

Adiponectin and its polymorphism: relation to coronary artery disease

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Background

Adiponectin is an adipocytokine with important role in atherosclerosis. Increasing interest has been directed toward the role of adiponectin gene polymorphism in the human genome and its implication in the pathogenesis of coronary artery disease (CAD).

Objectives

The present study investigates the association between the single nucleotide polymorphism +276 G/T of the adiponectin gene and serum adiponectin level in patients with CAD.

Methods

In this study, 100 Egyptian patients with CAD of both sexes and 100 age-matched and sex-matched control volunteers were investigated. All patients were genotyped for +276 G/T polymorphism of adiponectin gene. Lipid profile, fasting blood glucose, and hemoglobin A1c were measured. Adiponectin and high-sensitivity C-reactive protein (hsCRP) levels were determined by ELISA technique. PCR based on restriction fragment length polymorphism was used to determine the genotypes of the studied population.

Results

The lowest serum adiponectin value was observed in patients with CAD compared with control group. The T allele of single nucleotide polymorphisms (SNPs) +276 G/T in the adiponectin gene was found to be associated with CAD (odd ratio 2.23; 95% confidence interval: 1.44–3.45; P=0.001). The significant association of the T allele (GT+TT) of this SNP with lower adiponectin level and hsCRP levels was confirmed in the study (P=0.003 and 0.006, respectively).

Conclusions

Our results concluded that +276 G/T SNP in the adiponectin gene is associated with CAD. Furthermore, carriers of the at-risk T allele had lower serum adiponectin level and higher serum hsCRP, causing in turn an increased risk to develop CAD.

Keywords:

adiponectin gene, coronary artery disease, PCR-RFLP, polymorphism

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Introduction

Adipose tissue, especially visceral fat, is considered as an endocrine organ not merely a store of excess energy, directly involved in the pathophysiology of the metabolic syndrome and cardiovascular diseases. In fact, visceral fat accumulation is recognized as a key player in the occurrence of multiple risk factors for coronary artery disease (CAD) and in vascular changes [1].

Adiponectin is an adipocytokine, secreted from white adipose tissue. Some studies suggest that it is also synthesized by osteoblasts, cardiomyocytes, and skeletal muscle [2]. It is a 30-kDa collagen-like protein, with favorable antiatherogenic and antidiabetic properties at elevated levels [3,4]. The average plasma concentration of this hormone ranges between 5 and 10 µg/ml, and levels vary according to sex, body fat distribution, and metabolic status [5].

Levels of circulating adiponectin are 30–80% heritable, suggesting that they are, at least partly, under genetic control. The ADIPOQ gene in chromosome 3q27 and several other loci has been reported by genome-wide association studies to associate with serum adiponectin [6–8].

Low adiponectin has been linked to the presence of CAD [9] and has been shown to be a risk factor for cardiovascular events [10]. Hypoadiponectinemia is strongly linked to central adiposity, dyslipidemia, insulin resistance, and high blood pressure [11,12]. Adiponectin also has anti-inflammatory properties

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affecting the nuclear factor- α pathway and inhibiting monocyte adhesion to aortic endothelial cells [13].

Many old gene association studies showed that single nucleotide polymorphisms (SNPs) of adiponectin gene affect the adiponectin production in adipose tissue and modulate circulating adiponectin, but results are controversial and inconsistent [14]. SNP +276 G/T (rs1501299) has been associated with low serum adiponectin level, insulin resistance, and diabetes [15].

However, recent studies investigated adiponectin in CAD are still controversial [16]. Some studies did not support a causal role of adiponectin levels in CAD pathogenesis [17] and others named it as a predictor of increased cardiovascular and all-cause mortality rate [18].

Many studies had investigated SNP of adiponectin gene, but none of them as far as we know was on Egyptian patients with CAD. Therefore, the aim of this study was to investigate the association between SNP +276 G/T of the adiponectin gene and serum adiponectin level in patients with CAD in a cross-sectional case-control study among a group of Egyptians.

Patients and methods

Patients

A cross-sectional case-control study was conducted on a total of 200 Egyptian subjects from Kasr Al Aini Hospital from September 2017 to November 2018. A total of 100 patients with CAD, with mean age of 53.8 \pm 5.2 years, were recruited from critical care medicine unit and internal medicine department. Control patients were 100 unrelated individuals without history of CAD and have normal ECG and echocardiography findings, having a mean age of 55.3 \pm 6.3 years. Diagnosis of CAD was done by coronary angiography (presence of one or more stenosis >50% in at least one major coronary artery). Patients with current liver or renal disease were excluded from the study. Diagnosis of type 2 diabetes mellitus was based on fasting blood glucose of at least 126 mg/dl, hemoglobin A1c of at least 6.5%, and/or history of hypoglycemic treatment [19]. Diagnosis of hypertension was based on the presence of elevated systolic and/or diastolic blood pressure of at least 140/90 mmHg and/or the current use of antihypertensive medications according to Eighth Joint National Committee guidelines [20]. The study protocol was approved by the ethics committee of our institution, and all patients gave informed consent before participation.

Laboratory methods

Fasting serum glucose, hemoglobin A1c, total cholesterol, triglycerides, and high density lipoproteins-cholesterol (HDL-C) were determined by manual enzymatic colorimetric assays (Analyticon Biotechnologies, Lichtenfels, Germany). Low density lipoproteins-cholesterol (LDL-C) was calculated according to the Friedewald formula [21]. Serum adiponectin and high-sensitivity C-reactive protein (hsCRP) levels were measured by ELISA technique using Quantikine human total adiponectin (R&D System, Minneapolis, Minnesota, USA) [22] and hsCRP (DRG International Inc., Springfield Township, New Jersey, USA) [23].

DNA analysis

DNA was isolated from whole blood using Wizard genomic DNA purification kit (Promega, USA) according to the manufacturer's protocol. PCR-restriction fragment length polymorphism method was used to determine the distribution of genotype and alleles frequencies of the SNP +276 G/T of adiponectin gene. The PCR was performed in a total volume of 25 μ l containing 5 U of Taq DNA polymerase (Bioron, Ludwigshafen, Germany), 0.1 mmol/l of each dNTP (Bioron), and 1 μ mol of each of the primers (Metabion International AG, Planegg, Germany). Amplification was done by initial denaturation at 94°C for 5 min followed by 30 cycles of 95°C for 1 min, 58°C for 1 min and 72°C for 1 min. Final extension of 5 min at 72°C was done. PCR fragments (196 bp) were digested using the restriction endonuclease BsmI (Fermentas, St Leon-Rot, Germany) as described by Musso *et al.* [24]. The digestion products were separated in 1.5% (weight/volume) agarose gel along with 50-base pair (bp) marker (Axygen Biosciences, Union City, California, USA). The products were visualized under UV light following staining with ethidium bromide. The resultant fragments include 196 bp for T allele and 146, 50 bp for G allele.

Statistical analysis

The genotype and allele frequencies for +276 G/T polymorphism of adiponectin gene were determined by direct counting. Hardy-Weinberg's equilibrium was evaluated using a χ^2 -test. Statistical comparisons between healthy populations and patients were performed with χ^2 -test for categorical variables, whereas independent Student's *t*-test was used for continuous variables. Associations of genotypes with plasma adiponectin and hsCRP levels and serum lipid profile concentrations were evaluated by Student's *t*-test. To estimate the association of CAD with adiponectin gene SNP, odd ratios and 95% confidence interval were calculated. The values of *P*

less than 0.05 were considered as statistically significant. All statistical analysis was performed with SPSS, version 15 (SPSS Inc., Chicago, Illinois, USA).

Results

Study population and risk factors for coronary artery disease

Table 1 showed the clinical characteristics and biochemical parameters of study participants. Hypertension, diabetes mellitus, and family history of CAD showed significant differences between patients with CAD and non-CAD controls. Patients with CAD had significantly higher levels of total cholesterol, triglycerides, LDL-C, VLDL-C, and hsCRP than in control patients. On the contrary, serum HDL-C and adiponectin level were significantly lower in patients with CAD than in control group.

Table 1 General characteristics and laboratory measures of the study population

Variables	Control (n=100)	CAD (n=100)
Age (years)	54.8±5.3	55.3±5.3
Sex (male/female) (n)	61/39	58/42
BMI (kg/m ²)	29.3±3.3	30.4±4.2
Waist circumference (cm)	98.9±10.6	99.7±11.8
Hypertension [n (%)]	13 (13)	62 (62)*
Smoking [n (%)]	26 (26)	39 (39)
Diabetes mellitus [n (%)]	10 (10)	32 (32)*
Family history for CAD [n (%)]	19 (19)	40 (40)*
Total cholesterol (mg/dl)	186.2±25.6	213.7±61.4*
Triglycerides (mg/dl)	161.1±45.7	210.9±77.5*
HDL-C (mg/dl)	42.5±7.9	40.6±11.5
LDL-C (mg/dl)	115.1±21.9	135±55.4*
VLDL-C (mg/dl)	32.6±9.3	40.7±14.4*
Fasting blood glucose (mg/dl)	95.1±29.2	124.8±45.8*
Hemoglobin A1c (%)	5.7±1.8	6.8±2.9*
hsCRP (mg/dl)	3.7±2.0	7.6±3.1*
Adiponectin level (ng/ml)	5.98±1.8	4.26±1.38*

Data are mean±SD, and comparisons were performed by Student *t*-test and χ^2 -test. CAD, coronary artery disease; hsCRP, high-sensitivity C-reactive protein. **P*<0.05, statistically significant.

Table 2 Allele frequencies and genotypes distribution of single nucleotide polymorphism +276 G/T of adiponectin gene in control patients and patients with coronary artery disease patients

	Control (n=100) [n (%)]	Patients with CAD (n=100) [n (%)]	<i>P</i>	OR (95% CI)
G allele	154 (77)	120 (60)		
T allele	46 (23)	80 (40)	0.001 ^a	2.232 (1.446–3.445)
Genotype				
GG	60	39		
GT	34	42	0.037 ^{a,b}	1.901 (1.037–3.483)
TT	6	19	0.001 ^{a,c}	4.872 (1.788–13.276)

Comparisons were performed by the χ^2 -test. CAD, coronary artery disease; CI, confidence interval; OR, odds ratio. ^aT versus G. ^bGT versus GG. ^cTT versus GG. **P*<0.05, statistically significant.

Allele frequencies and genotype distribution of adiponectin gene +276 G/T polymorphism

Allele frequency and genotype distribution are shown in Table 2. Genotype and allele frequencies differed significantly between patients with CAD and control patients for the +276 G/T SNP of the adiponectin gene. Both allele frequencies and genotypes were in Hardy–Weinberg equilibrium.

Anthropometric and metabolic risk factors among patients with coronary artery disease according to the genotype distribution

To test the effect of 276 G/T polymorphism on risk factors of CAD, patients were divided into two groups: TT+GT genotype and GG genotype (assuming a codominant model of inheritance). As shown in Table 3, among all risk factors of CAD, only hsCRP and plasma adiponectin were significantly different between patients with GG genotypes and those with GT+TT genotypes. Carriers of the T allele (GT+TT genotypes) have higher serum hsCRP and lower serum adiponectin than those with the GG genotype.

Discussion

CADs constitute a major health problem in many parts of the world and are an important cause of morbidity and mortality. These diseases have remained the leading causes of death globally in the last 15 years [25].

Hypoadiponectinemia correlates with several coronary heart disease (CHD) risk factors. The causal implication of adiponectin in CHD pathogenesis is still unconfirmed. Many previous studies regarding the genetic association of adiponectin gene +276 G/T SNP and the concomitant presence of CAD were done, with nearly no report from Egyptian population. Moreover, the overall reported associations of 276 G/T polymorphism and cardiometabolic disease were diverse. It has been shown that the 276 G/T polymorphism in intron 2 is associated with insulin resistance, obesity, and the type 2 diabetes as risk factors of atherosclerosis [26]. Several studies have

Table 3 Anthropometric and metabolic risk factors among patients with coronary artery disease according to the genotype distribution

Variables	Carriers of GG (n=39)	Carriers of GT+TT (n=61)	P	95% CI
Age (years)	55.28±6.3	55.0±6.4	NS	0.96–1.052
Men [n (%)]	24 (61.5)	39 (63.9)	NS	0.621–3.368
BMI (kg/m ²)	30.1±4.5	29.2±3.8	NS	0.97–1.09
Waist circumference (cm)	100.3±9.9	98.9±10.3	NS	0.96–1.06
T2DM [n (%)]	8 (20.5)	14 (22.9)	NS	0.267–1.621
Smoking [n (%)]	10 (25.6)	15 (24.6)	NS	0.278–1.817
Hypertension [n (%)]	12 (30.8)	21 (34.4)	NS	0.278–1.359
Family history [n (%)]	11 (28.2)	19 (31.1)	NS	0.320–1.598
TG (mg/dl)	202.04 ±76.6	215.7±77.9	NS	0.808–1.085
TC (mg/dl)	213.9 ±62.1	214.79±61.6	NS	0.808–1.117
HDL-C (mg/dl)	43.5±11.4	37.6±10.9	NS	1.04–1.29
LDL-C (mg/dl)	136.7 ±58.6	141.1±57.2	NS	0.87–1.22
VLDL-C (mg/dl)	39.4±13.1	42.5±16.3	NS	0.8–1.07
FBG (mg/dl)	127.7 ±58.8	124.5±55.6	NS	0.86–1.23
Hemoglobin A1c (%)	6.7±3.1	6.9±2.8	NS	0.89–1.21
hsCRP (mg/dl)	6.81±2.6	8.5±3.37	0.006*	1.068–1.457
Adiponectin (ng/ml)	4.65±1.27	3.9±1.21	0.004*	1.059–1.346

Comparisons were performed by χ^2 or Student *t*-tests. CI, confidence interval; hsCRP, high-sensitivity C-reactive protein. **P*<0.05, statistically significant.

reported the associations between ADIPOQ45 T/G and 276 G/T polymorphisms and atherosclerosis, but the results are inconclusive [27].

This study provides evidence of association between the +276 G/T SNP of the adiponectin gene and CAD in this sample of Egyptian population. More precisely, a significant relation of minor T allele with the presence of CAD was approved (odd ratio=2.2, confidence interval =1.44–3.45, *P*=0.001). In accordance with the findings of the present study, Filippi *et al.* [28] first reported that T allele of 276 G/T is associated with higher risk of CAD than G allele carriers. Another study on Saudi population confirmed the same findings [29]. However, other studies have reported opposite results [30,31], providing direct evidence that the major G allele of 276 G/T of adiponectin gene may lead to target organ damage.

Adiponectin serum levels have been demonstrated consistently to be reduced in patients with CAD, and

there was significant association between +276 G/T variant and the adiponectin level [32,33], suggesting a central role in the mechanisms leading to the metabolic abnormalities present in this disorder [28]. Moreover, another study by Pischon *et al.* [34] has demonstrated that high adiponectin concentrations are associated with a lower incidence of myocardial infarction, suggesting that low adiponectin could be a causal risk factor for CAD. In favor of this hypothesis is the study done in animal model of atherosclerosis, which demonstrates that adenovirus-mediated increased adiponectin significantly suppressed the progression of atherosclerotic lesions [35]. The mechanism by which adiponectin affects CAD may be explained by the fact that adiponectin has been shown to exert several effects on vascular structure and function, including inhibition of endothelial thickening, induction of arterial vasodilatation, inhibition of foam cell formation, and suppression of adhesion molecules [36,37].

Previous studies focused on the association between plasma adiponectin level and the adiponectin gene 276 G/T SNP were not consistent and occasionally discrepant [28,31]. Our findings support the hypothesis that the +276 G/T SNP of the adiponectin gene may determine a reduced expression of the protein [38], as patients with T allele in homozygotes and heterozygotes forms (GT+TT) have a lower serum adiponectin levels than patients with GG genotype. Another possibility is that this SNP is in linkage disequilibrium with another mutation either within or in other genes close to the adiponectin gene that determines its negative effects. In support of our finding, genome-wide association studies using plasma adiponectin as a quantitative trait demonstrated the adiponectin gene as the only major gene for plasma adiponectin in white population [39]. Our findings are contradictory to Mendelian Randomization study of Borges *et al.* [17], which is not supportive of a protective role of adiponectin in CHD and indicates that the association of genetically increased adiponectin levels and lower risk of CHD is mainly driven by horizontal pleiotropy and does not support a causal role of adiponectin levels in CHD pathogenesis. Boumaiza *et al.* [40] found that mutated genotypes at +276 G/T (TT + GT) seem to reduce the risk of significant coronary stenosis in the studied population and were associated with a protective effect, and Zhang *et al.* [41] concluded that SNP +276 T allele might be associated with decreased risk of CHD in the Chinese Han population. The meta-analysis by Mansourian and Javanmard [42] in 2013 showed that there is no association between ADIPOQ 276 G/T polymorphism and atherosclerosis.

hsCRP has been demonstrated to contribute to vascular inflammation by inhibiting nitric oxide

production [43]. The role of adiponectin and hsCRP as predictive biomarkers of CVD is controversial [18,44]. High-quality evidence was found pointing out hsCRP, both as risk factor in the general population and as prognostic factor in those with CV events [45]. Our data showed increased plasma hsCRP and hypo adiponectinemia in patients with CAD. Interestingly, our data demonstrated that serum hsCRP was higher in carriers of the T allele (GT +TT genotypes) than those with the GG genotype, who already had lower level of serum adiponectin.

Conclusion

+276 G/T SNP in the adiponectin gene is associated with CAD. Furthermore, carriers of the at-risk T allele had lower serum adiponectin level and higher serum hsCRP, causing in turn an increased risk to develop CAD. Further larger-scale high-throughput genotyping of Egyptians is needed to investigate the other polymorphic sites of adiponectin gene that may affect its serum level.

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Conflicts of interest

There are no conflicts of interest.

References

- Matsuzawa Y. White adipose tissue and cardiovascular disease. *Best Pract Res Clin Endocrinol Metab* 2005; 19:637–647.
- Lisowska A, Tycinska A, Knapp M, Sawicki R, Lisowski P, Musiał WJ, *et al.* Adiponectin – an independent marker of coronary artery disease occurrence rather than a degree of its advancement in comparison to the IMT values in peripheral arteries. *Clin Chim Acta* 2012; 413:749–752.
- Scherer PE. The multifaceted roles of adipose tissue-therapeutic targets for diabetes and beyond: the 2015 Banting Lecture. *Diabetes* 2016; 65:1452–1461.
- Shibata R, Ouchi N, Murohara T. Adiponectin and cardiovascular disease. *Circ J* 2009; 73:608–614.
- Salmenniemi U, Zacharova J, Ruotsalainen E, Vauhkonen I, Pihlajamäki J, Kainulainen S, *et al.* Association of adiponectin level and variants in the adiponectin gene with glucose metabolism, energy expenditure, and cytokines in offspring of type 2 diabetic patients. *J Clin Endocrinol Metab* 2006; 90:4216–4223.
- Wu Y, Li Y, Lange EM, Croteau-Chonka DC, Kuzawa CW, McDade TW, *et al.* Genome-wide association study for adiponectin levels in Filipino women identifies CDH13 and a novel uncommon haplotype at KNG1-ADIPOQ. *Hum Mol Genet* 2010; 19:4955–4964.
- Dastani Z, Hivert MF, Timpson N, Perry JR, Yuan X, Scott RA, *et al.* Novel loci for adiponectin levels and their influence on type 2 diabetes and metabolic traits: a multi-ethnic meta-analysis of 45,891 individuals. *PLoS Genet* 2012; 8:e1002607.
- Qi L, Menzaghi C, Salvemini L, De Bonis C, Trischitta V, Hu FB. Novel locus FER is associated with serum HMW adiponectin levels. *Diabetes* 2011; 60:2197–2201.
- Kumada M, Kihara S, Sumitsuji S, Kawamoto T, Matsumoto S, Ouchi N, *et al.* Association of hypo adiponectinemia with coronary artery disease in men. *Arterioscler Thromb Vasc Biol* 2003; 23:85–89.
- Giannessi D, Maltinti M, Del Ry S. Adiponectin circulating levels: a new emerging biomarker of cardiovascular risk. *Pharmacol Res* 2007; 56:459–467.
- Weyer C, Funahashi T, Tanaka S, Hotta K, Matsuzawa Y, Pratley RE, *et al.* Hypoadiponectinemia in obesity and type2 diabetes: close association with insulin resistance and hyperinsulinemia. *J Clin Endocrinol Metab* 2001; 86:1930–1935.
- Trujillo ME, Scherer PE. Adiponectin – journey from an adipocyte secretory protein to biomarker of the metabolic syndrome. *J Intern Med* 2005; 257:167–175.
- Ouchi N, Walsh K. Adiponectin as an anti-inflammatory factor. *Clin Chim Acta* 2007; 380:24–30.
- Yang WS, Chuang LM. Human genetics of adiponectin in the metabolic syndrome. *J Mol Med (Berl)* 2006; 84:112–121.
- Hara K, Boutin P, Mori Y, Tobe K, Dina C, Yasuda K, *et al.* Genetic variation in the gene encoding adiponectin is associated with an increased risk of type 2 diabetes in the Japanese population. *Diabetes* 2002; 51:536–540.
- Dai X, Wiernek S, Evans JP, Runge MS. Genetics of coronary artery disease and myocardial infarction. *World J Cardiol* 2016; 8:1–23.
- Borges MC, Lawlor DA, de Oliveira C, White J, Horta BL, Barros AJ. Role of adiponectin in coronary heart disease risk: a Mendelian randomization study. *Circ Res* 2016; 119:491–499.
- Menzaghi C, Trischitta V. The adiponectin paradox for all-cause and cardiovascular mortality. *Diabetes* 2018; 67:12–22.
- American Diabetes Association. Standards of medical care in diabetes. *Diabetes Care* 2017; 40(Suppl 1):S13–S25.
- James PA, Oparil S, Carter BL, Cushman WC, Dennison-Himmelfarb C, Handler J, *et al.* 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). *JAMA* 2014; 311:507–520.
- Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. *Clin Chem* 1972; 18:499–502.
- Aritaa Y, Kiharaa S, Ouchia N, Takahashia M, Maedaa K, Miyagawaa J, *et al.* Paradoxical decrease of an adipose specific protein, adiponectin, in obesity. *Biochem Biophys Res Commun* 1999; 267:79–83.
- Ridker PM. C-reactive protein and risks of future myocardial infarction and thrombotic stroke. *Eur Heart J* 1998; 19:1–3.
- Musso G, Gambino R, De Michieli F, Durazzo M, Pagano G, Cassader M. Adiponectin gene polymorphisms modulate acute adiponectin response to dietary fat: Possible pathogenetic role in NASH. *Hepatology* 2008; 47:1167–1177.
- WHO (24 May 2018) The top 10 causes of death www.who.int/news-room/fact-sheets/detail/the-top-10-causes-of-death
- Gong M, Long J, Liu Q, Deng HC. Association of the ADIPOQ rs17360539 and rs266729 polymorphisms with type 2 diabetes: a meta-analysis. *Mol Cell Endocrinol* 2010; 325:78–83.
- Dallinga-Thie GM, Dullaart RP. Do genome-wide association scans provide additional information on the variation of plasma adiponectin concentrations? *Atherosclerosis* 2010; 208:328–329.
- Filippi E, Sentinelli F, Romeo S, Arca M, Berni A, Tiberti C, *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<=50 years). *J Mol Med (Berl)* 2005; 83:711–719.
- Mackawy A, Alzohairy M, Ahmed E, Badawy M. Adiponectin gene polymorphism and the incidence of type 2 diabetes mellitus in obese patients in Qassim region, Saudi Arabia. *J Am Sci* 2011; 7:191–203.
- Iacobellis G, Petrone A, Leonetti F, Buzzetti R. Left ventricular mass and +276 G/G single nucleotide polymorphism of the adiponectin gene in uncomplicated obesity. *Obesity (Silver Spring)* 2006; 14:368–372.
- Leu HB, Chung CM, Lin SJ, Jong YS, Pan WH, Chen JW. Adiponectin Gene Polymorphism is selectively associated with the concomitant presence of metabolic syndrome and essential hypertension. *PLoS One* 2011; 6:19999.
- Szmitko PE, Teoh H, Stewart DJ, Verma S. Adiponectin and cardiovascular disease: state of the art? *Am J Physiol Heart Circ Physiol* 2007; 292:1655–1663.
- Melanie C, Amelie C, Anee Q, Benoit J, Isabelle L, Jean P, *et al.* Adiponectin and Risk of Coronary Heart Disease in Apparently Healthy Men and Women (from the EPIC-Norfolk Prospective Population Study). *Am J Cardiol* 2011; 108:367–373.
- Pischon T, Girman CJ, Hotamisligil GS, Rifai N, Hu FB, Rimm EB. Plasma adiponectin levels and risk of myocardial infarction in men. *JAMA* 2004; 291:1730–1737.
- Okamoto Y, Kihara S, Ouchi N, Nishida M, Arita Y, Kumada M, *et al.* Adiponectin reduces atherosclerosis in apolipoprotein E-deficient mice. *Circulation* 2002; 106:2767–2770.
- Arita Y, Kihara S, Ouchi N, Maeda K, Kuriyama H, Okamoto Y, *et al.* Adipocyte-derived plasma protein adiponectin acts as a platelet-derived growth factor-BB-binding protein and regulates growth factor-induced

- common postreceptor signal in vascular smooth muscle cell. *Circulation* 2002; 105:2893–2898.
- 37 Fernández-Real JM, Castro A, Vázquez G, Casamitjana R, López-Bermejo A, Peñarroja G, *et al.* Adiponectin is associated with vascular function independent of insulin sensitivity. *Diabetes Care* 2004; 27:739–745.
- 38 Yang WS, Tsou PL, Lee WJ, Tseng DL, Chen CL, Peng CC, *et al.* Allele-specific differential expression of a common adiponectin gene polymorphism related to obesity. *J Mol Med (Berl)* 2003; 81:428–434.
- 39 Heid IM, Henneman P, Hicks A, Coassin S, Winkler T, Aulchenko YS, *et al.* Clear detection of ADIPOQ locus as the major gene for plasma adiponectin: results of genome-wide association analyses including 4659 European individuals. *Atherosclerosis* 2010; 208:412–420.
- 40 Boumaiza I, Omezzine A, Rejeb J, Rebhi L, Ben Rejeb N, Nabli N, *et al.* Single-nucleotide polymorphisms at the adiponectin locus and risk of coronary artery disease in Tunisian coronaries. *J Cardiovasc Med (Hagerstown)* 2011; 12:619–624.
- 41 Zhang BC, Li WM, Xu YW. A meta-analysis of the association of adiponectin gene polymorphisms with coronary heart disease in Chinese Han population. *Clin Endocrinol (Oxf)* 2012 76:358-364.
- 42 Mansourian M, Javanmard SH. Adiponectin gene polymorphisms and susceptibility to atherosclerosis: a meta-analysis. *J Res Med Sci* 2013; 18:611–616.
- 43 Verma S, Wang CH, Li SH, Dumont AS, Fedak PW, Badiwala MV, *et al.* A self-fulfilling prophecy: C-reactive protein attenuates nitric oxide production and inhibits angiogenesis. *Circulation* 2002; 106:913–919.
- 44 Shreshtha S, Sharma P, Kumar P, Sharma R, Gupta S, Mahapatra T. Study of serum adiponectin and high sensitivity C-reactive protein in diabetic patients. *Asian J Pharm Clin Res* 2018; 11:163–166.
- 45 Brito V, Alcaraz A, Augustovski F, Pichón-Riviere A, García-Martí S, Bardach A, *et al.*; Grupo de Evaluación de Tecnologías Sanitarias. High sensitivity C protein as an independent risk factor in people with and without history of cardiovascular disease. *Arch Cardiol Mex* 2015; 85:124–135.