DERMATO-ENDOCRINOLOGY
2018, VOL. 10, NO. 1, e1477902 (7 pages)
https://doi.org/10.1080/19381980.2018.1477902

Taylor & Francis
Taylor & Francis Group

RESEARCH PAPER

OPEN ACCESS Check for updates

The Relationship of adiponectin level and *ADIPOQ* gene variants with BMI among young adult women

Omar F. Khabour [a], Mahmoud A. Alomari[b], and Asmaa A. Abu Obaid[a]

[a]Department of Medical Laboratory Sciences, Jordan University of Science and Technology, Irbid, Jordan 22110; [b]Division of Physical Therapy, Department of Rehabilitation Sciences, Jordan University of Science and Technology, Irbid, Jordan 22110.

ABSTRACT

The current study examined the effect of single nucleotide (SNPs) polymorphisms in the *ADIPOQ* gene (I146T and G276T) on body mass index (BMI) of young adult women. The women were divided into underweight, normal, overweight and obese according to BMI. The circulating levels of adiponectin were measured using commercially available ELISA kits. Genetic polymorphisms were genotyped using the PCR-RFLP method. G276T and I164T SNPs are common in the examined population as the frequency of G allele of 276 SNP was 54.8% and for the T allele of 164 SNP it was 41.7%. Circulating adiponectin levels were related to BMI and were lowest in the obese versus overweight, normal weight and underweight groups ($p<0.01$). However, *ADIPOQ* gene SNPs (I146T and G276T) showed no association with BMI groups. In conclusion, the results may suggest that adiponectin level, but not *ADIPOQ* gene SNPs, is a good indicator to BMI in young adult women.

ARTICLE HISTORY
Received 8 March 2018
Accepted 15 May 2018

KEYWORDS
Adiponectin; *ADIPOQ* gene; BMI; G276T and I164T SNPs; Jordan; Obesity; Women

Introduction

Obesity is an independent risk factor for early morbidity and mortality and has been implicated in cardiovascular, metabolic, musculoskeletal, immune, and nervous disorders. It has become a global epidemic, especially in developing countries including Jordan. The etiology is multifactorial, with genetic, environmental, socioeconomic, behavioral, and psychological contributions.[1,2]

Opposites to originally believe, adipose tissue is a dynamic organ that might contribute to whole-body metabolism.[3] These actions are mediated by cytokines secreted from the adipocytes.[45] Adiponectin is a cytokine that appears to play an important metabolic role, as it has been implicated in controlling insulin sensitivity and lipid metabolism.[6,7] It is a protein circulating abundantly in the plasma[8,9] yet it is lowered in patients with obesity,[10] insulin resistance,[6] and type 2 diabetes.[11,12]

The adiponectin gene (*ADIPOQ*) has been located on chromosome 3q27, with polymorphisms that influence the level and activity of adiponectin, SNP 276 (G>T) and I164T. The first is associated with type 2 diabetes,[13,14] insulin resistance, and obesity,[15] while the latter is a missense mutation associated with the metabolic syndrome and coronary artery disease (CAD).[16,17] However, the exact underlying mechanism for these actions are still unclear. Therefore, this study verified the relationship of body mass index (BMI), a measure of obesity, with adiponectin level. Subsequently, the contribution of *ADIPOQ* gene variants (I146T and G276T) to the prevalence of obesity was examined.

Materials and methods

Subjects

Young adult females were invited to participate in the study. Exclusion criteria included known pregnancy, diabetes, and thyroid abnormalities. Written informed consent form was obtained from all participants in accordance with the requirements of the Institutional Review Boards in the university. The subjects were divided into four groups, underweight, normal weight, overweight, and obese according to BMI.

CONTACT Omar Khabour, PhD khabour@just.edu.jo Main Street, Department of Medical Laboratory Sciences, Faculty of Applied Medical Sciences, Jordan University of Science and Technology, Irbid, Jordan, 22110.

Sample Collection and Handelling

Venous blood samples were obtaied from participants after fasting overnight. Each sample was distributed in 2 evacuated EDTA tube (4.5 ml) and 1 plain tube (4 ml). Part of the EDTA blood sample was stored at -4 and used for DNA extraction. The remaining EDTA samples and plain blood were centrifuged at 3500xg for 5 minutes and the resulting plasma and serum were isolated and stored at -80 °C until used except for 500 µl of serum were sent to the Health Center of Jordan University of Science and Technology for lipid profile analysis.[18] Lipid profiles were analyzed using the Roche Chemistry Analyzer and Roche kits (Roche Diagnostics, Germany).

Body mass index

Body mass index (BMI) of the participants were calculated from their respective height and weight using the following equation: BMI = weight in kg/(height in meters).[2] Subsequently, the participants were stratified to underweight; ≤ 18.49, normal weight; 18.5-24.9, overweight; 25–29.9, and obese; ≥ 30.[19]

Adiponectin plasma Level

Human Adiponectin ELISA based on sandwich enzyme immunoassay was used for quantitative measurement of human adiponectin. The Human Adiponectin ELISA kit was purchased from R&D systems for research purposes (DuoSet; Minneapolis, MN, USA). Plasma samples were diluted at 1/800 (concentration of reagent diluent solution: plasma) followed by the addition of 100 µl of the diluted plasma into mouse anti-human adiponectin antibody microtiter wells. Streptavidin conjugated to horseradish peroxidase (HRP) was used for detection (R&D; Minneapolis, MN, USA). Reaction steps, incubation times and number of washes after each step were as described the kit instructions. The absorbance was measured spectrophotometrically at 450 nm using an ELx800 microplate reader (BioTek Instruments, Winooski, VT, USA). The concentration of adiponectin was directly proportional to color intensity of the test sample. Finally, the concentration of samples was determined using the standard curve.[18]

Molecular analysis

The polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) technique was used for genotyping[18,20,3] DNA was extracted from whole blood using a DNA extraction kit purchased from Promega as described in the protocol. Then the DNA fragments of the SNPs (G276T and I164T) were amplified by using Go Taq Green Master Mix purchased from Promega (Madison, WI, USA) with primers and PCR conditions described in Table 1.

The amplified PCR fragments of G276T and I164T SNPs were restricted with *Bsm1* (3 units/reaction, Fermentas, Germany) and *Bcc1* (10 units, Fermentes, Germany) respectively. Restriction conditions were 4 hours at 65 °C for G276T SNP and Overnight at 37 °C for I164T SNP. Reaction

Table 1. The PCR conditions and primers used for ADIPOQ SNPs G276T and I164T.

SNP	PCR conditions	Primers	Fragment length
G276T	Denaturation at 94°C for 5 min 35 cycles of: Denaturation at 94°C for 35 sec Annealing at 58°C for 35 sec Extention at 72 °C for 35 sec Final extention at 72 °C for 7 min	F: 5′-GTCTAGGCCTTAGTTAATAATGAATG-3′ R: 5′-GAGAAAGGAGATCCAGGTAAGA-3′	104 bp
I164T	Denaturation at 94°C for 5 min 35 cycles of: Denaturation at 94°C for 1 min Annealing at 60°C for 1 min Extention at 72°C for 1 min Final extention at 72°C for 7 min	F: 5′-CCC ATT CGC TTT ACC AAG ATC-3′ R: 5′-GAA GAA AGC CTG TGA AGG TG-3′	339 bp

products were subsequently detected on a 3% agarose gel stained with ethidium bromide.

Statistical analysis

The genotype distributions of *AQIPOQ* gene SNPs were examined for Hardy–Weinberg equilibrium using Chi square analysis. Statistical procedures (ANOVA and frequency distributions) were performed using SPSS software (Version 19, SPSS Inc Company, USA). $P < 0.05$ was considered significant.

Results

Participant Characteristics

Four hundred young women from Northern Jordan agreed to participate in the study. They were divided into underweight (n = 78), normal weight (n = 116), overweight (n = 103), and obese (n = 103), according to BMI. Age, waist circumference, waist to hip ratio, and percent body fat were shown in Table 2.

Relationship of adiponectin with BMI

Plasma adiponectin range in the participants was 1.6-3.3 µg/ml. Adiponectin concentration in the plasma correlated with BMI (r = -0.23; p<0.0001). Additionally, as shown in Figure 1, the ANOVA revealed that adiponectin was lowest in the obese versus overweight, normal weight and underweight groups (p<0.01), without differences between the other groups (p>0.05).

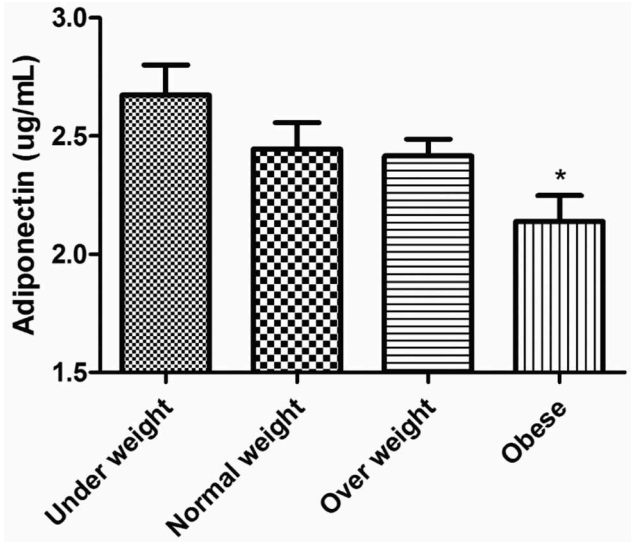

Figure 1. Plasma adiponectin levels among participants.
Plasma adiponectin levels were measured using ELISA procedure. Adiponectin plasma level was lower in obese participants compared to other groups. Data are expressed as mean ± SEM. $P < 0.05$ was considered significant.

Effect of ADIPOQ polymorphisms on BMI and adiponectin concentration

Tables 3 and 4, show the distribution of genotypes and alleles of *ADIPOQ* gene SNPs, G276T and I164T. The frequency of G allele of G276T SNP was 54.8%, while it was 45.2% for the A allele. Also the frequency of the C allele of I164T SNP was 58.3% while it was 41.7% for T allele. The distribution of alleles is in Hardy-Weinberg equilibrium.

No differences (p<0.05) in the distribution of *ADIPOQ* gene SNPs G276T (G versus A allele) and I164T genotypes (C versus T allele), according to BMI groups. The ANOVA in Table 5 shows no

Table 2. Clinical and biochemical characteristics of the study population.

	Underweight (n = 78)	Normal weight (n = 116)	Overweight (n = 103)	Obese (n = 103)	P-value*
Age (years)	21.15±3.134 ‡•	21.85±5.334 †•	24.77±9.07 †‡	30.82±12.1 †‡•	<0.0001*
BMI (kg/m^2)	17.62±0.858 ‡•	22.04±1.657 †•	26.9±1.305 †‡	34.24±4.09 †‡•	<0.001*
WC	65.4±3.231 ‡•	72.69±5.316 †•	82.73±5.65 †‡	96.42±9.21 †‡•	<0.0001*
Waist/hip ratio	0.74±0.04•	0.74±0.046 •	0.77±0.054 ‡	0.8±0.067 †‡•	<0.0001*
% BF	23.81±5.5 ‡•	27.31±5.316 †•	33.87±5.60 †‡	44.85±7.71 †‡•	<0.0001
TC	4.17±0.883	4.14±0.777	4.41±1.021	4.65±1.129 †‡	<0.0001
HDL	1.46±0.284	1.39±0.28	1.39±0.307	1.35±0.31 †‡•	0.129
LDL	2.33±0.769	2.38±0.745	2.62±0.887	2.74±0.808 †‡	0.0001
Triglycerides	0.81±0.424	0.76±0.312	0.9±0.347	1.29±0.692†‡•	<0.0001

Data were represented as mean±SD. *ANOVA test used. Post hoc tests: † = p<0.05 versus underweight. ‡ p<0.05 versus normal weight. • = p<0.05 versus overweight. WC: waist circumference; BMI: body mass index; WHR: waist to hip ratio; %BF: percent body fat; TC: total cholesterol; HDL: high-density lipoprotein; LDL: low-density lipoprotein.

Table 3. The genotype frequencies of adiponectin G276T SNP in BMI groups.

	G276T SNP*				
	GG N (%)	GT N (%)	TT N (%)	G allele N (%)	T allele N (%)
Underweight (n = 78)	24 (30.8)	43 (55.1)	11 (14.1)	91 (58.3)	65 (41.7)
Normal weight (n = 116)	22 (20)	82 (70.7)	12 (10.3)	126 (54.3)	106 (45.7)
Overweight (n = 103)	22 (21.4)	63 (61.2)	18 (17.4)	107 (51.9)	99 (48.1)
Obese (n = 103)	24 (23.3)	66 (64.1)	13 (12.6)	114 (55.3)	92 (44.7)

No significant difference using Chi square $p > 0.05$

Table 4. The genotype frequencies of adiponectin I164T SNP in BMI groups.

	I164T SNP*				
	CC N (%)	TC N (%)	TT N (%)	C allele N (%)	T allele N (%)
Underweight (n = 78)	14 (17.9)	63 (80.8)	1 (1.3)	91 (58.3)	65 (41.7)
Normal weight (n = 116)	22 (19)	90 (77.6)	4 (3.4)	134 (57.8)	98 (42.2)
Overweight (n = 103)	20 (19.4)	80 (77.7)	3 (2.9)	120 (58.3)	86 (41.7)
Obese (n = 103)	18 (17.5)	85 (82.5)	0 (0)	121 (58.7)	85 (41.3)

*No significant difference using Chi square $p > 0.05$

Table 5. Effect of G276T and I164T SNPs on adiponectin and BMI.

	G276T SNP		
	GG (n = 92)	GT (n = 254)	TT (n = 54)
Adiponectin	2462.8±838.1	2290.5±985.9*	2593.9±812.2
BMI	25.3±7.1	25.6±6.24	25.7±6.2
	I164T SNP		
	CC (n = 74)	CT (n = 318)	TT (n = 8)
Adiponectin	2524.5±897.6	2331.7±947.1	2516.7±787.7
BMI	25.3±6.3	25.6±6.5	24.0±4.2

* = $p<0.05$ versus GG and TT

differences ($p>0.05$) the participants' BMI or adiponectin between the G276T or I164T SNP genotypes.

Discussion

The current study examined the association of obesity with adiponectin level and genetic variations in young Jordanian women. The results showed correlations of BMI with plasma adiponectin but not with the examined *ADIPOQ* SNPs, the G276T and I164T.

The incidence of obesity has dramatically increased, reaching global epidemics.[21] Obesity is associated with several adverse effects as it increases the likelihood of various diseases, particularly heart disease, type 2 diabetes, obstructive sleep apnea, cancer, osteoarthritis and asthma.[22] The etiology is multifactorial; most commonly caused by a combination of excessive food energy intake, and lack of physical activity. However, in some cases it is caused by a genetic susceptibility, endocrine disorders, medications, or psychiatric illnesses.

The relationship of adiponectin with BMI, found herein, is consistent with the majority of previous reports, suggesting that adiponectin can positively modify obesity. Studies have shown that elevated circulatory adiponectin is associated with reduced obesity.[23-27] For example, overexpression of adiponectin by the transgene offsets the development of diet-induced obesity in rats.[28] In addition, administration of adiponectin decreases insulin resistance and circulatory glucose in animal models.[29]

The mechanisms through which adiponectin exerts these metabolic actions are largely unknown. It is believed, however, that adiponectin exerts insulin-mimetic and -sensitizing actions, including

stimulation of glucose uptake in skeletal muscle and suppression of glucose production in the liver.[30] In addition, adiponectin has been shown to decrease the influx of fatty acids in the liver and to increase fatty acid oxidation via PPAR activation, which lead to decreased body triglycerides.[31] In contrast, few studies presented lack of association between adiponectin level and BMI.[32,33]

The genotype frequencies of G276T SNPs of *ADIPOQ* gene were investigated and no interaction was found between the four BMI groups and genotypic distribution or differences in BMI and adiponectin between the genotypes of G276T and I164T SNPs. Several studies showed no differences in G276T SNP according to BMI groups in various populations. These populations include healthy Japanese,[34] type 2 diabetics,[35] black and white women,[23,26] none-diabetic Koreans,[36] Chinese with obstructive sleep apnea,[37] and Framingham offspring type 2 diabetics.[38]

On the other hand, different studies detected variation according to BMI. For example G/G genotype in women,[39] a G/T genotype in Italian none-diabetics and Taiwan elderly individuals[40,41] and G/G or G/T had higher BMI.[42] Meanwhile, T/T genotype was more frequent in lean individuals than nondiabetic obese Italians.[43] It appears that G276T polymorphism may not affect BMI in healthy individuals and may be related to BMI only in specific populations. Similarly, I164T polymorphism of adiponectin gene has shown the same trend. No significant association between genotype frequencies of I164T SNP and BMI categories which is in contrast with two studies among Japanese.[16,17]

It is noteworthy that BMI might be controlled by several environmental and genetic factors. For example, lifestyle plays a crucial role in gaining weight; such as physical activity and exercises, the amount and type of food intake, glycemic load and high-caloric diet.[44,45] Also, some acquired conditions like hypothyroidism or medications are known to cause weight gain or changes in body composition such as insulin, antidepressants, steroids, certain anticonvulsants (phenytoin and valproate), and hormonal contraception.[46] Moreover, genetic factors as polymorphisms in various genes controlling appetite and metabolism have been shown to predispose to obesity (e.g. fat mass and obesity associated gene FTO gene), as well as several rare genetic syndromes (e.g. Prader-Willi syndrome).[47] Therefore, the absence of association does not necessarily indicate a lack of effect because body composition changes may be conferred by a collection of variants rather than a single one.

Conclusions

The current study found that plasma adiponectin and BMI correlated negatively, with obese participants showed least adiponectin. However, BMI or adiponectin were not related to G276T and I164T SNPs of ADIPOQ gene in young adult women.

Conflict of interest

The authors have nothing to declare.

Acknowledgement

The current research was fully funded by the Deanship of Research in Jordan University of Science and Technology with grant number OK-MA 111–2014.

ORCID

Omar F. Khabour http://orcid.org/0000-0002-3006-3104

References

1. Reue K. Sex differences in obesity: X chromosome dosage as a risk factor for increased food intake, adiposity and co-morbidities. Physiology & behavior. 2017;176:174–82. doi:10.1016/j.physbeh.2017.02.040.
2. Yang C, Kong APS, Cai Z, Chung ACK. Persistent Organic Pollutants as Risk Factors for Obesity and Diabetes. Curr Diab Rep. 2017;17:132. doi:10.1007/s11892-017-0966-0. PMID:29098478
3. Luo L, Liu M. Adipose tissue in control of metabolism. J Endocrinol. 2016;231:R77–99. doi:10.1530/JOE-16-0211. PMID:27935822
4. Rega-Kaun G, Kaun C, Wojta J. More than a simple storage organ: adipose tissue as a source of adipokines involved in cardiovascular disease. Thromb Haemost. 2013;110:641–50. doi:10.1160/TH13-03-0212. PMID:23846791
5. Khan M, Joseph F. Adipose tissue and adipokines: the association with and application of adipokines in obesity. Scientifica. 2014;2014:328592. doi:10.1155/2014/328592. PMID:25309775
6. Al-Azzam SI, Khabour OF, Alzoubi KH, Mukattash TL, Ghanma M, Saleh H. The role of adiponectin

gene variants in glycemic control in patients with Type 2 diabetes. Endocr Res. 2014;39:13–7. doi:10.3109/07435800.2013.794427. PMID:23772547
7. Cottam D, Schaefer P, Shaftan G, Velcu L, George Angus L. Effect of Surgically-Induced Weight Loss on Leukocyte Indicators of Chronic Inflammation in Morbid Obesity. Obes Surg. 2002;12:335–42. doi:10.1381/096089202321088101. PMID:12082883
8. Ghadge AA, Khaire AA, Kuvalekar AA. Adiponectin: A potential therapeutic target for metabolic syndrome. Cytokine & growth factor reviews. 2018;39:151–158. doi:10.1016/j.cytogfr.2018.01.004.
9. Martin LJ. Implications of adiponectin in linking metabolism to testicular function. Endocrine. 2014;46:16–28. doi:10.1007/s12020-013-0102-0. PMID:24287788
10. Nagaraju GP, Aliya S, Alese OB. Role of adiponectin in obesity related gastrointestinal carcinogenesis. Cytokine & growth factor reviews. 2014.
11. Liu C, Feng X, Li Q, Wang Y, Li Q, Hua M. Adiponectin, TNF-alpha and inflammatory cytokines and risk of type 2 diabetes: A systematic review and meta-analysis. Cytokine. 2016;86:100–9. doi:10.1016/j.cyto.2016.06.028. PMID:27498215
12. Su JR, Lu ZH, Su Y, Zhao N, Dong CL, Sun L, Zhao SF, Li Y. Relationship of Serum Adiponectin Levels and Metformin Therapy in Patients with Type 2 Diabetes. Hormone and metabolic research = Hormon- und Stoffwechselforschung = Hormones et metabolisme. 2016;48:92–8. doi:10.1055/s-0035-1569287. PMID:26808583
13. Li Y, Li X, Shi L, Yang M, Yang Y, Tao W, Xiong Y, Zhang Y, Yao Y. Association of adiponectin SNP+45 and SNP+276 with type 2 diabetes in Han Chinese populations: a meta-analysis of 26 case-control studies. PLoS One. 2011;6:e19686. doi:10.1371/journal.pone.0019686. PMID:21589658
14. Vasseur F, Helbecque N, Dina C, Lobbens S, Delannoy V, Gaget S, Boutin P, Vaxillaire M, Leprêtre F, Dupont S, et al. Single-nucleotide polymorphism haplotypes in the both proximal promoter and exon 3 of the APM1 gene modulate adipocyte-secreted adiponectin hormone levels and contribute to the genetic risk for type 2 diabetes in French Caucasians. Hum Mol Genet. 2002;11:2607–14. doi:10.1093/hmg/11.21.2607. PMID:12354786
15. Li P, Jiang R, Li L, Liu C, Yang F, Qiu Y. Correlation of serum adiponectin and adiponectin gene polymorphism with metabolic syndrome in Chinese adolescents. Eur J Clin Nutr. 2014;69(1): 62–67.
16. Kotani K, Sakane N, Saiga K, Tsuzaki K, Hamada T, Kurozawa Y. Adiponectin I164T gene polymorphism and the obesity-related effects on the Japanese female population. Clin Chim Acta. 2007;384:182–3. doi:10.1016/j.cca.2007.06.006.
17. Ohashi K, Ouchi N, Kihara S, Funahashi T, Nakamura T, Sumitsuji S, Kawamoto T, Matsumoto S, Nagaretani H, Kumada M, et al. Adiponectin I164T mutation is associated with the metabolic syndrome and coronary artery disease. J Am Coll Cardiol. 2004;43:1195–200. doi:10.1016/j.jacc.2003.10.049. PMID:15063429
18. Khabour OF, Abu-Rumeh L, Al-Jarrah M, Jamous M, Alhashimi F. Association of adiponectin protein and ADIPOQ gene variants with lumbar disc degeneration. Experimental and therapeutic medicine. 2014;8:1340–4. doi:10.3892/etm.2014.1909. PMID:25187851
19. Adams GM, Beam WC. Exercise physiology: laboratory manual. Boston: McGraw-Hill;2008.
20. Khabour OF, Wehaibi SH, Al-Azzam SI, Alzoubi KH, El-Akawi ZJ. Association of Adiponectin with Hypertension in Type 2 Diabetic Patients: the Gender Effect. Clinical and experimental hypertension (New York, NY: 1993) 2012.
21. Xu L, Lam TH. Stage of obesity epidemic model: Learning from tobacco control and advocacy for a framework convention on obesity control. Journal of diabetes. 2018. doi:10.1111/1753-0407.12647.
22. Oestreich AK, Moley KH. Developmental and Transmittable Origins of Obesity-Associated Health Disorders. Trends Genet. 2017;33:399–407. doi:10.1016/j.tig.2017.03.008. PMID:28438343
23. Cohen SS, Gammon MD, North KE, Millikan RC, Lange EM, Williams SM, Zheng W, Cai Q, Long J, Smith JR, et al. ADIPOQ, ADIPOR1, and ADIPOR2 polymorphisms in relation to serum adiponectin levels and BMI in black and white women. Obesity (Silver Spring, Md). 2011;19:2053–62. doi:10.1038/oby.2010.346. PMID:21273992
24. Okauchi Y, Kishida K, Funahashi T, Noguchi M, Ogawa T, Ryo M, Okita K, Iwahashi H, Imagawa A, Nakamura T, et al. Changes in Serum Adiponectin Concentrations Correlate With Changes in BMI, Waist Circumference, and Estimated Visceral Fat Area in Middle-Aged General Population. Diabetes Care. 2009;32:e122. doi:10.2337/dc09-1130. PMID:19793996
25. Sanjari M, Khodashahi M, Gholamhoseinian A, Shokoohi M. Association of adiponectin and metabolic syndrome in women. Journal of research in medical sciences: the official journal of Isfahan University of Medical Sciences. 2011;16:1532–40.PMID:22973360
26. Cohen SS, Gammon MD, Signorello LB, North KE, Lange EM, Fowke JH, Hargreaves MK, Cai Q, Zheng W, Blot WJ, et al. Serum Adiponectin in Relation to Body Mass Index and Other Correlates in Black and White Women. Ann Epidemiol. 2011;21:86–94. doi:10.1016/j.annepidem.2010.10.011. PMID:21109453
27. Toda M, Tsukinoki R, Morimoto K. Measurement of salivary adiponectin levels. Acta Diabetol. 2007;44:20–2. doi:10.1007/s00592-007-0236-8. PMID:17357881
28. Shklyaev S, Aslanidi G, Tennant M, Prima V, Kohlbrenner E, Kroutov V, Campbell-Thompson M, Crawford J, Shek EW, Scarpace PJ, et al. Sustained peripheral expression of transgene adiponectin offsets the development of diet-induced obesity in rats. Proc Natl Acad Sci U S A. 2003;100:14217–22. doi:10.1073/pnas.2333912100. PMID:14617771

29. Diez JJ, Iglesias P. The role of the novel adipocyte-derived hormone adiponectin in human disease. Eur J Endocrinol. 2003;148:293–300. doi:10.1530/eje.0.1480293.
30. Fang X, Sweeney G. Mechanisms regulating energy metabolism by adiponectin in obesity and diabetes. Biochem Soc Trans. 2006;34:798–801. doi:10.1042/BST0340798. PMID:17052201
31. Combs TP, Pajvani UB, Berg AH, Lin Y, Jelicks LA, Laplante M, Nawrocki AR, Rajala MW, Parlow AF, Cheeseboro L, et al. A transgenic mouse with a deletion in the collagenous domain of adiponectin displays elevated circulating adiponectin and improved insulin sensitivity. Endocrinology. 2004;145:367–83. doi:10.1210/en.2003-1068. PMID:14576179
32. 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. doi:10.1038/ijo.2011.20. PMID:21364526
33. Pereira RI, Wang CC, Hosokawa P, Dickinson LM, Chonchol M, Krantz MJ, Steiner JF, Bessesen DH, Havranek EP, Long CS. Circulating adiponectin levels are lower in Latino versus non-Latino white patients at risk for cardiovascular disease, independent of adiposity measures. BMC Endocr Disord. 2011;11:13. doi:10.1186/1472-6823-11-13. PMID:21736747
34. Tsuzaki K, Kotani K, Sano Y, Fujiwara S, Gazi IF, Elisaf M, Sakane N. The relationship between adiponectin, an adiponectin gene polymorphism, and high-density lipoprotein particle size: from the Mima study. Metabolism. 2012;61:17–21. doi:10.1016/j.metabol.2011.06.021. PMID:21820140
35. Yoshioka K, Yoshida T, Umekawa T, Kogure A, Takakura Y, Toda H, Yoshikawa T. Adiponectin gene polymorphism (G276T) is not associated with incipient diabetic nephropathy in Japanese type 2 diabetic patients. Metabolism. 2004;53:1223–6. doi:10.1016/j.metabol.2004.03.021. PMID:15334388
36. Kim B, Jang Y, Paik JK, Kim OY, Lee S-H, Ordovas JM, Lee JH. Adiponectin Gene Polymorphisms Are Associated with Long-Chain ω3-Polyunsaturated Fatty Acids in Serum Phospholipids in Nondiabetic Koreans. Journal of Clinical Endocrinology & Metabolism. 2010;95:E347–E51. doi:10.1210/jc.2010-0391.
37. Cao J, Su SC, Huang HP, Ding N, Yin M, Huang M, Zhang XL. A preliminary study on correlation between adiponectin genotype polymorphisms and obstructive sleep apnea hypopnea syndrome. Chin Med J. 2012;125:2094–8.PMID:22884135
38. Hivert M-F, Manning AK, McAteer JB, Florez JC, Dupuis J, Fox CS, O'Donnell CJ, Cupples LA, Meigs JB. Common Variants in the Adiponectin Gene (ADIPOQ) Associated With Plasma Adiponectin Levels, Type 2 Diabetes, and Diabetes-Related Quantitative Traits. Diabetes. 2008;57:3353–9. doi:10.2337/db08-0700. PMID:18776141
39. Dolinkova M, Krizova J, Lacinova Z, Dolezalova R, Housova J, Krajickova J, Bosanska L, Papezova H, Haluzik M. [Polymorphisms of adiponectin and resistin genes in patients with obesity and anorexia nervosa]. Cas Lek Cesk. 2006;145:562–6.PMID:16921786
40. Filippi E, Sentinelli F, Trischitta V, Romeo S, Arca M, Leonetti F, Di Mario U, Baroni MG. Association of the human adiponectin gene and insulin resistance. Eur J Hum Genet. 2004;12:199–205. doi:10.1038/sj.ejhg.5201120. PMID:14673476
41. Yang W-S, Yang Y-C, Chen C-L, Wu I-L, Lu J-Y, Lu F-H, Tai T-Y, Chang C-J. Adiponectin SNP276 is associated with obesity, the metabolic syndrome, and diabetes in the elderly. Am J Clin Nutr. 2007;86:509–13. doi:10.1093/ajcn/86.2.509. PMID:17684226
42. Xita N, Georgiou I, Chatzikyriakidou A, Vounatsou M, Papassotiriou GP, Papassotiriou I, Tsatsoulis A. Effect of adiponectin gene polymorphisms on circulating adiponectin and insulin resistance indexes in women with polycystic ovary syndrome. Clin Chem. 2005;51:416–23. doi:10.1373/clinchem.2004.043109. PMID:15590747
43. Filippi E, Sentinelli F, Romeo S, Arca M, Berni A, Tiberti C, Verrienti A, Fanelli M, Fallarino M, Sorropago G, et al. The adiponectin gene SNP +276G>T associates with early-onset coronary artery disease and with lower levels of adiponectin in younger coronary artery disease patients (age <or = 50 years). J Mol Med. 2005;83:711–9. doi:10.1007/s00109-005-0667-z. PMID:15877215
44. Slack T, Myers CA, Martin CK, Heymsfield SB. The geographic concentration of US adult obesity prevalence and associated social, economic, and environmental factors. Obesity (Silver Spring, Md). 2014;22:868–74. doi:10.1002/oby.20502. PMID:23630100
45. Gianfrancesco MA, Acuna B, Shen L, Briggs FB, Quach H, Bellesis KH, Bernstein A, Hedstrom AK, Kockum I, Alfredsson L, et al. Obesity during childhood and adolescence increases susceptibility to multiple sclerosis after accounting for established genetic and environmental risk factors. Obesity research & clinical practice. 2014;8:e435–47. doi:10.1016/j.orcp.2014.01.002.
46. Panagiotopoulos C, Ronsley R, Davidson J. Increased prevalence of obesity and glucose intolerance in youth treated with second-generation antipsychotic medications. Can J Psychiatry. 2009;54:743–9. doi:10.1177/070674370905401104. PMID:19961662
47. Tauber M, Diene G, Mimoun E, Cabal-Berthoumieu S, Mantoulan C, Molinas C, Muscatelli F, Salles JP. Prader-Willi syndrome as a model of human hyperphagia. Front Horm Res. 2014;42:93–106.PMID:24732928