special diets were all excluded from the study.

This study was approved by the Ethics Committee of the Gombe State Ministry of Health, Gombe, and the study procedures adhered to the recommendations of the Declaration of Helsinki. All the study subjects gave informed consent.

Data collection

The study subjects were evaluated in the morning following a10-12 hours overnight fast. History and physical examination were carried out on each of the study subjects at the time of blood sample collection. Data on age, sex and dietary intake were noted and recorded. During physical examination, blood pressure measurements were obtained with each subject in a sitting position using a mercury Sphygmomanometer. Systolic and diastolic blood pressures were measured and recorded. Body weight and height were measured with subjects standing erect and not wearing shoes or headgear. A wall-mounted measuring tape was used for the measurement of body height and a weighing scale for the body weight measurements. Body mass index (BMI) was calculated as weight in kilogram (kg) divided by height in meter squares (m^2).

Dietary assessment

During the interview a food frequency questionnaire was used to assess the intake of food items over the preceding week. To determine the frequency of consumption, nine response options were given, from rarely (less than once in month) to more than once a day. And to determine portion size, a standard portion size for each food item was specified according to local household measures, and each participant was asked to specify his/her portion size as half the standard, the standard or one and half times the standard portion size.

The average daily intake of each of the food items was determined by multiplying the frequency of daily consumption and the standard portion size by the participant portion size. Dietary intakes of energy and selected nutrients were estimated from the Nigerian Food Composition Table.[30]

Estimation of Dietary Acid Load

The dietary acid intake was estimated using the Potential Renal Acid Load (PRAL) score;

The PRAL score was calculated using the following equation:

PRAL (mEq/day) = 0.4888 × Dietary Protein (g/day) + 0.0366 × Dietary Phosphorus (mg/day) - 0.0205 × Dietary Potassium (mg/day) - 0.0125 × Dietary Calcium (mg/day) - 0.0263 × Dietary Magnesium (mg/day).[31]

Laboratory analysis

Overnight fasting venous blood samples were collected in to lithium heparin bottles for the quantification of Adiponectin and Glucose. Blood samples were immediately centrifuged for 15 minutes for separation of plasma, which was stored in aliquots at -20^{0}C until analysis. Fasting plasma Glucose was measured using the Glucose oxidase method (Agappe Diagnostics Limited, India) and plasma total Adiponectin was measured using an Enzyme-Linked Immunosorbent Assay (ELISA) kit (Bioassay Technology

Laboratory BT Lab. China) which utilizes an antibody specific for human Adiponectin coated on the walls of the micro wells. The Adiponectin present in the plasma samples bound to the wells, by the immobilized antibody, on adding the samples into the wells. Subsequent addition of biotinylated anti-human Adiponectin antibody and HRP-conjugated streptavidin into the wells, together with a substrate (TMB) resulted in the development colored solution whose intensity is directly proportional to the concentration of the Adiponectin in the samples. Stop Solution (Sulphuric acid) changes the color from blue to yellow, and the intensity of the color was measured at 450nm. Standard curve of Adiponectin determination was plotted and the Adiponectin level in each sample was determined from the curve.

All laboratory analyses were done at the Chemical Pathology laboratory of Gombe State University/Federal Teaching Hospital, Gombe.

Statistical analysis

Statistical analysis of the generated data was done using the Statistical package for social sciences (SPSS) version 20.0. Kolmogorow-Smirnov test was used to test for normality of distribution of data and logarithmic transformation was used to improve the normality of distribution of skewed data. Quantitative variables were presented using proportions and measures of central tendency and dispersion. The mean values of quantitative variables were compared across the PRAL quartiles categories using ANOVA test. Partial correlation analyses were used to determine relationship between dietary acid load and plasma Adiponectin and to adjust for confounders. All p-values were two-sided and considered significant if less than 0.05.

RESULTS

Demographic, dietary and biochemical parameters of the study subjects are shown in Table 1. The mean age of the study subjects, which were predominantly males (55.2%), was 34.0 ± 5.4 years and the mean BMI was 24.5 ± 4.4kg/m^2. There were no significant differences in the age and BMI levels between male and female subjects (34.1 ± 5.6 vs. 34.0 ± 4.1 years, $p > 0.05$) and (24.8 ± 4.3 vs. 24.1 ± 4.4kg/m^2, $p > 0.05$) respectively. The mean energy intake of the study subjects was 2245 ± 423kcal/day. There were no statistically significant differences in the intake of energy, protein, Calcium, Phosphorus, Potassium and Magnesium among the male and female subjects (p-values for all > 0.05).

The relationship between dietary acid load and plasma level of Adiponectin in the study subjects was examined (Figures 1 and 2.) A significant inverse relationship, independent of age and BMI, was found between PRAL scores and plasma Adiponectin levels ($r = -0.56$, $p < 0.05$) in all the study subjects (Figure 1). When the study subjects were categorized into males and females, the inverse relationships between PRAL scores and plasma Adiponectin levels was observed to be stronger in male subjects. The subjects were categorized in to four quartiles according to their median dietary acid intake (Figure 2). Study subjects consuming higher levels of dietary acid in the fourth quartile were observed to have a significantly lower level of plasma Adiponectin level compared with the study subjects consuming lower levels of dietary acid (12.6 ± 2.2µg/mL vs. 6.1 ± 2.5µg/mL).

Table 1: Demographic and Biochemical Parameters of the Study Subjects.

	All (m ± SD)	Male (m ± SD)	Female (m ± SD)	*p*-value
Sample size (n)	232	128	104	-
Age (years)	34.0 ± 5.4	34.1 ± 5.6	34.0 ± 4.1	0.793
Sex ratio	128/104	-	-	-
Body Mass Index (kg/m^2)	24.5 ± 4.4	24.8 ± 4.3	24.1 ± 4.4	0.221
Systolic BP (mmHg)	118.0 ± 5.3	118.0 ± 5.1	118.0 ± 5.6	0.469
Diastolic BP (mmHg)	78.6 ± 3.9	78.8 ± 3.8	78.4 ± 3.8	0.451
Energy (kcal/day)	2245 ± 423	2282 ± 416	2200 ± 430	0.143
Protein (g/day)	89.8 ± 17.8	89.4 ± 18.3	90.4 ± 17.3	0.655
Calcium (mg/day)	526 ± 156	522 ± 157	530 ± 156	0.678
Phosphorus (mg/day)	974 ± 181	967 ± 185	979 ± 177	0.667
Potassium (mg/day)	3057 ± 716	3057 ± 697	3057 ± 742	0.994
Magnesium (mg/day)	845 ± 615	898 ± 610	780 ± 617	0.144
PRAL (mEq/day)[*]	+9.1	+9.0	+9.9	0.221[#]
Fasting PG (mmol/L)	4.3 ± 0.7	4.2 ± 0.7	4.3 ± 0.6	0.463
Adiponectin (µg/mL)	7.3 ± 3.8	7.5 ± 4.0	7.1 ± 3.7	0.393

Keys: m, mean, SD, standard deviation, BP, blood pressure, PG, plasma glucose
PRAL, potential renal acid load, [*]median values, [#]Mann- Whitney test

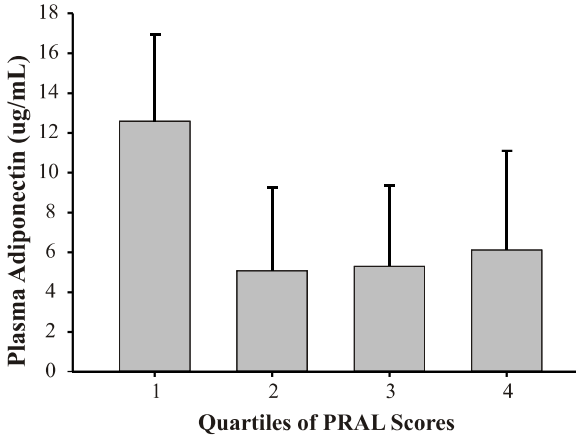

Figure 1: Plasma Adiponectin Level among the Study Subjects. Mean and Standard Deviation are shown. *PRAL, potential renal acid load.*

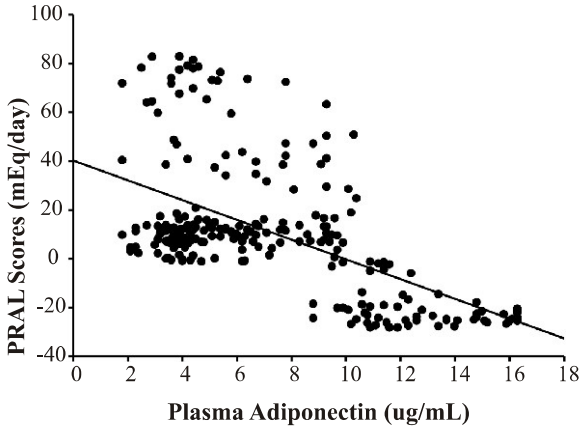

Figure 2: Correlation of Plasma Adiponectin and Dietary Acid Load Scores among the Study Subjects. *PRAL, potential renal acid load*

DISCUSSION

We examined the impact of diet induced metabolic acidosis on the circulating level of Adiponectin in a group of apparently healthy adult Nigerians. We found a significant negative association between diet-induced acidosis and circulating Adiponectin level among the study subjects independent of age, gender and body weight status.

Our results are supported by previous prospective studies carried out mainly among Caucasians, in which habitual consumption of acidifying foods (high PRAL foods), as red meat, processed meat, refined sugars and high-fat dairy products, is significantly associated with decreased circulating Adiponectin levels.[13-19]

In support of our findings, Luisi et al[24] and Spadafranca *et al*[25] reported that adherence to Mediterranean diet, which consists largely of low PRAL foods as vegetables and fruits, is associated with significant increase in circulating Adiponectin levels compared to non-adherence. Similar findings of significant increase in circulating Adiponectin levels

among individuals whose eating pattern consists mainly of alkalinizing food items were also reported by many other investigators.[20-23,26]

However, findings from some other studies do not support these. Lovrencic *et al*[27] did not find a significant correlation between following a vegetarian diet and Adiponectin circulating level in male adults.[27] Adherence to Mediterranean diet was also not significantly related to Adiponectin circulating level in female adults and adolescents of both sexes according to reports from a study by Sureda *et al*.[20] Adding to the controversy, Gunn et al[28] reported a decreased total Adiponectin circulating level in postmenopausal women following three months dietary intervention with low PRAL foods (fruits and vegetables).

Differences in sample sizes and heterogeneity of the study subjects, including differences in dietary patterns, and whether total Adiponectin or high molecular weight Adiponectin was measured in the different studies might partly explain the discrepancies in the findings from the previous studies.

Nutrient composition of food items plays an essential role in the maintenance of acid base homeostasis by supplying acid or base precursors. Diets rich in animal proteins, including red meat, eggs and high fat dairy products among others, enhance the production of acid in the body, while diets rich in vegetables and fruits increase production of alkali in the body.[32] The potential renal acid load (PRAL) score defines the capacity of any food item to generate acid or base precursors in the body.[30] Habitual consumption of diet containing high PRAL food items causes a decrease in blood pH towards the lower end of normal which, if not compensated for by the normal homeostasis or modification of diets, can induce a state of chronic low grade metabolic acidosis (diet-induced acidosis) in the body.[32]

Chronic acidosis induces cellular oxidative stress, and adipocytes that secrete Adiponectin are sensitive to oxidative stress.[33] Exposure of adipocytes to reactive oxygen species suppressed Adiponectin mRNA expression and secretion and also increased the mRNA expression of pro-inflammatory cytokines such as interleukin (IL) 6.[34] Interleukin (IL) 6 is also a negative regulatory factor of Adiponectin gene.[35,36] Thus, the higher level of interleukin (IL) 6 further suppresses the transcription of Adiponectin gene in adipose cells. Additionally, metabolic acidosis has been shown to directly inhibit the transcription of Adiponectin gene in adipocytes.[12]

LIMITATIONS

Firstly, the assessment of energy and nutrient intake was done using a self-reported food frequency questionnaire which might be affected by recall bias. Secondly, causality cannot be inferred from the findings because the design of the study is cross sectional. Although potential confounders were adjusted for, residual confounding is still possible and could weaken the strength of association.

CONCLUSION

We conclude that among apparently healthy adult individuals in this study, higher intake of dietary acid is associated with decreased circulating Adiponectin levels. This finding may require replication from studies involving larger sample size and various ethnic groups. We recommend further longitudinal studies that will investigate the impact of dietary acid reduction/restriction on the circulating Adiponectin level in our setting.

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CONFLICT OF INTEREST: Nil

ETHICS APPROVAL

The Health Research Ethics Committee of the Gombe State Ministry of Health, Gombe, Nigeria approved the study protocol.

REFERENCES

1. Freitas-Lima LC, Braga VA, do Socorro de França Silva M, Cruz JC, Sousa Santos SH, de Oliveira Monteiro MM et al. Adipokines, diabetes and atherosclerosis: an inflammatory association. Front. Physiol 2015;6:304.
2. Giannessi D, Maltinti M, Del Ry S. Adiponectin circulating levels: a new emerging biomarker of cardiovascular risk. Pharmacol Res 2007;56:459-67.
3. Khoramipour K, Chamari K, Hekmatikar AA, Ziyaiyan A, Taherkhani S, Elguindy NM, et al. Adiponectin: Structure, Physiological Functions, Role in Diseases, and Effects of Nutrition. Nutrients 2021;13:1180.
4. Abdella NA, Mojiminiyi OA. Clinical Applications of Adiponectin Measurements in Type 2 Diabetes Mellitus: Screening, Diagnosis, and Marker of Diabetes Control. Disease Markers. 2018:5187940.
5. Ebrahimi-Mamaeghani M, Mohammadi S, Arefhosseini SR, Fallah P, Bazi Z. Adiponectin as a potential biomarker of vascular disease. Vasc. Health Risk Manag 2015;11:55-70.
6. Hui X, Lam KSL, Vanhoutte PM, Xu A. Adiponectin and cardiovascular health: an update. Br J Pharmacol 2012;165:574-90.
7. Zhang L, Yuan Q, Li M, Chai D, Deng W, Wang W. The association of leptin and adiponectin with hepatocellular carcinoma risk and prognosis: a combination of traditional, survival, and dose-response meta-analysis. BMC Cancer 2020;20:1167.
8. Mele C, Sama MT, Bisoffi AA, Caputo M, Bullara V, Mai S *et al*. Circulating adipokines and metabolic setting in differentiated thyroid cancer. Endocr Connect 2019;8:997-1006.
9. Lu W, Huang Z, Li N, Liu H. Low circulating total adiponectin, especially its non-high-molecular weight fraction, represents a promising risk factor for colorectal cancer: a meta-analysis. OncoTargetsTher 2018;11:2519-31.
10. Yoon YS, Kwon AR, Lee YK, Oh SW. Circulating adipokines and risk of obesity related cancers: a systematic review and meta-analysis. Obes Res Clin Pract 2019;13:329-39.
11. Janiszewska J, Ostrowska J, Szostak W, Egierek D. The Influence of Nutrition on Adiponectin. A Narrative Review. Nutrients 1;13:94.202
12. Disthabanchong S, Niticharoenpong K, Radinahamed P, Stitchantrakul W, Ongphiphadhanakul B, Hongeng S. Metabolic acidosis lowers circulating adiponectin through inhibition of adiponectin gene transcription. Nephrol Dial Transplant 2011;26:592-8.
13. Ley SH, Sun Q, Willett VC, Eliassen AH,Wu K, Pan A et al. Associations between red meat intake and biomarkers of inflammation and glucose metabolism in women. Am. J. Clin. Nutr 2014;99:352-60.
14. Meshkini M, Alaei-Shahmiri F, Mamotte C, Dantas J. Ethnic Variations in Adiponectin Levels and Its Association with Age, Gender, Body Composition and Diet: Differences Between Iranians, Indians and Europeans Living in Australia. J. Immigr. Minor. Health 2018; 20:1362-72.
15. Fargnoli JL, Fung TT, Olenczuk DM, Chamberl and JP, Hu FB, Mantzoros CS. Adherence to healthy eating patterns is associated with higher circulating total and high-molecular-weight adiponectin and lower resistin concentrations in women from the Nurses' Health Study. Am. J. Clin. Nutr 2008;88:1213-24.
16. Jafari-Vayghan H, Tarighat-Esfanjani A, Jafarabadi MA, Ebrahimi-Mameghan M, Lalezadeh GZSS.

Association between Dietary Patterns and Serum Leptin-to-Adiponectin Ratio in Apparently Healthy Adults. J. Am. Coll. Nutr 2015;34:49-55.

17. Alves-Santos NH, Cocate PG, Eshriqui I, Benaim C, Barros EG, Emmett PM et al. Dietary patterns and their association with adiponectin and leptin concentrations throughout pregnancy: A prospective cohort. Br. J. Nutr 2018;119:320-9.
18. Pereira RI, Wang CCL, Wolfe P, Havranek EP, Long CS, Bessesen DH. Associations of Adiponectin with Adiposity, Insulin Sensitivity, and Diet in Young, Healthy, Mexican Americans and Non-Latino White Adults. Int. J. Environ. Res. Public Health 2016;13:54- 63.
19. Rezvani R, Cianflone K, McGahan JP, Berglund L, Bremer AA, Keim NL et al. Effects of Sugar-Sweetened Beverages on Plasma Acylation Stimulating Protein, Leptin and Adiponectin: Relationships with Metabolic Outcomes. Obesity 2013;21:2471-80.
20. Sureda A, Bibiloni MM, Julibert A, Bouzas C, Argelich E, Llompart I et al. Adherence to the Mediterranean Diet and Inflammatory Markers. Nutrients 2018;10:62-75.
21. AlEssa HB, Ley SH, Rosner B, Malik VS, Willett WC, Campos H et al. High Fiber and Low Starch Intakes Are Associated with Circulating Intermediate Biomarkers of Type 2 Diabetes among Women. J. Nutr 2016;146:306-17.
22. Mirmiran P, Hosseini S, Hosseinpour-Niazi S, Azizi F. Legume consumption increase adiponectin concentrations among type 2 diabetic patients: A randomized crossover clinical trial. Endocrinol Diabetes Nutr 2019;66:49-55.
23. Kouvari M, Boutari C, Chrysohoou C, Fragkopoulou E, Antonopoulou S, Tousoulis D et al. Mediterranean diet is inversely associated with steatosis and fibrosis and decreases ten-year diabetes and cardiovascular risk in NAFLD subjects: Results from the ATTICA prospective cohort study. Clin. Nutr 2020;7:1-11.
24. Luisi MLE, Lucarini L, Biffi B, Rafanelli E, Pietramellara G, Durante M et al. Effect of Mediterranean Diet Enriched in High Quality Extra Virgin Olive Oil on Oxidative Stress, Inflammation and Gut Microbiota in Obese and Normal Weight Adult Subjects. Front. Endocrinol 2019;10:1366-79.
25. Spadafranca A, Piuri G, Bulfoni C, Liguori I, Battezzati A, Bertoli S et al. Adherence to the Mediterranean Diet and Serum Adiponectin Levels in Pregnancy: Results from a Cohort Study in Normal Weight Caucasian Women. Nutrients 2018;10:928-36.
26. Monda V, Polito R, Lovino A, Finaldi A, Valenzano A, Nigro E et al. Short-Term Physiological Effects of a Very Low-Calorie Ketogenic Diet: Effects on Adiponectin Levels and Inflammatory States. Int J Mol Sci 2020;21:3228.
27. Lovrencic MV, Geri´c M, Kosuta I, Dragicevi´c M, Garaj-Vrhovac V, Gajski G. Sex-specific effects of vegetarian diet on adiponectin levels and insulin sensitivity in healthy non obese individuals. Nutrition 2020;70:1-5.
28. Gunn CA. Increased intake of vegetables, herbs and fruit: effects on bone in postmenopausal women. PhD Thesis on the internet. Massey University, Manawatu, New Zealand; 2013. Available from: https://mro.massey.ac.nz/handle/10179/6288
29. Oyewole O, Atinmo T. Nutrition transition and chronic diseases in Nigeria. Proceedings of the Nutrition Society. 2015;74:460-5.

30. Nigeria Food Composition Available from http://nigeriafooddata.ui.edu.ng/Database.
31. Remer T, Dimitriou T, Manz F. Dietary potential renal acid load and renal net acid excretion in healthy, free-living children and adolescents. Am J Clin Nutr 2003;77:1255-60.
32. Osuna-Padillaa IA, Leal-Escobarb G, Garza-Garcíac CA, Rodríguez-Castellanos FE. Dietary acid load: Mechanisms and evidence of its health repercussions. nefrologia. 2019;39:343-54.
33. Matsuda M, Shimomura I. Roles of oxidative stress, adiponectin, and nuclear hormone receptors in obesity-associated insulin resistance and cardiovascular risk. Horm Mol Biol Clin Invest 2014;19:75-88.
34. Furukawa S, Fujita T, Shimabukuro M, Iwaki M, Yamada Y, Nakajima Y et al. Increased oxidative stress in obesity and its impact on metabolic syndrome. J Clin Invest 2004;114: 1752-61.
35. Wueest S, Seelig E, Timper K, Lyngbaek MP, Karstoft K, Donath MY *et al.* IL-6 Receptor Blockade Increases Circulating Adiponectin Levels in People with Obesity: An Explanatory Analysis. Metabolites 2021;11:79.
36. Fasshauer M, Kralisch S, Klier M, LossnerU, Bluher M, Klein J et al. Adiponectin gene expression and secretion is inhibited by interleukin-6 in 3T3-L1 adipocytes. BiochemBiophys Res Commun 2003;301:1045-50.