Adiponectin as Biomarker in Coronary Artery Disease

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Abstract

Adiponectin is one of the main proteins produced and released by mature adipocytes. It was identified at the same time by four different groups and assigned the following names: Acrp30, adipoQ, GBP28, and apM1. This last one makes reference to the gene, which is localized in the chromosome 3q27. The adiponectin protein has four domains: a signal peptide, a variable region among species, a collagenous domain and a carboxyterminal globular domain. Usually,

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the adiponectin forms dimers, trimers, or structures which are more complex. Thus, monomers are not found in plasma. Their circulating levels represent the 0.01 % of total plasma proteins. Several studies have described their anti-atherogenic and insulin sensitizer properties because patients with CAD or T2DM had low plasma levels of this protein. Moreover, a range from 3.3. to 4.2 μg/mL can determine lesion complexity in patients with ACS. These results suggest that adiponectin levels are associated with CAD and its extension or severity. Moreover, they can be a good predictor of CAD because the included patients in the CACTI study with low adiponectin levels progressed with high coronary artery calcium volume. In fact, lower levels than 4.4 μg/mL were described as predictors of higher risk of death and myocardial infarction in patients who underwent coronary angiography with stable angina. The main considered CAD risk factors such as obesity, diabetes, dyslipidemia, and hypertension were associated with low concentrations of plasma adiponectin. In this sense, loss of weight, some antidiabetic and antihypertensive drugs, and statins were found to be good inducers of an increment of plasma adiponectin levels with benefits over endothelial and muscle cells.

Keywords

Adiponectin • Coronary artery disease • Cardiovascular risk factors • Indicators • Diagnosis • Prognosis • Regulators

Abbreviations

aa	Amino acids
ACRP30	Adipocyte complement-related 30 kDa protein
ACS	Acute coronary syndrome
apM1	Adipocyte C1q and collagen domain-containing protein
BIP	Bezafibrate Infarction Prevention
BMI	Body mass index
CACTI	Coronary artery calcification in type 1 diabetes
CAD	Coronary artery disease
cDNA	Complementary deoxyribonucleic acid
GBP28	Gelatin-binding protein
GLP-1	Glucagon-like peptide-1
HDL-C	High-density lipoprotein cholesterol
LDL-C	Low-density lipoprotein cholesterol
MESA	Multi-Ethnic Study of Atherosclerosis
mRNA	Messenger ribonucleic acid
ROS	Reactive oxygen species
STEMI	ST segment elevation myocardial infarction
T1DM	Type 1 diabetes mellitus
T2DM	Type 2 diabetes mellitus
TCFA	Thin-capped fibroatheroma
TG	Triglycerides
UniProt	Universal Protein Resource

Key Facts of Adipogenesis

- Process involving molecular, cytoskeletal, and functional changes to adipocyte, with spherical shape, development from preadipocytes, with fibroblast-like shape, or mesenchymal stem cells.
- Mechanism involving transcription factors, proteins that bind to DNA-specific region for increasing gene expression, such as peroxisome proliferator-activated receptor gamma.
- Differentiation of preadipocytes or mesenchymal stem cells to mature adipocytes that are able to produce and release adipokines which exert effect on several target organs for regulating appetite (leptin), insulin sensitizing (adiponectin), inflammation (resistin, chemerin), etc.
- Differentiation process in adipose tissue which is necessary for inducing adiponectin expression and secretion. This protein is an adipokine with anti-inflammatory, anti-atherogenic, and insulin sensitizer properties.

Definitions

Acute coronary syndrome Obstruction of coronary artery lumen by plaque disruption in combination of platelet aggregates, fibrin, and red blood cells. This process alters the sequence of depolarization reflected as changes in the surface of QRS. A high percentage of patients have an electrocardiogram with ST elevations because of Q wave's evolution in the leads overlying the infarct zone, but there are patients without ST elevation or unstable angina.

Coronary artery disease Obstruction of the coronary arteries by atheromatous plaque without uniform signs and symptoms. The tool for the quantification of CAD burden is the coronary angiography.

Gensini score Coronary angiographic score determined by Gensini G.G. for detecting the stenotic lesions severity of the plaque.

ST segment elevation myocardial infarction Acute coronary syndrome associated with ST elevations in the electrocardiogram.

Introduction

General Definition of Adiponectin

The catalog of information on proteins, UniProt, describes on its web page http://www.uniprot.org/uniprot/Q15848 the main characteristics of adiponectin. We can find, in the literature, alternative names as 30 kDa adipocyte complement-related protein, ACRP30, adipocyte C1q and collagen domain-containing protein, apM-1,

Fig. 1 Domains of adiponectin

or GBP28. The amount of alternative names is due to this protein was discovered by four independent groups (Scherer et al. 1995; Hu et al. 1996; Maeda et al. 1996; Nakano et al. 1996) using different methods. But, the first data were published by Philipp E. Scherer et al. on 1995 (Scherer et al. 1995) after analyzing the full-length cDNA library templated by mRNA from 3T3-L1 adipocytes at day 8 of differentiation. With these experiments they identified a specific protein of mature adipocytes, called adiponectin. This is constituted by four domains. The C-terminal globular domain contains 137 aa, the next C1q and collagen-like domain contains 65 aa, the variable domain with 28 aa, and the N-terminal and signal sequence with 17 aa (Goldstein et al. 2009) as Fig. 1 shows.

Collagen-like domain forms homo-trimers, which further combine to make oligomeric complexes. In serum, adiponectin can be found as low or high molecular weight complex. The first one is constituted by dimers or trimers. However, most of the studies showed adiponectin concentrations without considering the proportion of different complexes.

Plasma Adiponectin Levels and Coronary Artery Disease

At this moment, the inflammatory process on CAD is well known (Libby et al. 2002). Thus, the atherosclerosis progression involves inflammatory cells which release pro-inflammatory mediators (cytokines, chemokines, reactive oxygen species, and nitrogen species) (Moore et al. 2013) as protector mechanism against modified lipids or proteins by ROS (Miller et al. 2011), sugar (Price and Knight 2007), etc. In this sense, after perceiving the anti-inflammatory property of adiponectin, several groups have tried to identify the association between this protein and CAD. Table 1 summarized some findings with respect to this subject. In 2005, Kojima et al. described lower levels of adiponectin in patients with CAD (5.8 ± 3.2 vs. 9.1 ± 5.2 μg/mL). They defined CAD patients whose coronary angiography showed $\geq$50 % narrowing of the major coronaries and control group who had atypical chest pain at rest or following minimal exercise associated with coronary spasm or $\leq$25 % narrowing of the major coronaries. The exclusion criteria were thiazolidinedione treatment, symptoms of atrial fibrillation, peripheral artery diseases, or other inflammatory diseases (Kojima et al. 2005). However, in this CAD group, there was a higher proportion of patients with glucose intolerance and high levels of pulse pressure and C-reactive protein than those without CAD. After analyzing its correlation to these factors, they found a negative association with glucose intolerance and C-reactive protein. These results determined the relationship between adiponectin and CAD, glucose metabolism, and inflammation process. Although they signed differences regarding gender, Kumada et al. had described, 2 years earlier, a cutoff value (<4 μg/mL) of adiponectin for detecting CAD prevalence, in men, with independence of the other risk factors

Table 1 Adiponectin levels in CAD patients

Author	Year	Clinical patients	Adiponectin levels (μg/mL)
Dabelea D	2003	T1DM with prediction of coronary atherosclerosis	5.2
Kumada M	2003	≥75 % stenosis, men, stable CAD	<4.0 cutoff
Kojima S	2005	≥50 % stenosis, stable CAD	5.8 ± 3.2
Otsuka F	2006	ACS and single complex lesions	4.21 [3.36–5.41]
Otsuka F	2006	ACS and multiple complex lesions	3.26 [2.26–4.46]
Cavusoglu E	2006	Angina and non-STEMI with prediction of death or myocardial infarction	≤4.4
Sawada T	2008	≥75 % stenosis, men, without TCFA	10.9 ± 4.3
Sawada T	2008	≥75 % stenosis, men, with TCFA	Similar to Otsuka F

(Kumada et al. 2003). In spite of the fact that they considered CAD group whose coronary angiography narrowed ≥75 %, at least in one of the major coronary arteries, their adiponectin levels were similar to those described by Kojima et al. (2005). Two years later, (Otsuka et al. 2006) tested 207 men with CAD and determined, even, lower levels in those patients with ACS and multiple complex lesions. Thus, patients with ACS and single complex lesions had 4.21 [range 3.36–5.41] μg/mL of adiponectin and patients with multiple complex lesions contained 3.26 [range 2.26–4.46] μg/mL. These data suggested the association between low adiponectin levels and CAD extension.

Another important point is the severity of the disease which can be calculated by assigning a score to each coronary stenosis according to (a) the degree of luminal narrowing and (b) its importance due to localization, as it was described by Gensini (1983). Hence, the association between adiponectin and severity of CAD was confirmed after visualizing an inverse correlation between adiponectin levels and Gensini score (Hara et al. 2007). But the development of imaging techniques as multislice computed tomography, angiography, and virtual histology intravascular ultrasound together with optical coherence tomography (Sawada et al. 2008) let the scientific community know the vulnerable plaques and classify them according to their composition (fibrotic, fibrofatty, necrotic core, dense calcium) as fibrocalcific, fibroatheroma, and TCFA (van Velzen et al. 2009). This last plaque type identifies the patients more vulnerable with percentage of necrotic core >10, without evidence of an overlying fibrous component and percentage of plaque volume >40. This approach allowed detecting the association between adiponectin levels and TCFA presence (Sawada et al. 2008). These authors selected men patients with stable CAD, coronary stenosis ≥75 %, without occluded, highly calcified vessels, significant left main artery disease, or severe tortuous lesion. These inclusion and exclusion criteria could explain their higher levels of adiponectin in patients with stable CAD without TCFA (10.9 ± 4.3 μg/mL) than those described previously (Otsuka et al. 2006). However, the found levels in patients with multivessel TCFA were comparable to those described in patients with ACS and multiple complex lesions. The high frequency of an ACS past history in patients with TCFA might suggest the contribution of plasma adiponectin analysis for stratifying the patients with high risk.

The importance to identify targets for primary prevention of CAD determined that further analyses were carried out regarding plasma adiponectin levels. The finding of new molecules or parameters as predictors needs occasionally prospective cohort studies in progression. Like this, one of the useful studies for this analysis was the CACTI study for evaluating the development and progression of subclinical CAD in subjects with T1DM and without diabetes (Dabelea et al. 2003). In this study, the coronary artery calcium volume was collected from each patient with follow-up for 1.6–3.3 years and their plasma adiponectin levels. The next analysis determined the association between low plasma adiponectin levels and progression of calcium volume score (Maahs et al. 2005). Thus, the median range 5.2 μg/mL levels of this protein might add a new appreciated value as predictor of coronary atherosclerosis progression. Later, Cavusoglu et al. (2006) described adiponectin values $\leq$4.4 μg/mL as predictors of higher risk of death and myocardial infarction at 2 years of follow-up in patients who underwent coronary angiography with stable angina, troponin-negative unstable angina, and non-STEMI. But, also, in other prospective study, low adiponectin levels after myocardial infarction in patients with STEMI were predictors of any cause of death of patients (Lindberg et al. 2012).

So far, low adiponectin levels seem to be a good indicator of CAD, predictor of all-cause mortality in these patients, and predictor of higher risk of death and myocardial infarction in patients without CAD. In opposite, high adiponectin levels were found to be a good predictor of all-cause mortality in patients with carotid atherosclerotic disease (Persson et al. 2012). It is a paradox because both diseases are characterized by an atherosclerotic process which is associated with low adiponectin levels (Nishida et al. 2007). This situation is comparable to obesity paradox (Vemmos et al. 2011) where obese and overweight stroke patients have better early and long-term survival rates compared to those with normal BMI. Some authors explain that adiponectin might increase in response to extension of neurological damage (Kuwashiro et al. 2014); however, it should take into account the differential mechanisms between CAD and stroke. Thus, CAD is characterized by homogeneous risk factors such as obesity, diabetes, or dyslipidemia. The adiponectin levels regarding these factors are summarized in Table 2.

Plasma Adiponectin and Coronary Artery Disease Risk Factors

Obesity

Hyperplasia and hypertrophy of adipocytes are the main characteristics of adipose tissue in obese subjects (Avram et al. 2007). At this point, their adipocytes should be expressing higher levels of adiponectin because of a mature adipocyte – protein. However, the negative correlation between adiponectin plasma levels and BMI determined a paradoxical finding (Arita et al. 1999). This result was unexpected because adiponectin expression appears during the adipogenesis process (Avram et al. 2007; Fernandez-Trasancos et al. 2014) as Fig. 2 shows. After considering obese subjects with BMI major than 26.4, the authors found 8.9 $\pm$ 5.4 μg/ml of plasma adiponectin levels in healthy voluntaries with normal weight and 3.7 $\pm$ 3.2 μg/ml

Table 2 Adiponectin levels and CAD risk factors (obesity, dyslipidemia, hypertension, gender)

Author	Year	Clinical patients	Adiponectin levels (μg/mL)
Arita Y	1999	Subjects with normal weight	8.9 ± 5.4
Arita Y	1999	Obese	3.7 ± 3.2
Delporte ML	2003	Women with anorexia	16.1 ± 0.9
Delporte ML	2003	Women without anorexia	11.8 ± 0.9
Hotta K	2000	T2DM with CAD and men	4.0 ± 0.4
Hotta K	2000	T2DM with CAD and women	6.3 ± 0.4
Hotta K	2000	T2DM without CAD and men	6.6 ± 0.4
Hotta K	2000	T2DM with CAD and women	7.6 ± 0.7
Matsubara M	2002	Dyslipidemia (high TG levels)	5.9 ± 0.5
Matsubara M	2002	Low TG levels	9.2 ± 0.2
Nowak L	2005	Hypertension for 8–9 years	12.5
Nowak L	2005	Hypertension for 8–9 years with antihypertensive treatment	16.9

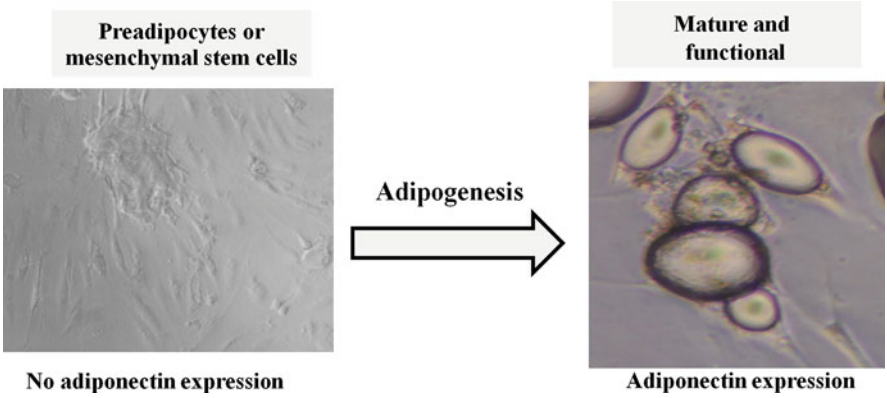

Fig. 2 Adipogenesis and adiponectin expression

in obese subjects (Arita et al. 1999). The reduction of body weight increases the adiponectin levels (Madsen et al. 2008), although it has to exceed the 10 % reduction. In fact, situations of severe weight loss, like anorexia nervosa, provoke hyperlipidemia (Delporte et al. 2003). These findings suggest that adipocytes with low hypertrophy might express more adiponectin levels. However, in familial partial lipodystrophy patients, who suffer loss of body fat after the onset of puberty, there are low levels of adiponectin (Wong et al. 2005). These patients have insulin resistance but the anorexic patients do not (Tagami et al. 2004). These findings associate the low adiponectin levels with insulin resistance. The data in anorexia nervosa can be contradictory because these patients do not have enough adipose tissue but contain high adiponectin levels. The closer explanation might be related to fasting (Kadowaki and Yamauchi

2005). Thus, after Ramadan, which is characterized by an intermittent representative fasting, the plasma adiponectin levels are augmented (Feizollahzadeh et al. 2014). However, the mechanism was not yet described. Perhaps, this adipokine is not only produced by adipose tissue, as it was found in macrophages (Luo et al. 2010) and can be regulated by self-starvation and other factors.

Diabetes

Hyperinsulinemia, associated with low glucose oxidation and energy expenditure, and hyperglycemia, associated with insulin resistance, can be regulatory factors of hypoadiponectinemia (Salmenniemi et al. 2004). These elements contribute to develop T2DM which is a disorder with atherosclerotic vascular complications (Zimmet 1992). In fact, mice with adiponectin deficiency showed mild insulin resistance and glucose intolerance (Kubota et al. 2002). In this sense, hypoadiponectinemia has been determined as a good predictor marker of diabetes development in the included patients, with fasting glucose levels between 100 and 125 mg/dL, of BIP study (Knobler et al. 2006). The classification of patients with diabetes, regarding CAD presence or absence, has determined lower levels of plasma adiponectin in patients with diabetes and CAD than those diabetic patients without CAD. The first group of patients had 4.0 ± 0.4 μg/mL in men and 6.3 ± 0.4 μg/mL in women of plasma adiponectin, and in the second group, the patients without CAD had 6.6 ± 0.4 μg/mL in men and 7.6 ± 0.7 μg/mL in women. Although plasma levels of adiponectin are higher in women than in men, there was, in both, an increase when they have neither diabetes nor CAD (Hotta et al. 2000). This association was found in different ethnic groups, (Daimon et al. 2003; Snehalatha et al. 2003) for example, Pima Indians (Weyer et al. 2001), who have tendency to be obese with T2DM. In general, the diabetic and CAD patients have low levels of adiponectin which can be playing a protector role. The next step of the scientific community was to determine the ability of diabetic treatment of increased adiponectin levels in these patients. Thus, several clinical trials with glucose-lowering agents have determined that thiazolidinedione (synthetic PPAR-γ ligands that regulate adipocyte differentiation and its endocrine function (Saltiel 1996)) treatment alone (Bailey 2005) or in combination with fibrates (Boden et al. 2007) (synthetic PPAR-α ligands that regulate lipid metabolism (Fruchart et al. 2001)) can regulate the increase of plasma adiponectin levels. These antidiabetic drugs involve nuclear receptors related with preadipocyte differentiation. In this way, their role on adiponectin regulation is comprehensible. Other and new class of antidiabetic drugs is based on GLP-1, hormone secreted by intestinal L-cells that stimulates insulin secretion. The GLP-1-related drugs also increased circulating adiponectin levels, but the mechanism is still unknown (Hibuse et al. 2014). However, the increment of insulin secretion by these drugs can improve the glucose uptake by adipocytes and induce their adiponectin production.

Dyslipidemia

The interaction between coronaries calcification and dyslipidemia regarding cardiovascular events was determined in the MESA study (Martin et al. 2014). Although

dyslipidemia and insulin resistance go hand in hand, the Japanese study, described by Matsubara et al. (2002) where diabetic patients were excluded, determined a negative correlation between plasma adiponectin levels and serum TG after adjusting for BMI. Contrary, adiponectin levels were positively correlated with serum high-density lipoprotein cholesterol (HDL-C). Thus, those patients with the highest tertile of TG contained 5.9 ± 0.5 μg/mL of adiponectin and patients with lowest tertile of TG had 9.2 ± 0.2 μg/mL of adiponectin. Moreover, low levels in patients with familial hypercholesterolemia, who contain high plasma concentrations of LDL-C serum levels, increase their risk of premature CAD (Bouhali et al. 2008). Statins, drugs for inhibiting hydroxymethylglutaryl-CoA reductase and changing the lipid profile, can be able or not to modify the serum adiponectin levels. Accordingly, the treatment with pravastatin for 16 weeks in female diabetic patients with hypercholesterolemia reduced the LDL cholesterol levels but was not able to increase adiponectin levels (Kim et al. 2013). However, in patients with isolated hypercholesterolemia, pravastatin with valsartan (angiotensin II type 1 receptor blocker) (Koh et al. 2013) or thiazolidinedione (activator of peroxisome proliferator-activated receptors) (Nezu et al. 2010) treatment decreased serum levels of LDL-C and augmented adiponectin concentration. The differential activity of pravastatin and simvastatin or the inclusion criteria of trials may explain their ability to increase or not the adiponectin concentrations. Even, simvastatin (Koh et al. 2008) or rosuvastatin (Koh et al. 2011), statin that decreases LDL-C levels and insulin sensitivity, reduced the adiponectin levels. On the other hand, pitavastatin, which has the capacity moreover to regulate HDL-C (Noji et al. 2002), increased the serum adiponectin concentrations in patients with hyperlipidemia and diabetes, but not in those without diabetes (Nomura et al. 2008).

Hypertension

The endothelial dysfunction contributes to hypertension and, in consequence, to atherosclerosis and CAD. One method for analyzing the endothelial function consists in the measure of vasodilation ability in response to reactive hyperemia after sublingual administration of nitroglycerin by strain-gauge plethysmography (Sanada et al. 2001; Ouchi et al. 2003). Thus, in patients with hypertension, defined as systolic blood pressure ≥140 mmHg and diastolic blood pressure ≥90 mmHg, but without antihypertensive treatment, the adiponectin plasma levels were associated with vasodilator response to reactive hyperemia (Ouchi et al. 2003). The conclusion is that low adiponectin plasma levels indicate an endothelial dysfunction and can contribute to clinical course of essential hypertension because their levels are associated with mean, diastolic, and systolic blood pressure (Adamczak et al. 2003). Actually, the administrated treatment against hypertension is focused on sympathetic or renin-angiotensin-aldosterone pathways and calcium channel blockers.

The reduction of sympathetic overactivity by the antihypertensive increased the adiponectin levels from 12.5 to 16.9 μg/mL in patients 25–53 aging with essential hypertension for 8–9 years (Nowak et al. 2005). In detail, although this sympathetic inhibition did not modify fat mass, BMI or insulin resistance suggests other regulator

mechanism of adiponectin levels. Again and most recent data showed that antihypertensive treatments that interrupt the angiotensin activity can also increase the adiponectin levels (Koh et al. 2007) in an independent manner of adiposity. Finally, although there was a controversy finding about the increase of adiponectin by calcium channel blockers, (Watanabe et al. 2006; Koh et al. 2009) without BMI modification, the data bear out that treatments improve the adiponectin levels in patients with hypertension, one of the CAD risk factors.

Adiponectin Expression on Coronaries

Over the coronaries exists an adipose tissue which can cover almost the 80 % of myocardium and constitute the 20 % of total heart weight (Rabkin 2007). This fat pad is named epicardial adipose tissue (EAT). Its thickness was measured by different image techniques and associated with CAD and its severity (Iacobellis et al. 2005a; Ahn et al. 2008; Gorter et al. 2008; Eroglu et al. 2009; Bettencourt et al. 2011). In spite of high EAT amount, patients with CAD expressed 40 % less mRNA adiponectin than those without CAD (Iacobellis et al. 2005b). Indeed, the protein concentration was even lower than mRNA levels. Thus, 1 g of EAT from patients without CAD had a 93 % more of adiponectin than those with CAD (Cheng et al. 2008). But, the adiponectin mRNA expression was dependent on CAD extension because it tended to fall as the number of injured coronary arteries increased (Eiras et al. 2008). In opposite, there were high concentrations of inflammatory adipokines or cytokines (Mazurek et al. 2003; Hirata et al. 2011; Zhou et al. 2011). The inflammatory process might reduce the ability of preadipocyte differentiation and, in consequence, adiponectin expression (Fernandez-Trasancos et al. 2014) as it is shown in Fig. 3. Once more, in this fat tissue, adiponectin was a good indicator of CAD but, also, of cardiovascular prognosis (Teijeira-Fernandez et al. 2012). Similar to plasma levels, adiponectin expression was also lower in patients with hypertension (Teijeira-Fernandez et al. 2008) and metabolic syndrome (Teijeira-Fernandez et al. 2011) but not in those with T2DM (Teijeira-Fernandez et al. 2010). In these last patients, some contra-regulatory mechanism might explain the differential behavior between EAT and plasma levels of adiponectin.

Adiponectin Effects on Coronaries

The atherosclerosis is an inflammatory process (Libby et al. 2002) where endothelial dysfunction promotes the induction of adhesion molecules for attaching monocytes. These cells are infiltrated into the intravascular layer and form macrophages, platelet degranulation, thrombosis, and vascular smooth muscle cell migration and proliferation (Badimon et al. 2009). The benefit effect of adiponectin between 5 and 25 μg/mL was demonstrated in human aortic endothelial cells after analyzing a reduction of TNF-α-induced monocyte adhesion (Ouchi et al. 1999) and tissue factor (Chen et al. 2008), which contributes to thrombus formation. Moreover, adiponectin

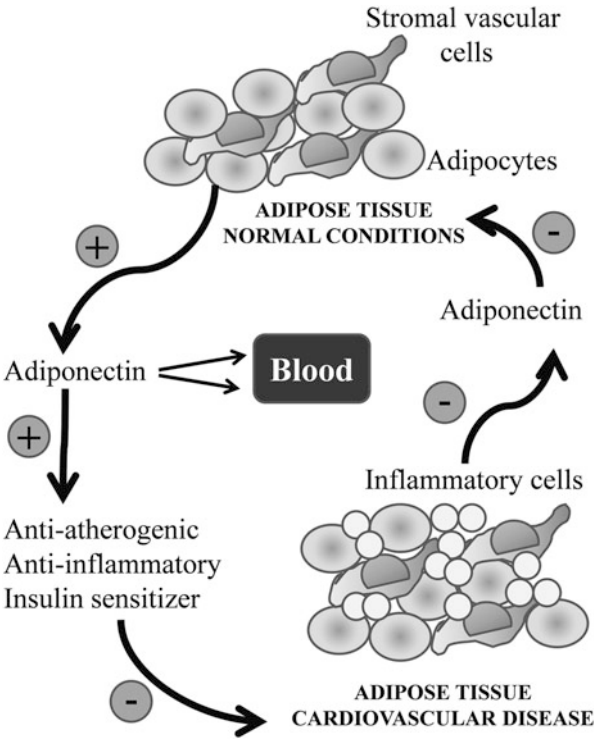

Fig. 3 Inflammation in cardiovascular disease and adiponectin regulation

induces the phosphorylation of endothelial nitric oxide synthase (Zhao et al. 2013) that produces nitric oxide for modulating vascular dilator tone and normal endothelial function. The protector effect of adiponectin was also established in smooth muscle cells where their contractile proteins and function were regulated (Ding et al. 2011).

Adiponectin Regulators

The activation of several transcription factors, PPARγ, PPARα, c/EBPβ, etc., is able to induce the adiponectin transcription. Several adipogenic drugs and hormones could increase the adiponectin expression as it is shown in Fig. 4. One adipogenic drug that regulates PPARγ is glitazone (Stumvoll and Haring 2002). This drug was a novel treatment for type 2 diabetes but its use was restricted in patients with coronary artery disease. Other adipogenic drugs are the fibrates, cardioprotectors in subjects with dyslipidemia, which are able to induce the adiponectin expression through PPARα (Sahebkar and Watts 2013). But not only drugs are good inducers of adipogenesis; there are several hormones that are able to regulate this process and also adiponectin expression. However, not all adipogenesis inducers are able to increase its expression. Thus, while growth hormone (GH), obestatin, and insulin

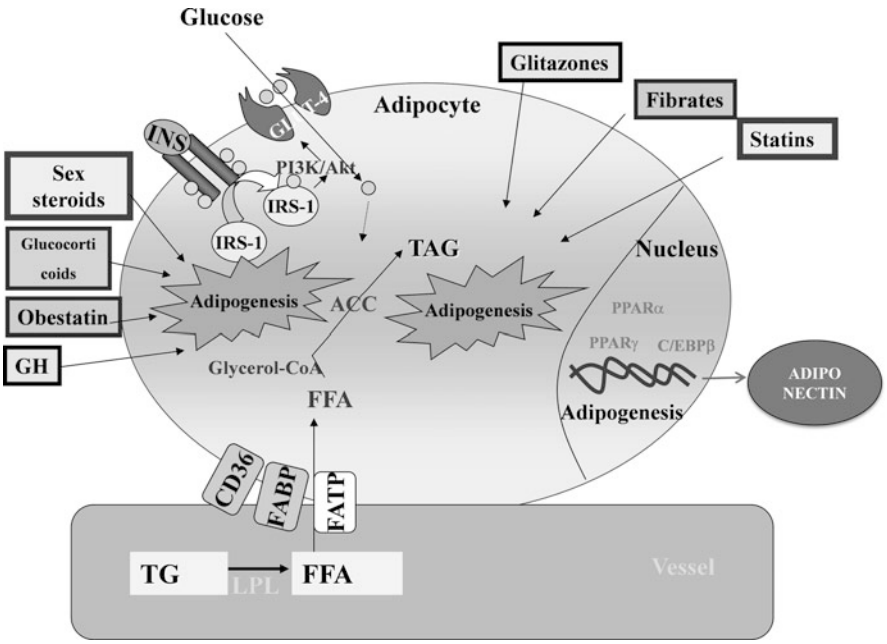

Fig. 4 Inducers of adipogenesis and adiponectin expression. *INS* insulin, *IRS-1*, insulin receptor substrate-1, *GH* growth hormone, *TAG* triacylglycerol, *ACC* acetyl-CoA carboxylase, *LPL* lipoprotein lipase, *FFA* free fatty acid, *FABP* fatty acid-binding protein, *FATP* fatty acid transporter protein

are all adipogenic hormones, insulin was not a good inducer of adiponectin expression (Xu et al. 2004; Granata et al. 2012; Koistinen et al. 2004). In fact, the adipogenic pathway might increase the adiponectin levels and prevent the coronary atherosclerosis progression. However, the rise of adipogenesis develops hypertrophic adipocytes with an inflammatory autocrine/paracrine and deleterious endocrine role. Accordingly, another pathway with a benefit on adipose tissue is the anti-inflammatory since simvastatin, pioglitazone, or their combination reduces the IL-6 expression in EAT and increases adiponectin (Grosso et al. 2014).

Potential Applications to Prognosis, Other Diseases, or Conditions

After analyzing the presented data by several authors, plasma adiponectin levels lower than 5.2 μg/mL might be considered as predictors of coronary atherosclerosis progression. However, in patients with stable angina, the limit range has to decrease because 4.4 μg/mL levels were good predictors of higher risk of death and myocardial infarction at 2 years of follow-up. Thus, adiponectin is a good indicator of CAD but, also, of cardiovascular prognosis. However, these levels do not have to be extrapolating to other atherosclerotic disorders like carotid atherosclerotic disease

because, in this situation, low adiponectin levels have a good prognosis. Moreover, because epicardial fat is the adipose tissue closer to myocardium and coronaries and its adiponectin expression is lower in patients with CAD, it might be considered as a future therapeutic target.

Summary Points

- Adiponectin is one of the main proteins produced by mature and functional adipocytes with anti-atherogenic and anti-inflammatory properties.
- Lower levels than 5.2 μg/mL of adiponectin are a good predictor of coronary artery disease.
- Lower levels than 4.4 μg/mL of adiponectin are associated with coronary artery disease.
- The adipose tissue around the coronaries, called epicardial adipose tissue, is a producer of adiponectin. But, their levels are also lower in patients with coronary artery disease.
- The epicardial adipose tissue from patients with coronary artery disease shows an increase in the inflammatory cell infiltration and inflammatory cytokines which might be decreasing the adiponectin expression.
- Hormones and drugs with effects on adiponectin upregulation might be useful as future coronary artery disease therapies.

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