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REVIEW

Adiponectin: a therapeutic target in the antiphospholipid syndrome?

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Abstract
The antiphospholipid syndrome (APS) is an autoimmune disease characterized by the presence of the IgG and/or IgM isotypes of the antiphospholipid antibodies, thrombosis and/or recurrent pregnancy losses. Various markers of inflammation are associated with clinical and/or laboratory features of APS. Adiponectin (Ad) is a member of the adipocytokines that exert its roles by binding to its receptors (AdR). Peroxisome proliferator-activated receptor gamma (PPAR-gamma) agonists induced Ad production. The aged Pparg null-mice represented the first animal model that spontaneously develops APS and this model emphasized the importance of PPAR-gamma signaling in the development of APS. Recombinant Ad (rAd) application was beneficial for the improvement of glucose, insulin and lipid levels in mice. Orally active AdR agonist exerted similar effects to Ad in mice. Due to the re-occurrence of thrombotic episodes in APS patients (despite life-long anticoagulation), administration of PPAR-gamma agonists, rAd, or AdR agonists should be further tested in experimental models of APS, which eventually, will provide more data for novel therapeutic strategies that will ameliorate clinical manifestations of the APS.

Keywords Adiponectin · Antiphospholipid antibodies · Antiphospholipid syndrome · Inflammation · PPAR-gamma agonist

Introduction

The antiphospholipid syndrome (APS) is regarded as an autoimmune disease. It can be primary (PAPS), secondary (SAPS), and catastrophic (CAPS). This categorization means that in the case of PAPS no other diseases are associated with APS, while in the case of SAPS, other diseases, like systemic lupus erythematosus (SLE), are associated with the syndrome. The most difficult form of the APS is CAPS and it is characterized by rapidly developing thrombosis of vital organs. The presence of the IgG and/or IgM isotypes of the antiphospholipid antibodies [aPL Abs: anticardiolipin (aCL), anti-beta2 glycoprotein I (aβ2gpI)] is the main laboratory feature of APS. The major clinical manifestations of APS are recurrent pregnancy losses (RPL) and/or thrombosis (arterial and/or venous) [1–4].

According to the latest classification criteria for APS [2], "thrombotic manifestations of the syndrome should be without any sign of the inflammation". However, recently published articles suggested otherwise (i.e., APS exerted features of the pro-inflammatory condition/state). Various markers of inflammation were associated with clinical and/or laboratory features of APS. Some of them were CRP, pro-inflammatory cytokines like TNF-alpha and IL-6, and C3c and C4 complement components [5–7]. In addition, premature atherosclerosis and metabolic syndrome were observed in patients with APS [8, 9].

Adipocytokines (or adipokines) represent the large group of proteins produced by adipocytes (white adipose tissue). They exert different roles and are associated with various clinical conditions including autoimmune diseases (AID), cancer, obesity, etc.

Adiponectin (Ad) is an interesting member of the adipocytokines. It is a 30 kDa protein composed from four distinct domains (N-terminal signal sequence, non-conserved variable region, collagen—like domain (cAd) and C-terminal globular domain (gAd) [10–15]. Various Ad multimers (trimer, hexamer, and oligomers) exert different

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physiological functions [11]. Adiponectin realizes its activities through its receptors.

Peroxisome proliferator-activated receptor gamma (PPAR-gamma) agonists have immunomodulatory and anti-inflammatory roles [16–19]. Natural ligands for PPAR-gamma are linoleic acid, arachidonic acid, oxidized alkyl phospholipids, while synthetic ligands are thiazolidinediones (pioglitazone, rosiglitazone, etc.) [16]. It was reported that PPAR-gamma agonist induced Ad production and Ad was a marker for adequate PPAR-gamma agonist ingestion [20, 21].

On one hand, due to the above-mentioned facts APS classification criteria excluded the inflammation, while on the other several articles [5–7] highlighted the significance of pro-inflammatory molecules in APS, we wanted to analyze Ad importance in APS settings. Despite life-long anticoagulation therapy, APS patients frequently develop recurrent thrombotic episodes. Search for new molecules that are involved in the complex pathology of APS, and which might be targeted, is promising therapeutic strategy. We strongly believe that one of these molecules is Ad.

Search strategy

We searched SCOPUS, PUBMED, and Web of Science [22] using the following keywords: adiponectin structure, adiponectin function, adiponectin receptors, adiponectin and autoimmune diseases, adiponectin and antiphospholipid syndrome, adiponectin and antiphospholipid antibodies, adiponectin and anticardiolipin antibodies, adiponectin and anti-beta2glycoprotein I antibodies, adiponectin and anti-annexin A5 antibodies, PPAR-gamma agonists and autoimmune diseases, PPAR-gamma agonists and antiphospholipid syndrome, PPAR-gamma agonists and adiponectin.

Preferences were given to articles written by prominent authors and published within the last 5 years. However, we included several older references due to their importance in the elucidation of structure and functions of Ad and its receptors and references that are still relevant for the diagnosis of APS. Comments expressed in this review article are based on authors' experience in writing and discussing review articles.

Adiponectin structure

Adipocytokines are involved in glucose and lipids metabolism and energy homeostasis. In addition, they exert important functions in cardiovascular and immune system and are involved in inflammatory response [23]. Adiponectin is included in C1q/TNF-related protein (CTRP) family. These proteins are predominantly expressed in adipose tissue [11] and are involved in metabolic and cardiovascular diseases associated with obesity [11]. Table 1 represents various synonyms for adiponectin (Ad) [10, 12].

The average Ad range is 2–20 μg/ml and it constitutes approximately 0.01–0.05% of blood proteins [10, 24], while the average plasma half-life was 45–75 min [24] and primary site of Ad clearance from blood was liver.

Healthy lean individuals expressed high circulating Ad levels which declined as body mass index (BMI) increased [25]. This downregulation occurred because pro-inflammatory cytokines (cyt) (which were upregulated in obesity) inhibited the synthesis of Ad by adipocytes [25]. Table 2 contains relevant data about Ad structure, its receptors (AdR) and multimers.

Adiponectin functions

Several Ad functions in non-autoimmune settings are presented in Table 3.

Adiponectin reduced C reactive protein (CRP) synthesis and secretion from rat primary hepatocytes and from human aortic endothelial cells (EC)s under hyperglycemia [13]. In addition, Ad levels were decreased in patients with coronary artery disease (CAD) [12] and these patients had inverse correlation between CRP and Ad and this suggested that dysregulated CRP elevation and Ad reduction in adipose tissue and plasma might participate in atherosclerosis development [23]. Serum Ad levels inversely correlated with the pro-inflammatory markers [CRP and interleukin 6 (IL-6)].

Low Ad levels and low AdR expression in obesity contributed to low-grade inflammation due to the absence of its anti-inflammatory activities [12]. Adiponectin affected sphingolipid metabolism and therefore it was involved in prevention of cellular inflammation. It was reported that Ad mediated its anti-inflammatory effects via induction of macrophages (Mf) tolerance. The treatment of Mf with HMW Ad inhibited IL-8 production (this IL is released by Mf during phagocytosis of the apoptotic cells in vitro) and this is the explanation for the absence of an inflammatory response in physiological conditions [11]. However, IL-8

Table 1 Synonyms for adiponectin

Synonyms	Explanation	References
ACRP30	Adipocyte complement-related protein of 30 kDa This name originates from the fact that Ad exhibits homology to C1q complement factor	[10, 12]
APM1	Adipose most abundant gene transcript 1	[10, 12]
adopoQ	–	[10, 12]
GBP28	Gelatin-binding protein of 28 kDa	[10, 12]

Table 2 Adiponectin structure, multimers, and receptors

Structure		References
Ad contains 244 amino acids	Conserved cys36 (at N-terminus in humans) is involved in intermolecular disulfide bridges and it is fundamental for Ad multimerization (and secretion)	[14]
	trp (W42) within the N-terminus is important in Ad multimer assembly	
	Lys65, Lys68, Lys67, and Lys101 (in collagenous domain of Ad) are involved in hydroxylation and glycosylation	
	pro71, pro76, and pro95 are required for hydroxylation	
	Ad multimerization is regulated by glycosylation and hydroxylation (in addition to disulfide bridge formation)	
Multimers		
	Adiponectin multimers (trimer, hexamer, and oligomers) circulate in blood	[11, 14]
	In the circulation various Ad multimers do not interconvert and they exhibit distinct physiological functions. In CNS, trimeric and hexameric Ad forms regulate energy expenditure and control appetite. Certain diseases (such as obesity) are characterized by decreased Ad-multimerization and suppression of total Ad levels	[14]
	Trimeric Ad has LMW (≈ 67 kDa), hexameric Ad has MMW (≈ 180 kDa), while oligomeric (dodecamers and octadecamers) Ad has HMW (≈ 300 kDa). The combination of these Ad polymeric forms is designated as FLAd	[13]
	Adiponectin trimers or LMW Ad represent the simplest Ad form, while Ad hexamers are comprised from two trimers connected via disulfide bridges	[11]
Receptors		
	Designated as adiponectin receptor 1 (AdR1), adiponectin receptor 2 (AdR2) and T-cadherin	[12, 13, 24]
AdR1 and AdR2	AdR1 and AdR2 have structural homology. Both receptors contain seven transmembrane domains, and both have an internal N-terminal and an external C-terminal domain. In addition, both receptors can bind FLAd and both stimulate the main downstream effector AMPK	
	AdR1 and AdR2 are expressed in Mo and Mf	[26]
	AdR1 is high-affinity receptor and is abundantly expressed in skeletal muscle fibers and EC, while moderate-affinity AdR2 is predominantly expressed in liver and is required in activation of PPAR-alpha	[13]
	Activated AdR1 and AdR2 increased glucose uptake, fatty acid oxidation and suppress inflammation and oxidative stress	[12, 13]
	Both receptors stimulate ACC phosphorylation in liver and skeletal muscle and therefore activate glucose transport and lipid oxidation (in muscle) and inhibit gluconeogenesis (in the liver)	[12]
T-Cadherin	The cell surface molecule without intracellular signaling domain that only binds HMW Ad and acts as a co-receptor in the heart and vasculature and therefore T-cadherin is required for Ad exertion of its cardioprotective activities	[13, 24]

ACC acetyl coenzyme A carboxylase, *Ad* adiponectin, *AdR1 and AdR2* adiponectin receptor 1 and 2, *AMPK* adenosine monophosphate-activated protein kinase, *Cys* cysteine, *EC* endothelial cells, *FLAd* full length Ad, *HMW* high molecular weight, *Lys* lysin, *LMW* low molecular weight, *MMW* medium molecular weight, *Mo* monocytes, *Mf* macrophages, *pro* proline, *PPAR-alpha* peroxisome proliferator-activated receptor alpha, *Trp* tryptophan

production was not inhibited in the presence of lipopolysaccharide (LPS) or at low Ad levels and this is the explanation for the exacerbated immune response and cyt storm in the response to infection in obesity [11, 12].

Adiponectin and autoimmune diseases

The Ad levels were reduced in metabolic diseases [27], but chronic inflammatory conditions and AID [diabetes mellitus 1 (DM1), rheumatoid arthritis (RA), osteoarthritis, chronic bowel disease, etc.] [12] were associated with the increased Ad levels [13] and in these conditions Ad exerts pro-inflammatory features (instead of previously described anti-inflammatory) [28].

In chronic AID, gAd induced the expression of IL-8, E-selectin, plasminogen-activator inhibitor 1 (PAI-1), ICAM-1, VCAM-1 in vascular EC [16]. In DM1 increased TNF-alpha, IL-6, and CRP levels were in positive correlation with high Ad levels. The synthesis of IL-6 and matrix metalloproteinase inhibitor 1 (MMP-1) in fibroblasts was induced by increased Ad levels in patients with RA [13]. In obesity, Ad induced pro-inflammatory phenotype of Mf (M1) and the release of pro-inflammatory cyts [13], while on the other hand increased Ad might be the compensation

Table 3 Several adiponectin functions in non-autoimmune settings

Functions		References
Metabolic	Increased appetite, insulin gene expression, insulin sensitivity, glucose uptake in adipose tissue and skeletal muscles and increased free fatty acid oxidation in the liver and skeletal muscles and decreased hepatic glucogenesis)	[10]
Protection of vascular endothelium	Increased eNOS activity and NO production through AMPK-mediated phosphorylation of eNOS and therefore it facilitated vasodilatation, inhibition of platelet aggregation, Mo activation and smooth muscle cells' proliferation Vascular effects of Ad are anti-atherogenic because it decreased the expression of endothelial adhesion molecules (ICAM-1, VCAM-1, and E-selectin) and decreased Mf transformation into foam cells	[15] [12]
Anti-inflammatory effects	EC: inhibited production of pro-inflammatory cyt (TNF-alpha, IL-6) and increased IL-10 production Mo: decreased secretion of TNF-alpha, IFN-gamma, IL-6, increased IL-10 and IL-1Ra) Ly: decreased activation and proliferation of B- and T-Ly, increased proliferation of Treg) Mf: decreased maturation, proliferation and phagocytosis activity, increased phagocytosis of apoptotic cells, decreased production of TNF-alpha, IFN-gamma and promoted the Mf polarization towards M2 phenotype (anti-inflammatory profile) NK: Ad decreased cytotoxicity DC: promoted the maturation and activation	[24] [10]

Ad adiponectin, *AMPK* adenosine monophosphate activated protein kinase, *cyt* cytokines, *EC, DC* dendritic cells, endothelial cells, *eNOS* endothelial nitric oxide synthase, *IL* interleukin, *NO* nitric oxide, *Mo* monocytes, *Mf* macrophages, *ICAM-1* intercellular adhesion molecule 1, *VCAM-1* vascular cells adhesion molecule 1, *Ly* lymphocytes, *NK* natural killers cells, *TNF-alpha* tumor necrosis alpha

for the increase of the markers of systemic inflammation (high levels of pro-inflammatory cyts) [13, 25].

Therefore, Ad has bidirectional (anti- and pro-inflammatory) effects and this is a consequence of changes in the relative proportion of its various isoforms (different MW and truncated forms of Ad exerted different activities) [10].

Li et al. [29] have examined the association of total Ad and its multimers in RA [180 recently diagnosed untreated RA with disease duration < 1 year and 160 age and sex matched control subjects (CS)]. The authors reported that levels of total Ad and each multimer of Ad were significantly lower in RA than in CS and that serum levels of total, HMW, MMW, and LMW were positively correlated with triglycerides (TG) levels and negatively correlated with the disease activity score (DAS) for 28 joints (DAS 28). In addition, the authors reported that LMW Ad is associated with DAS28 more strongly than total, HMW and MMW Ad.

Although patients with DM1 had increased Ad levels, diabetes mellitus type 2 (DM2) patients had decreased Ad levels [12, 13]. In addition, in female DM2 patients Ad was in positive correlation with HDL and apoA1 and in negative correlation with triglycerides, HbA1c and non-esterified fatty acid levels [30].

Patients with SLE had higher Ad levels compared to controls [31]. Previously it was shown [20] that Ad deficiency in a lupus model resulted in the disease exacerbation and therefore the Ad elevation in chronic AID may reflect a compensatory alteration in the level of Ad to suppress the inflammation [20]. In addition, the authors suggested that AID state results in the development of "Ad-resistance" that led to Ad elevation. Ad-resistance has been observed in animal models and in human tissues, but mechanisms that might elucidate this resistant state are not available yet. Factors that influence the Ad production were age, gender, metabolic status, and the presence of the inflammation [20]. Therefore, the impact of these factors on Ad expression might influence the severity of AID. Parker et al. [25] have reported that Ad exhibited gender-dependent influence on autoimmune phenotype and that female mice with Ad deficiency exerted more severe autoimmune phenotype [25].

de Souza Barbosa et al. [32] analyzed Ad levels in 52 SLE women (and 33 healthy women). Patients were further divided into subgroups with active SLE (SLEDAI score ≥ 3) and a subgroup with inactive SLE. The authors reported no significant difference in Ad levels between SLE patients and controls (although SLE patients had lower levels) nor between active and inactive SLE. In addition, no correlations between Ad levels and anticardiolipin (aCL) Abs, lupus anticoagulant (LA) nor clinical features were found. Adiponectin was not correlated with SLEDAI and ESR in SLE patients. Sada et al. [31] have reported significant Ad increase in SLE patients and they explained this Ad increased as a compensatory effect because Ad has anti-inflammatory, anti-atherogenic and anti-diabetic roles and different Ad activities might be explained by the fact that LMW Ad had anti-inflammatory activity, while HMW Ad had pro-inflammatory activity (this form is the most commonly found in plasma) [32].

de Souza Barbosa et al. [32] did not find any correlation between Ad and lipid profile, blood glucose and BMI in SLE patients. Chung et al. [33] have reported that SLE patients had higher Ad concentrations in comparison to control subjects. Moreover, the authors [33] found that Ad concentrations were negatively associated with the insulin resistance, BMI and CRP, while a positive correlation between Ad and HDL levels was observed in SLE patients.

It is not elucidated whether Ad deficiency alone is sufficient to provoke the autoimmune phenotype or whether it induces the exacerbation of the inflammation in the already established autoimmune settings [25]. Obesity in SLE was independently associated with markers of inflammation [34] and the inflammatory response in obesity and other conditions is different in regard to Ad regulation [20]. In addition, the pathogenesis of some systemic AID, including SLE was linked with the impaired clearance of the apoptotic debris and it was suggested that Ad exerted capacity of binding for early apoptotic cells by Mf through a receptor-mediated pathway [26, 35]. Moreover, it was suggested that Ad was capable to bind to (and to sequester) immuno-stimulatory material containing RNA or DNA which was released from apoptotic cells (this is supported by the fact that C1q, which is structurally similar to Ad is able to directly bind to DNA) [20].

Adiponectin and APS

Rodrigues et al. [36] analyzed the adipocytokines in 56 PAPS patients and in 72 control subjects. No significant differences were found in the concentrations of Ad ($p=0.10$) in both groups. Adiponectin levels were in inverse correlation with BMI ($r=-0.28$, $p=0.041$), VLDL-cholesterol ($r=-0.41$, $p=0.003$) and triglyceride levels ($r=-0.43$, $p=0.001$) and HOMA-IR ($r=-0.36$, $p=0.010$), but in direct correlation with HDL-cholesterol ($r=0.37$, $p=0.006$), aCL IgG ($r=0.41$, $p=0.02$) and anti-β2GPI IgM ($r=0.38$, $p=0.005$). Lower Ad levels significantly associated with the frequency of metabolic syndrome [16.0 (10.2–14.0) vs. 25.1 (14.1–39.0), $p<0.042$]. The variables that independently influenced the Ad concentration were the triglyceride levels ($p<0.001$), VLDL-cholesterol ($p=0.002$) and anti-β2GPI IgG ($p=0.042$). No significant differences were found regarding Ad ($p=0.09$) concentrations in PAPS patients with and without arterial events. This study provides evidence that various adipocytokines may be involved in low-grade inflammation [36].

In regard to novel aPL Abs and Ad, it was reported that Ad was in positive correlation with the IgM isotype of the anti-annexin A5 Abs in patients with DM2 [30]. However, except for the above-mentioned study [30] that analyzed aCL and anti-β2GPI Abs in PAPS, not a single article that analyze anti-annexinA5 or any other aPL Abs and Ad levels in APS was found.

Toffoli et al. [37] have reported that aged Pparg null-mice developed APS in association with lupus nephritis. It was characterized by the presence of microthrombi, increased titers of aβ2gpI Abs and deposition of C3, IgG, IgM in kidneys. The authors [37] reported that these Pparg null-mice represented the first animal model that spontaneously develop APS and this model emphasized the importance of PPAR-gamma signaling in the development of APS. The PPAR-gamma significance in inflammation and autoimmunity is well established, however, its role(s) in the context of APS and its potential as therapeutic target remains to be further established first in larger animal and eventually clinical studies.

Previously, we have mentioned that SAPS is the most frequently associated with SLE. Vadacca et al. [38] have reported no significant differences in Ad levels in SLE patient with or without APS. In various SLE murine models, it was reported that PPAR-gamma agonists had positive effects (improvement of cardiometabolic risk and renal inflammation, decrease of renal injury) [39, 40]. Therefore, in the context of the results obtained on Pparg null-mice, it appears that treatment with PPAR-gamma agonists might be justified for further testing in amelioration of APS. It was reported that PPAR-gamma activation provokes Mf activation and has the influence on the inflammatory response [41]. Activation of PPAR-gamma by its agonists in SLE models expands M2 subpopulation which resulted in efficient removal of apoptotic cells. Macrophages–M2 engulfed apoptotic cells, increased the production of anti-inflammatory and decreased production of pro-inflammatory cyt. The impairment of Mf activation and removal of apoptotic cells might be relevant mechanisms in SLE pathogenesis. The authors [41] concluded that activation of PPAR-gamma by its agonist had anti-inflammatory effects on Mf (from SLE patients) and, therefore, PPAR-gamma agonist could be introduced as anti-inflammatory therapy in SLE.

Pioglitazone and rosiglitazone treatment reduced SLE manifestations in the MRL.lpr mouse model (in a similar manner) [19–21]. Patients with SLE had increased risk for the development of premature atherosclerosis and increased incidence of CVD [42, 43]. In addition, SLE patients exert metabolic dysfunction [44]. Similarly, APS patients also suffer from premature atherosclerosis and high incidence of CVD and metabolic syndrome [8]. It was reported that PPAR-gamma agonists might be important in reducing the incidence of CVD and metabolic syndrome in SLE. The Ad induction is a major mechanism underlying the immunomodulatory roles of PPAR-gamma agonists [20]. The binding of Ad to AdipoR1 and AdipoR2 leads to the activation of AMPK and PPAR-gamma [44]. Recombinant Ad (rAd) application was beneficial for the improvement of glucose, insulin and lipids' levels in mice [45]. Anti-inflammatory properties of Ad and/or AdR treatment require further analysis, they represent "promising targets" for the development of therapeutic drugs to treat conditions associated with the inflammation. Okada-Iwabu et al. [46] have synthesized an orally active adipoR agonist (AdipoRon). In vitro, it bounds both AdR1 and AdR2 and exert similar effects to Ad (amelioration of insulin resistance and glucose intolerance) in mice. Previously, it was reported that Ad exerted anti-inflammatory features and therefore, it might be hypothesized that rAd, AdR agonists or PPAR-gamma agonists could be potential targets for the treatment of inflammatory conditions [47] such as SLE and APS.

Conclusions

A review of the literature revealed that the aged Pparg null-mice spontaneously develop APS and this model emphasized the importance of PPAR-gamma signaling in the development of APS [37]. PPAR-gamma agonists induce Ad production [20], and Ad concentrations were independently influenced by the IgG aβ2gpI Abs titers in PAPS patients [36]. Therefore, due to the re-occurrence of thrombotic episodes in APS patients (despite life-long anticoagulation), it might be beneficial to consider administration of PPAR-gamma agonists, rAd, or AdR agonists for further testing in experimental models of APS, which eventually, will provide more data for novel therapeutic strategies that will ameliorate clinical manifestations of APS.

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Compliance with ethical standards

Conflict of interest None of the authors has any potential financial nor non-financial conflict of interest related to this manuscript. No part of the review, including ideas, text and tables are copied or published elsewhere. The authors alone are responsible for the content and writing of the paper. MB is responsible for analysis, interpretation of data and writing the article. BN and SI are responsible for the final approval of the article. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Ethical standards Submitted paper is a review of relevant literature. This article does not contain any studies with human participants performed by any of the authors. All procedures performed in our study were in accordance with Helsinki Declaration (and its later amendments) and with the ethical standards of the institutional ethical committee.

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