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## Single nucleotide polymorphisms in adiponectin and its receptors' genes as potential risk factors for coronary artery disease in type 2 diabetes mellitus – an up-to-date overview

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## **Abstract**

**Introduction:** Type 2 diabetes mellitus (T2DM) is a chronic metabolic disease with still growing incidence among adults and young people worldwide. Patients with T2DM are more susceptible to develop coronary artery disease (CAD) than non-diabetic individuals. Several pre-clinical and clinical studies suggested that adiponectin, a pleiotropic hormone with anti-atherogenic, anti-inflammatory, and insulin-sensitizing properties, may be a molecular link between metabolic and cardiovascular diseases.

**Aim of the study:** This article summarizes the current knowledge on single nucleotide polymorphisms (SNPs) within the adiponectin and its receptors' genes on the risk of CAD in patients with T2DM.

**Description of knowledge:** Adiponectin, the most abundant circulating adipocytokine, is encoded by the Acrp30/adiponectin gene on chromosome 3q27, which constitutes a region specific for obesity-related metabolic syndrome. A genetic deficit of this adipokine may be responsible for the increased risk of CAD both in the general population and T2DM subjects. The results of recent years' studies highlight that SNPs at the adiponectin locus, +45 T>G and +276 G>T as well within its two receptors, are determinants of early onset atherosclerosis in individuals with T2DM.

**Conclusions:** SNPs in ADIPOQ, ADIPOR1 and ADIPOR2 may modify the risk of CAD in the group of patients with T2DM. SNP +45 and SNP +276 seem to be attractive, molecular markers for identification of diabetic individuals at especially high risk of CAD. The discovering of their exact mechanisms may result in novel screening options as well as diagnostic process and treatment scheme. Therefore, further research is required to determine the effects of adiponectin and its receptors' polymorphisms and their roles in the pathogenesis of obesity-related metabolic diseases.

**Key words:** adiponectin; AdipoR1; AdipoR2; type 2 diabetes mellitus; coronary artery disease; single nucleotide polymorphisms

## **Introduction**

Type 2 diabetes mellitus (T2DM) is a chronic metabolic disease characterized by hyperglycemia that results from a progressive beta-cell impairment, insulin secretion deficiency and concomitant insulin resistance [1]. The prevalence of diabetes mellitus has

been growing at an alarming rate over the past decades [2]. According to the latest epidemiological reports, T2DM has reached global epidemic proportions and it is one of the major public health challenges in the twenty-first century [3,4].

Patients with T2DM are at increased risk of development of cardiovascular diseases and associated clinical complications [5]. It is estimated that the incidence of coronary artery disease (CAD) is two to four times more frequent in diabetic patients than in non-diabetic individuals, representing the leading cause of mortality and morbidity in this population [6-8]. The mechanisms involved in the initiation of CAD in T2DM seem to be a combination of various genetic, molecular, and environmental factors [9-10]. Chronically elevated glucose level coexisting with dyslipidemia, especially increased levels of atherogenic low-density lipoprotein (LDL), oxidative stress, and increased inflammation are tightly involved in the pathogenesis of atherosclerosis at almost every step of the atherogenic process [11]. It is widely known that increased susceptibility to atherosclerosis results from unbalanced activity of pro- and anti-atherogenic factors, which are both environmental and genetic in origin [12].

Adiponectin, also known as adipocyte complement-related protein of 30 kDa (Acrp30), AdipoQ, apM1, gelatin binding protein of 28 kD (GBP-28), structurally belonging to C1q/TNF protein family, is one of anti-atherogenic and anti-inflammatory molecules with insulin-sensitizing properties that has recently draw much interest among researchers [13,14]. This highly bioactive adipocyte-derived adipocytokine acts not only locally in adipose tissue in an autocrine and paracrine manner, but it also circulates in the bloodstream, and thus it regulates processes in other tissues and distant organs [15,16]. What is more, adiponectin exerts its pleiotropic influence on glucose homeostasis, insulin sensitivity, lipid metabolism, and vascular endothelium integrity via two transmembrane receptors, called adiponectin receptor 1 (AdipoR1) and adiponectin receptor 2 (AdipoR2) [15-17].

The results of recent years' studies have revealed low plasma/serum adiponectin level both in T2DM and CAD [18]. It is suggested that single nucleotide polymorphisms (SNPs) in adiponectin and its receptors, AdipoR1, AdipoR2, genes are associated with increased risk of CAD in patients with T2DM, although the link between hypoadiponectinemia and adiponectin gene variants remains still unclear [19,20]. A thorough understanding of above-mentioned associations and gene-adipose tissue microenvironment interactions will likely result in innovative approach to diagnostic process and rationalizing treatment methods of these highly prevalent diseases in the future.

## **Aim of the study**

The aim of this systematic review was to present the potential role of SNPs within the adiponectin and its receptors' genes on the risk of CAD in patients with T2DM. Moreover, we also discussed the relationship between adiponectin gene polymorphisms and serum/plasma adiponectin level.

## **Materials and methods**

The available literature was subjectively selected due to its usefulness in showing genetic influence of the adiponectin, AdipoR1 and AdipoR2 genes polymorphisms in the development of CAD among patients with T2DM. Furthermore, selected SNPs in these genes as promising diagnostic and/or prognostic tools for CAD were evaluated. Data which reveals inconsistency in results was shown as well. Articles in English in the EBSCO and the PubMed database have been analyzed using key words in various combinations: 'single nucleotide polymorphisms', 'genetic markers' 'adiponectin', 'AdipoR1', 'AdipoR2', 'type 2 diabetes mellitus', and 'coronary artery disease'.

## **Adiponectin in type 2 diabetes mellitus and coronary artery disease – genetic background**

A growing number of pre-clinical and clinical studies have demonstrated that the development of CAD in patients with T2DM is usually initiated many years before the diagnosis of diabetes mellitus, due to the common association of glucose intolerance with the components of metabolic syndrome, including obesity, hypertension, dyslipidemia, and insulin resistance [21]. What is interesting, but not widely known it is hypothesized that T2DM and CAD share a common genetic background, and the adiponectin signaling-related gene is postulated to play crucial roles in these molecular pathways [22,23]. A genetic deficit of this adipocytokine may be responsible for the increased risk of CAD both in the general population and T2DM subjects. In support of this hypothesis is the recent finding that human recombinant adiponectin suppresses endothelial adhesion molecule expression, vascular smooth muscle cell proliferation, and macrophage to foam cell transformation as well as tumour necrosis factor  $\alpha$  (TNF- $\alpha$ ) production by macrophages in vitro [24,25].

Adiponectin, a 244 amino acids protein, is encoded by the APM1 gene located on the long arm of the third chromosome (locus 3q27), a genomic region identified as a susceptibility locus for the metabolic syndrome, T2DM and CAD [14]. The gene is 17 kb long and consists of three exons and two introns, basically regulated by peroxisome proliferator-activated receptors gamma (PPAR- $\gamma$ ), C-EBP, and ADDL, which are key transcription factors in adipogenesis [26]. Structurally, adiponectin consists of four domains: N-terminal signal

sequence, variable region, collagen-type domain, and C-terminal globular domain. In addition, adiponectin is one of the hormones with the highest plasma concentrations, and it circulates in the bloodstream in three major multimeric forms, which include low molecular weight (LMW) trimers, middle molecular weight (MMW) hexamers, and high molecular weight (HMW) multimers, which is suggested to be the most active form [14,15,26].

Adiponectin mediates its effects by two main receptors, AdipoR1 and AdipoR2 [26]. The human ADIPOR1 gene is located at chromosome 1p36.13-q41, whereas ADIPOR2 gene is located on chromosomal locus 12p13.33 [20,27]. AdipoR1 is primarily expressed in skeletal muscle and activated by AMPK (AMP-dependent protein kinase) phosphorylation, and AdipoR2 is mainly localized in liver and involved in the activation of peroxisome proliferator activating receptor alpha (PPAR- $\alpha$ ) [14]. These receptors are integral membrane proteins with seven transmembrane domains, similar to the family of G protein-coupled receptors, although, in contrary to them, adiponectin receptors have an internal N-terminal portion and external C-terminal domain [26].

According to the latest studies in many populations, several SNPs in ADIPOQ, ADIPOR1 and ADIPOR2 genes are associated with increased susceptibility to CAD development in patients with T2DM [19,20,27,29-39].

### **SNPs in ADIPOQ gene related to coronary artery disease in type 2 diabetes mellitus**

SNPs, in addition to insertions and deletions, are among the three types of DNA sequence variations. They occur when only one nucleotide in the DNA sequence changes, with a usual alternative of two possible nucleotides on a given position. What is more, to identify a polymorphism, the variation must occur at least on 1% of the general population, and those polymorphisms that affect the coding or regulatory sequence and that produce important changes within the protein structure or the expression mechanism appear as different phenotypes [28].

Based on the literature data, two SNPs at the adiponectin locus, +45 T>G (rs2241766) in exon 2 and +276 G>T (rs1501299) in intron 2, have been recently investigated as determinants of CAD risk in individuals with T2DM [19,29-35]. Some authors proved that susceptibility for CAD due to SNP +45 was independent of classic cardiovascular risk factors [29]. *Mohammadzadeh G et al.* in the clinical study indicated that not only GT and TT genotypes, but also T allele of SNP +276 G>T were related to an increased risk of CAD [34,35]. However, researchers did not find any significant association between the SNP +45 T>G and CAD in diabetic individuals which stands in contrary to several previous reports [29-31,33].

Despite serum/plasma adiponectin concentrations are highly heritable and are linked to ADIPOQ gene, there are only single studies evaluating the correlations between selected SNPs in the ADIPOQ gene and circulating levels of total adiponectin and its isoforms [19,31,32,34,36]. It is worth to underline that only the study conducted by *Oliveira CS et al.* showed that SNP +45 T>G was associated with total and HMW adiponectin levels, while SNP-11391 G>A was correlated with HMW adiponectin levels [32]. In turn, *Tong G et al.* have demonstrated that three genetic variants, such as -11377 C>G, -10066 G>A, and +276 G>T were associated with plasma adiponectin level, with the strongest effect for -11377 C>G and +276 G>T [36]. Moreover, some authors displayed that diabetic patients with CAD had more lower serum levels of adiponectin than those without CAD, but they found that different genotypes of SNP +45 T>G and +276 G>T were not significantly related to adiponectin concentrations [34,35].

The data about SNPs that are linked to cardiovascular risk in T2DM is limited and have been inconsistent. Therefore, in table 1 we attempted to summarize the most common SNPs in adiponectin and its receptor genes associated with increased risk of CAD in patients with T2DM as well their correlations with serum/plasma adiponectin levels [Table 1].

### **SNPs in ADIPOR1 and ADIPOR2 genes related to coronary artery disease in type 2 diabetes mellitus**

Currently, there is no concrete evidence for the association between SNPs of ADIPOR1 and CAD in diabetic individuals [20,27,37,38]. It is suggested that some genetic variants in ADIPOR1, such as rs7539542, rs10920531, rs4950894, rs3737884, rs16850797, and rs7514221 may be potentially engaged in the pathogenesis and increased susceptibility of CAD in T2DM, but further studies are necessary to evaluate their real clinical roles [Table 1].

Associations between ADIPOR2 gene variants with T2DM and CAD as well as another components of obesity-linked metabolic syndrome have been reported in several human populations [27,39,40]. The results of the Finnish Diabetes Prevention Study indicated that independent genetic signals in ADIPOR2 locus contribute to the risk of cardiovascular diseases and T2DM in individuals with impaired glucose tolerance. What is more, researchers revealed that rs11061937 and rs1058322 were significantly associated with cardiovascular disturbances, whereas subjects homozygous for the rare minor alleles of rs11061946 and rs11061973 had increased risk of converting from IGT to T2DM [27]. However, so far there is no study evaluating SNPs of ADIPOR2 as markers of increased CAD in the group of diabetic patients.

**Table 1.** Characteristics of SNPs in adiponectin and its receptor genes associated with increased risk of coronary artery disease in patients with type 2 diabetes mellitus.

<b>Authors, Year [Reference]</b>	<b>Ethnicity</b>	<b>Study Group vs. Control Group T2DM with CAD vs. T2DM without CAD</b>	<b>SNPs</b>	<b>Adiponectin/ AdipoR1 gene</b>	<b>Genotyping Method</b>	<b>Correlation with serum/plasma adiponectin</b>
Bacci S et al., 2004 [19]	Europe (Italian)	<i>n</i> = 142 vs. <i>n</i> = 234	SNP+276 (G>T)	adiponectin gene	PCR followed by dot blotting and allele-specific hybridization	serum adiponectin level did not correlate with SNPs at +276 loci of adiponectin gene
Lacquemant C et al., 2004 [29]	Caucasian/Europe (French and Swiss)	<i>n</i> = 162 vs. <i>n</i> = 315	SNP+45 (T>G)	adiponectin gene	PCR-DS or LightCycler™ technology	not examined
Al-Daghri NM et al., 2011 [30]	South Asia (Saudi Arabia)	<i>n</i> = 123 vs. <i>n</i> = 295	SNP+45 (T>G)	adiponectin gene	PCR-RFLP	not examined
Esteghamati A et al., 2012 [31]	West Asia (Iranian)	<i>n</i> = 114 vs. <i>n</i> = 127	SNP+45 (T>G)	adiponectin gene	PCR-RFLP	serum adiponectin level did not correlate with SNPs at +45 and +276 loci of adiponectin gene
Oliveira CS et al., 2012 [32]	America (African, Amerindian, Asian, European Caucasian of several different countries of origin reflecting the Brazilian population)	<i>n</i> = 225 vs. <i>n</i> = 70	SNP+45 (T>G), SNP+276 (G>T)	adiponectin gene	ABD kits from Applied Biosystems	plasma total and HMW adiponectin levels correlated with SNP+45 (T>G), while SNP-11391 (G>A) was associated with HMW adiponectin level
Tong G et al., 2013 [36]	East Asia (Chinese)	<i>n</i> = 560 vs. <i>n</i> = 550	SNP-11377 (C>G)	adiponectin gene	Taqman technology	plasma adiponectin level correlated with SNPs at -11377 (C>G), -10066 (G>A), and +276 (G>T) with the strongest effect for -11377 (C>G) and +276 (G>T)
Mofarrah M et al., 2016 [33]	West Asia (Iranian)	<i>n</i> = 152 vs. <i>n</i> = 72	SNP+45 (T>G)	adiponectin gene	HRM analysis	not examined
Mohammadzadeh G et al., 2016 [34]	West Asia (Iranian)	<i>n</i> = 100 vs. <i>n</i> = 100	SNP+276 (G>T)	adiponectin gene	PCR-RFLP	serum adiponectin level did not correlate with SNPs at +45 and +276 loci of adiponectin gene
Soccio T et al.,	Caucasian/Europe,	<i>n</i> = 426 vs. <i>n</i> = 518	rs7539542,	AdipoR1	PCR followed by	not examined

2006 [37]	America (Italian, Boston)		rs10920531, rs4950894		SBE/fluorescence polarization, Taqman technology	
Jin Z et al., 2014 [38]	East Asia (Chinese)	<i>n</i> = 174 vs. <i>n</i> = 165*	rs3737884 (C>T), rs16850797 (G>C)**	AdipoR1	HRM analysis, PCR- RFLP	not examined
Wang F et al., 2016 [20]	East Asia (Chinese)	<i>n</i> = 302 vs. <i>n</i> = 295***	rs3737884-G, rs7514221- C****	AdipoR1	PCR-RFLP, HRM analysis	not examined

\*173 subjects with CAD and 145 healthy controls were also analyzed in the study. \*\* rs3737884-G was simultaneously associated with an increased risk of T2D, CAD, and T2D+CAD, and 16850797-C was separately associated with T2D and T2D+CAD. \*\*\*316 subjects with CAD and 268 healthy controls were also analyzed in the study. \*\*\*\*rs3737884-G and rs7514221-C were associated with an increased susceptibility to CAD, T2D, and T2D+CAD. rs16850797-C was associated with T2D and T2D+CAD. T2DM – type 2 diabetes mellitus; CAD – coronary artery disease; SNP – single nucleotide polymorphism; AdipoR1 – adiponectin receptor 1; RefSNP or rs – Reference SNP; HMW – high molecular weight; PCR – Polymerase Chain Reaction; PCR-DS – Polymerase Chain Reaction-direct sequencing; PCR-RFLP – Polymerase Chain Reaction-Restriction Fragment Length Polymorphism; ABD – Assay by Design; HRM – High Resolution Melt; SBE – single-base extension; SNP+45 (T>G) = rs2241766; SNP+276 (G>T) = rs1501299; SNP-11377 (C>G) = rs266729; SNP-10066 (G>A) = rs182052; SNP-11391 (G>A) = rs17300539



## Conclusions

To conclude, it is worth to emphasize that SNPs in ADIPOQ, ADIPOR1 and ADIPOR2 may modify the risk of CAD in the group of patients with T2DM. SNP +45 and SNP +276 seem to be attractive, molecular markers for identification of diabetic individuals at especially high risk of CAD. The discovering of their exact mechanisms may result in novel screening options as well as diagnostic process and treatment scheme. Therefore, further research is required to determine the effects of adiponectin and its receptors' polymorphisms and their roles in the pathogenesis of obesity-related metabolic diseases.

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