Analysis of -11391G>A and +45T>G polymorphisms of ADIPOQ gene in women with excessive weight gain during pregnancy

Analiza polimorfizmów -11391G>A oraz +45T>G genu ADIPOQ u kobiet z nadmiernym przyrostem masy ciała w ciąży

Hubert Wolski[1,2], Witold Kraśnik[1], Anna Bogacz[3,4], Joanna Bartkowiak-Wieczorek[3,4], Krzysztof Drews[1,5], Agnieszka Greber[3], Bogusław Czerny[6,7], Krzysztof Piątek[8], Agnieszka Seremak-Mrozikiewicz[1,4,5]

[1] Division of Perinatology and Women's Diseases, Poznan University of Medical Sciences, Poznan, Poland
[2] Division of Gynecology and Obstetrics, Podhale Multidisciplinary Hospital, Nowy Targ, Poland
[3] Laboratory of Experimental Pharmacogenetics, Department of Clinical Pharmacy and Biopharmacy, University of Medical Sciences, Poznan, Poland
[4] Department of Pharmacology and Phytochemistry, Institute of Natural Fibers and Medicinal Plants, Poznan, Poland
[5] Laboratory of Molecular Biology in Division of Perinatology and Women's Diseases, Poznan University of Medical Sciences, Poznan, Poland
[6] Department of General Pharmacology and Pharmacoeconomics, Pomeranian Medical University, Szczecin, Poland
[7] Department of Stem Cells and Regenerative Medicine, Institute of Natural Fibres and Medicinal Plants, Poznan, Poland
[8] Department of Gynecology and Obstetrics with Gynecological Oncology Subdivision, Regional Hospital in Zielona Góra, Poland

Abstract

Objectives: *The aim of our study was to evaluate the frequency of genotypes and alleles of the -11391G>A and +45T>G polymorphisms of the ADIPOQ gene in Polish women with excessive weight gain during pregnancy. A possible correlation between these polymorphisms and selected clinical and anthropometric parameters has been analyzed.*

Material and methods: *A total of 153 pregnant Caucasian women of Polish origin with normal pre-pregnancy body mass were analyzed: 78 women with excessive weight gain (study group) and 75 women with normal weight gain during pregnancy (control group). The analysis of the polymorphisms was performed by PCR/RFLP.*

Results: *The influence of the -11391G>A polymorphism on body mass and BMI values at the end of pregnancy ($p<0.05$) was observed. We also detected a correlation of the +45T>G polymorphism with body mass at the end of pregnancy and pre-pregnancy WHR values ($p<0.05$).*

Conclusions: *The observed effect of the -11391G>A polymorphism on the parameters assessed at the end of pregnancy (BMI and body mass), suggests a protective role of the -11391A genetic variant in excessive weight gain. It is claimed that the mutated +45G allele of the +45T>G ADIPOQ polymorphism shows a possible connection with higher pre-pregnancy WHR values and body mass at the end of pregnancy. Our findings suggest a possible contribution of the -11391G>A and +45T>G polymorphisms of the ADIPOQ gene to the pathomechanism of excessive weight gain in pregnant women from the Polish population. This observation should be confirmed in a larger sample size study.*

Key words: **excessive weight gain** / **genetic polymorphism** / **adiponectin** / **ADIPOQ** /

Corresponding author:
Magdalena Barlik
Department of Perinatology and Women's Diseases, University of Medical Sciences, Poznan, Poland
ul. Polna 33, 60-535 Poznań, Poland
tel. 0048 61 8419 613
e-mail: magda.barlik@op.pl

Otrzymano: **13.05.2014**
Zaakceptowano do druku: **17.08.2014**

Streszczenie

Cel pracy: *Celem pracy była ocean częstości występowania genotypów i alleli polimorfizmu -11391G>A oraz +45T>G genu ADIPOQ u kobiet z nadmiernym przyrostem masy ciała w ciąży w populacji polskiej. Zbadano również korelację obydwu polimorfizmów z wybranymi parametrami klinicznymi i antropometrycznymi.*

Materiały i metody: *Badaniem objęto 153 kobiety ciężarne rasy kaukaskiej z prawidłową masą ciała: 78 kobiet z nadmiernym oraz 75 kobiet z prawidłowym przyrostem masy ciała w ciąży stanowiących grupę kontrolną. Analizę badanych polimorfizmów przeprowadzono z wykorzystaniem metody PCR/RFLP.*

Wyniki: *Odnotowano wpływ polimorfizmu -11391G>A na masę ciała i wartość BMI pod koniec ciąży ($p<0.05$). Obserwowano również korelację polimorfizmu +45T>G z masą ciała pod koniec ciąży i wartość WHR przed ciążą ($p<0.05$).*

Wnioski: *Obserwowany wpływ polimorfizmu -11391G>A na parametry badane po koniec ciąży: wskaźnik BMI oraz masę ciała, sugeruje protekcyjną rolę wariantu -11391A na nadmierny przyrost masy ciała. Potwierdzono, że zmutowany allel +45G polimorfizmu +45T>G wykazuje możliwy związek z większą wartością WHR przed ciążą oraz masą ciała pod koniec ciąży. Uzyskane wyniki sugerują możliwy udział polimorfizmów -11391G>A oraz +45T>G genu ADIPOQ z w patomechanizmie nadmiernego przyrostu masy ciała u ciężarnych kobiet z populacji polskiej. Obserwacja ta powinna być potwierdzona w większej liczebnie grupie pacjentek.*

Słowa kluczowe: **nadmierny przyrost masy ciała** / **polimorfizm genetyczny** / / **adiponektyna** / **ADIPOQ** /

Introduction

In the general population, excessive weight gain and obesity are the causes of cardiovascular complications, atherosclerosis, hypertension, diabetes due to insulin resistance, and respiratory disorders. Maternal overweight and obesity induce a number of antenatal and intra-partum complications and, consequently, the need for special perinatal care [1, 2]. Recently, much attention has been paid to overweight and obesity, pathological accumulation of adipose tissue and contribution of adipocytokines in this process.

Adiponectin (APM1) belongs to the adipocytokine family and its largest quantities are produced in adipose tissue [3,4]. Its concentration decreases in obesity, insulin resistance or type 2 diabetes, negatively correlating with body mass, fat accumulation and body mass index (BMI), as well as age and sex (lower in men than in women) [5]. APM1 supports the action of insulin, inhibiting the process of gluconeogenesis and hepatic synthesis of fatty acids. This protein plays an essential role in the regulation of lipid and glucose metabolism [6]. It reduces the flow of low-esterified fatty acids through the liver, affects fatty acid oxidation, reduces the glucose formation in the liver, and increases its metabolism in skeletal muscles [4]. It also affects appetite control via receptors in the hypothalamus [7].

Adiponectin acts as an anti-inflammatory and anti-atherogenic agent [8, 9]. It acts directly on the vascular endothelium with a vasoprotective effect, inhibits the conversion of macrophages into foam cells, increases nitric oxide synthesis, and inhibits the adhesion of monocytes to the endothelial cells [10, 11, 12]. Furthermore, APM1 inhibits the activation and proliferation of immunologically active cells, thereby reducing pro-inflammatory cytokine secretion [13, 14].

A decreased level of adiponectin positively correlates with the occurrence of metabolic syndrome and increased insulin resistance, especially in patients with abdominal obesity. APM1 is connected with higher concentration of free fatty acids, triglycerides, LDL-cholesterol, and lower HDL cholesterol levels. In addition, decreased level of APM1, which is associated with decreased protective effect on the vascular wall, leads to hypertension and development of arteriosclerosis, i.e. two components of metabolic syndrome [15]. The gene encoding for APM1 (*ADIPOQ* gene) contains sequences whose expression may influence carbohydrate metabolism and lipid composition of adipose tissue: receptor activated by peroxisome proliferators (PPAR), protein binding element regulating sterols (SREBP), and the glucocorticoid receptor (GR) [16,17]. APM1 expression is decreased in obese patients, which is the result of glucocorticoid, TNF-γ, and β-adrenergic receptor agonists action [12, 14, 18].

The aim of our study was to evaluate the frequency of genotypes and alleles of the *-11391G>A* and *+45T>G* polymorphisms of the *ADIPOQ* gene in Polish pregnant women with excessive weight gain during pregnancy. A possible correlation between these polymorphisms of the *ADIPOQ* gene and selected clinical and anthropometric parameters has been also investigated.

Material and methods

Patients:

A total of 153 pregnant Caucasian women, inhabitants of the Wielkopolska region, nondiabetic, with normal pre-pregnancy body mass, were analyzed: 78 women with excessive weight gain during pregnancy (mean age 27.4±4.7 years, mean body mass 58.9±6.4 kg, BMI and WHR before pregnancy 21.27 kg/m² and 0.72, respectively, BMI at the end of pregnancy 28.07 kg/m², δBMI 6.81) and 75 controls with correct weight gain (mean age 26.7±4.3 years, mean body mass before pregnancy 55.3±6.2 kg, BMI and WHR before pregnancy 20.06 kg/m² and 0.71, respectively, BMI at the end of pregnancy 22.70 kg/m², δBMI 3.19). Clinical studies were performed at the Division of Perinatology and Women's Diseases, Poznan University of Medical Sciences. The results of the anthropometric examinations, i.e. height, body mass, and BMI, were calculated before and at the end of pregnancy (within 48 hours before birth). The waist and hip circumference needed to calculate the waist-hip ratio (WHR) were measured before pregnancy. Evaluation of placental and newborn birth weight was also included. All patients gave their written informed consent. Local Bioethics Committee approved of the study (No. 903/03).

Analysis of -11391G>A and 45T>G polymorphisms:

Genetic analysis was performed at the Laboratory of Experimental Pharmacogenetics, Department of Clinical Pharmacy and Biopharmacy, Poznan University of Medical Sciences, Poland. DNA was isolated from peripheral blood leukocytes using QIAamp DNA Blood Mini Kit (Qiagen, USA). Analysis of the *-11391G>A* and *+45T>G* polymorphisms of the ADIPOQ gene was performed by polymerase chain reaction and restriction fragment length polymorphism (PCR/RFLP) method. Primer sequences for the *-11391G>A* polymorphism of the *ADIPOQ* gene were as follows: forward 5'-GGT GCT GGC ATC CTA AGC C-3', reverse 5'-TGA CAG CTA CCT TGG TAT GTG, and for the *+45T>G* polymorphism: forward 5'-TGG ACG GAG TCC TTT GTA GG-3', reverse 5'-CCT TTC TCA CCC TTC TCA CC-3'. PCR reactions were performed in a thermocycler (PTC-200, MJ Research, USA). The PCR products were subjected to restriction analysis, for which the *Msp*I and *Sma*I restriction enzymes were used. In order to analyze the genotypes, the RFLP products were subjected to electrophoretic separation in a 2.75% agarose gel. The length of fragments for the *-11391G>A ADIPOQ* polymorphism was as follows: for the *-11391GG* genotype 253 bp, 68 bp, for *-11391GA* genotype 321 bp, 253 bp, 68 bp, and for the *-11391AA* genotype 321 bp. The observed fragments for the *+45T>G ADIPOQ* polymorphism were: for *+45TT* genotype 298 bp, for *+45TG* genotype 298 bp,164 bp, 134 bp, and for *+45GG* genotype 164 bp, 134 bp. PCR/RFLP results were analyzed in agarose gels by visualization in the UV light using documentation system (KS 4000/Image PC, Syngen Biotech Molecular Biology Instruments).

Statistical analysis:

The statistical significance of differences between control and study groups was assessed by SPSS 17.0 software using one-way ANOVA test (SPSS Inc.). The value of $p<0.05$ was considered as statistically significant.

Results

The analysis revealed statistically significant differences for the values of pre-pregnancy body mass (control group 55.3±6.2 kg, study group 58.9±6.4 kg, $p=0.001$) and at the end of pregnancy (control group 61.8±9.3 kg, study group 77.5±8.8 kg, $p<0.0001$); pre-pregnancy BMI (control group 20.06 kg/m², study group 21.27 kg/m², $p<0.0001$) and at the end of pregnancy (control group 22.70 kg/m², study group 28.07 kg/m², $p<0.0001$). Infant status based on their birth mass was also compared. A statistically significantly higher mean newborn birth mass was observed in the study group as compared to controls (p=0.001).

The frequency of the analyzed genotypes of the *-11391G>A* and *+45T>G* polymorphisms of the ADIPOQ gene was consistent with the Hardy-Weinberg law. The analysis of the *-11391G>A* polymorphism showed a similar frequency of genotypes and alleles in both investigated groups. There was a higher incidence of homozygous dominant *-11391GG* genotypes in both groups (83.3% and 86.67% in the study group and controls, respectively). The presence of the recessive homozygous *-11391AA* genotypes was not observed. For *+45T>G ADIPOQ* polymorphism, the *+45TT* genotype occurred most often in both groups (92.31% in overweight women, 92% in controls). Homozygous recessive genotype *45GG* was present in one case in the study group (1.28%). No differences in the occurrence of genotypes and alleles of the *+45T>G* ADIPOQ polymorphism between both analyzed groups were found (Tables I and II).

Additionally, the analysis of a correlation between selected clinical and anthropometric parameters and particular genotypes of the *-11391G>A* and *+45T>G* polymorphism was also performed. In women with excessive weight gain, body mass as well as BMI values at the end of pregnancy were lower in carriers of the *-11391GA* genotype than in carriers of the *-11391GG* genotype ($p<0.05$). Also, body mass at the end of pregnancy and WHR before pregnancy were higher in carriers of the heterozygous *+45TG* genotype as compared to the *+45TT* genotype ($p<0.05$).

Discussion

Adipose tissue produces a multitude of hormones contributing to excessive weight gain and development of obesity. A number of studies have confirmed a negative correlation with clinical parameters (body weight, BMI, WHR). Additionally, several studies have also shown the significance of genetic polymorphism of the *ADIPOQ* gene in overweight and obese patients.

Menzaghi et al., performed a meta-analysis that showed a correlation of the *-11391A* allele of the *-11391G>A ADIPOQ* polymorphisms with increased concentration of adiponectin [5]. Another study conducted on Iranian male population revealed lower BMI values in individuals with the *-11391GA* and *-11391AA* genotypes (mean BMI 21 kg/m² for *-11391GA/-11391AA vs*. 24 kg/m² for *-11391GG* ($p=0.041$)). Also, in the female population mean BMI was higher in carriers of the *-11391GG* genotype (27 kg/m²) as compared to the carriers of the *-11391GA* and *-11391AA* genotypes (25 kg/m², $p=0.038$). That study also showed a higher waist circumference in individuals with the *-11391GG* genotype. Additionally, male carriers of the *+45TT* genotype of *+45T>G* ADIPOQ polymorphism had significantly higher BMI values than their male peers with the *45GG* genotype ($p=0.018$) [19].

In our study, the analysis of the *-11391G>A ADIPOQ* polymorphism confirmed its impact on the clinical parameters such as body mass and BMI values at the end of pregnancy. The obtained results indicated higher BMI value and body mass in women with the *-11391GG* genotype as compared to carriers of the *-11391GA* genotype ($p<0.05$). Mean BMI at the end of pregnancy was 28.41 kg/m² for homozygous *-11391GG* genotype and 26.36 kg/m² for heterozygous *-11391GA* genotype ($p<0.05$).

Similar results were demonstrated in a study carried out on a Caucasian-American population. A correlation between genotypes and the examined anthropometric parameters was also observed. Carriers of the *-11391A* allele had a statistically significantly lower body mass ($p=0.029$), BMI (p=0.019), waist circumference ($p=0.003$), and hip circumference ($p=0.004$), what may suggest a protective effect of this genetic variant [20].

In contrast, a meta-analysis carried out on a group of children from Spain and Italy showed that carriers of the *-11391AA* and *-11391GA* genotypes had elevated adiponectin levels and higher BMI, what suggests that *-11391A* allele correlates with the occurrence of obesity. Additionally, mean BMI value was 22.1 kg/m² for the wild-type (*-11391GG*) and 23.7 kg/m² for the *-11391GA* and *-11391AA* genotypes, respectively [21].

In our study, we also examined the impact of the *+45T>G* polymorphism of the *ADIPOQ* gene on selected clinical

Table I. The frequency of genotypes and alleles of -11391G>A ADIPOQ polymorphism.

	Women with excessive weight gain during pregnancy		Women with correct weight gain during pregnancy	
	Observed value n (%)	Expected value %	Observed value n (%)	Expected value %
Genotypes				
-11391GG	65 (83.33)	84.04	65 (86.67)	87.1
-11391GA	13 (16.67)	15.27	10 (13.33)	12.5
-11391AA	0 (0,00)	0.69	0 (0.00)	0.4
Total	**78 (100)**	**100**	**75 (100)**	**100**
Alleles				
-11391G	143 (91.67)		140 (93.33)	
-11391A	13 (8.33)		10 (6.67)	
Total	**156 (100)**		**150 (100)**	

Table II. The frequency of genotypes and alleles of +45T>G ADIPOQ polymorphism.

	Women with excessive weight gain during pregnancy		Women with correct weight gain during pregnancy	
	Observed value n (%)	Expected value %	Observed value n (%)	Expected value %
Genotypes				
+45TT	72 (92.31)	92.41	69 (92.00)	92.16
+45TG	5 (6.41)	7.44	6 (8.00)	7.68
+45GG	1 (1.28)	0.15	0 (0.00)	0.16
Total	**78 (100)**	**100**	**75 (100)**	**100**
Alleles				
+45T	149 (96.13)		144 (96.00)	
+45G	6 (3.87)		6 (4.00)	
Total	**155 (100)**		**150 (100)**	

parameters. The obtained results showed an increase in body weight at the end of pregnancy and WHR before pregnancy in carriers of the *45TG* genotype as compared to carriers of the *+45TT* genotype ($p<0.05$).

The effect of the *+45T>G ADIPOQ* polymorphism on the risk of excessive weight gain and obesity has been proven in numerous studies, but the results remain unclear. For *+45T>G* polymorphism, the impact on the concentration of the hormone-encoding gene by itself was also observed [22]. Several studies have shown that the presence of the mutated 45G allele is associated with elevated BMI values, and consequently an increased risk of excessive weight gain, overweight, and obesity. This relationship was observed in a group of 371 patients. The authors showed a higher BMI for the *+45GG* genotype and *+45TG* as compared to the *+45TT* genotype. In addition, they also claimed that the *+45G* allele was significantly associated with obesity. The BMI for *homozygous wild*-type *genotype carriers* averaged 25.3 kg/m², heterozygous *+45TG* genotype 26.7 kg/m² and mutant homozygous *+45GG* genotype 27.6 kg/m² (p=0.02). Based on the above research, it was concluded that the presence of *+45GG* and *+45TG* genotypes may increase the risk of obesity and insulin resistance [23]. Similar results were obtained in a meta-analysis performed by Wu et al. They summarized 18 studies (2819 obese patients and 3024 controls), indicating that the GG genotype was associated with augmentation of obesity [24].

Other studies found no correlation between the *+45T>G* polymorphism and obesity. In Chinese population, no relationship

between the studied *+45T>G* polymorphism and clinical parameters was observed. The *+45GG* genotype occurred in 19.71% and 14.49% of patients with BMI of 30.8 kg/m² and 22.4 kg/m², respectively (p>0.05) [25]. Based on the abovementioned results, at present the influence of the *+45T>G* polymorphism on excessive weight gain and obesity cannot be not confirmed.

The majority of studies confirmed the effect of *ADIPOQ* gene polymorphisms on clinical parameters such as body weight, BMI, WHR, as well as its involvement in the pathogenesis of excessive weight gain and obesity. Obesity, a disease of complex etiology, is probably conditioned by simultaneous cooperation of several polymorphisms that act together with hormones, cytokines and environmental factors (diet, physical activity, nutritional status). Ethnic differences among the examined populations should be additionally evaluated. Thus, further genetic studies on a larger population are needed to predict the polymorphic sites which will serve as genetic markers in assessing the risk of excessive weight gain and obesity [9, 26, 27, 28].

Conclusions

1. The observed effect of the *-11391G>A ADIPOQ* polymorphism on parameters assessed at the end of pregnancy (BMI and body mass), suggests a protective role of the -11391A genetic variant in excessive weight gain.
2. The mutated *+45G* allele of the *+45T>G ADIPOQ* polymorphism shows a possible connection with higher pre-pregnancy WHR and body mass at the end of pregnancy.
3. Our findings suggest a possible contribution of the *-11391G>A* and *+45T>G* polymorphisms of the *ADIPOQ* gene to the pathomechanism of excessive weight gain in pregnant women from the Polish population. This observation should be confirmed in a larger group of patients.

Oświadczenie autorów:

1. Hubert Wolski – autor koncepcji i założeń pracy, analiza i interpretacja wyników, przygotowanie manuskryptu i piśmiennictwa, zebranie materiału – autor zgłaszający i odpowiedzialny za manuskrypt,.
2. Witold Kraśnik – zebranie materiału, analiza statystyczna wyników, przygotowanie manuskryptu.
3. Anna Bogacz – współautor tekstu pracy i protokołu, korekta i aktualizacja literatury.
4. Joanna Bartkowiak-Wieczorek – analiza i interpretacja wyników, przygotowanie, korekta i akceptacja ostatecznego kształtu manuskryptu.
5. Krzysztof Drews – analiza i interpretacja wyników, przygotowanie, korekta i akceptacja ostatecznego kształtu manuskryptu.
6. Agnieszka Greber – wykonanie badań laboratoryjnych, opracowanie wyników badań, przechowywanie dokumentacji.
7. Bogusław Czerny – analiza i interpretacja wyników, przygotowanie, korekta i akceptacja ostatecznego kształtu manuskryptu.
8. Krzysztof Piątek – zebranie materiału, analiza statystyczna wyników, przygotowanie manuskryptu.
9. Agnieszka Seremak-Mrozikiewicz – analiza i interpretacja wyników, ostateczna weryfikacja oraz akceptacja manuskryptu.

Źródło finansowania:

Badania statutowe Kliniki Perinatologii i Chorób Kobiecych, Uniwersytet Medyczny im. Karola Marcinkowskiego w Poznaniu; No. 502-01-02218344-03344.

Konflikt interesów:

Autorzy nie zgłaszają konfliktu interesów oraz nie otrzymali żadnego wynagrodzenia związanego z powstawaniem pracy.

References

1. Kushner RF, Blatner DJ. Risk assessment of the overweight and obese patient. *J Am Diet Assoc.* 2005, 105, 53-62.
2. Kozakowski J, Kapuścińska R, Zgliczyński W. Associations of vitamin D concentration with metabolic and hormonal indices in women with polycystic ovary syndrome presenting abdominal and gynoidal type of obesity. *Ginekol Pol.* 2014, 85, 765-770.
3. Lee H, Lee IS, Choue R. Obesity, inflammation and diet. Pediatr Gastroenterol Hepatol Nutr. 2013, 16, 143-152. doi: 10.5223/pghn.2013.16.3.143.
4. Nigro E, Scudiero O, Monaco ML, [et al.]. New insight into adiponectin role in obesity and obesity-related diseases. *Biomed Res Int.* 2014;2014:658913. doi: 10.1155/2014/658913.
5. Menzaghi C, Trischitta V, Doria A. Genetic influences of adiponectin on insulin resistance, type 2 diabetes, and cardiovascular disease. *Diabetes.* 2007, 56, 1198-209.
6. Kadowaki T, Yamauchi T. Adiponectin and adiponectin receptors. *Endocr Rev.* 2005, 26, 439-451.
7. Qi Y, Takahashi N, Hileman SM, [et al.]. Adiponectin acts in the brain to decrease body weight. *Nat Med.* 2004, 10, 524-529.
8. Fantuzzi G. Adiponectin in inflammatory and immune-mediated diseases. *Cytokine.* 2013, 64, 1-10. doi: 10.1016/j.cyto.2013.06.317.
9. Scotece M, Conde J, López V, [et al.]. Adiponectin and leptin: new targets in inflammation. *Basic Clin Pharmacol Toxicol.* 2014, 114, 97-102. doi: 10.1111/bcpt.12109.
10. Lee YY, Lee NS, Cho YM, [et al.]. Genetic association study of adiponectin polymorphisms with risk of Type 2 diabetes mellitus in Korean population. *Diabet Med.* 2005, 22, 569-575.
11. Withers SB, Bussey CE, Saxton SN, [et al.]. Mechanisms of adiponectin-associated perivascular function in vascular disease. *Arterioscler Thromb Vasc Biol.* 2014, 34, 1637-1642. doi: 10.1161/ATVBAHA.114.303031.
12. Ntaios G, Gatselis NK, Makaritsis K, Dalekos GN. Adipokines as mediators of endothelial function and atherosclerosis. *Atherosclerosis.* 2013, 227, 216-221.
13. Gómez R, Conde J, Scotece M, [et al.]. What's new in our understanding of the role of adipokines in rheumatic diseases? *Nat Rev Rheumatol.* 2011, 7, 528-536.
14. Itoh N. FGF21 as a Hepatokine, Adipokine, and Myokine in Metabolism and Diseases. Front Endocrinol (Lausanne). 2014, 5, 107. doi: 10.3389/fendo.2014.00107. *eCollection* 2014.
15. Sabouri S, Ghayour-Mobarhan M, Moohebati M, [et al.]. Association between 45T/G Polymorphism of Adiponectin Gene and Coronary Artery Disease in an Iranian Population. *Scientific World Journal.* 2011, 11, 93-101.
16. Lim S, Quon MJ, Koh KK. Modulation of adiponectin as a potential therapeutic strategy. *Atherosclerosis.* 2014, 233, 721-728. doi: 10.1016/j.atherosclerosis.2014.01.051.
17. Shibata R, Ohashi K, Murohara T, Ouchi N. The potential of adipokines as therapeutic agents for cardiovascular disease. *Cytokine Growth Factor Rev.* 2014, 25, 483-487. doi: 10.1016/j.cytogfr.2014.07.005.
18. de Faria AP, Modolo R, Fontana V, Morenott A. Adipokines: novel players in resistant hypertension. *J Clin Hypertens* (Greenwich). 2014, 16, 754-759. doi: 10.1111/jch.12399.
19. Tabatabaei-Malazy Z, Hasani-Ranjbar S, Amdi MM, [et al.]. Gender-specific differences in the association of adiponectin gene polymorphisms with body mass index. *Rev Diabet Stud.* 2010, 7, 241-246.
20. Warodomwichit D, Shen J, Arnett DK, [et al.]. ADIPOQ polymorphisms, monounsaturated fatty acids, and obesity risk: the GOLDN study. *Obesity* (Silver Spring). 2009, 17, 510-517.
21. Morandi A, Maffeis C, Lobbens S, [et al.]. Early detrimental metabolic outcomes of rs17300539-A allele of ADIPOQ gene despite higher adiponectinemia. *Obesity* (Silver Spring). 2010, 18, 1469-1473.
22. Lee S, Kwak HB. Role of adiponectin in metabolic and cardiovascular disease. J Exerc Rehabil. 2014, 10, 54-59. doi: 10.12965/jer.140100.
23. Yang WS, Ling Tsou PL, Lee WJ, [et al.]. Allele-specific differential expression of a common adiponectin gene polymorphism related to obesity. *Mol Med.* 2003, 81, 428-434.
24. Wu J, Liu Z, Meng K, Zhang L. Association of adiponectin gene (ADIPOQ) rs2241766 polymorphism with obesity in adults: a meta-analysis. PLoS One. 2014, 9(4):e95270. doi: 10.1371/journal.pone.0095270.
25. Yan WL, Chen SF, Huang JF, [et al.]. Common SNPs of APM1 gene are not associated with hypertension or obesity in Chinese population. *Biomed Environ Sci.* 2006, 19, 179-184.
26. Fisman EZ, Tenenbaum A. Adiponectin: a manifold therapeutic target for metabolic syndrome, diabetes, and coronary disease? *Cardiovasc Diabetol.* 2014, 13, 103. doi: 10.1186/1475-2840-13-103.
27. O'Neill SM, Hinkle C, Chen SJ, [et al.]. Targeting adipose tissue via systemic gene therapy. *Gene Ther.* 2014, 21, 653-661. doi: 10.1038/gt.2014.38.
28. Khan S, Shukla S, Sinha S, Neeran SM. Role of adipokines and cytokines in obesity-associated breast cancer: therapeutic targets. *Cytokine Growth Factor Rev.* 2013, 24, 503-513. doi: 10.1016/j.cytogfr.2013.10.001.