Adiponectin and inflammation: Consensus and controversy

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Circulating levels of adiponectin decrease with increasing visceral obesity and are lower in patients with type 2 diabetes, the metabolic syndrome, and cardiovascular disease compared with controls matched by body mass index. Several reports demonstrated anti-inflammatory effects of adiponectin. Because increased adipose tissue is associated with low-grade chronic inflammation and proinflammatory factors inhibit adiponectin production, the current hypothesis states that chronic inflammation associated with visceral obesity inhibits production of adiponectin, perpetuating inflammation. The negative correlation between adiponectin and markers of inflammation in the aforementioned conditions supports this hypothesis. In contrast with disorders typically associated with excess adiposity and positive energy balance, adiponectin levels are elevated—rather than decreased—in classic chronic inflammatory/autoimmune diseases that are unrelated to increased adipose tissue, such as rheumatoid arthritis, SLE, inflammatory bowel disease, type 1 diabetes, and cystic fibrosis. In these patients, adiponectin levels positively—rather than negatively—correlate with inflammatory markers. Furthermore, proinflammatory effects of adiponectin have been reported in tissues such as joint synovium and colonic epithelium. Thus, adiponectin is regulated in the opposite direction and may exert differential functions in classic versus obesity-associated inflammatory conditions. This article discusses this apparent paradox and presents possible alternative and/or complementary explanations.
(J Allergy Clin Immunol 2008;121:326-30.)

Key words: *Adipose tissue, inflammation, autoimmunity, adipokines, cytokines*

Adiponectin, a protein mainly produced by adipocytes and therefore belonging to the adipokine family, is being extensively investigated as a promising therapeutic target for type 2 diabetes (T2D), the metabolic syndrome, and cardiovascular disease (CVD). The complex structure of adiponectin, its 2 specific receptors, and their biological functions are the subject of many excellent reviews.[1,2] Adiponectin increases insulin sensitivity and is protective against CVD in several experimental animal models.

Abbreviations used
BMI: Body mass index
CF: Cystic fibrosis
CRP: C-reactive protein
CVD: Cardiovascular disease
RA: Rheumatoid arthritis
T1D: Type 1 diabetes
T2D: Type 2 diabetes

In human beings, adiponectin levels decrease with increasing obesity and are consistently lower in patients with T2D, the metabolic syndrome, and CVD compared with healthy controls matched by body mass index (BMI).[1] The current hypothesis states that chronic inflammation associated with obesity and CVD inhibits production of adiponectin—probably through increased levels of proinflammatory cytokines—leading to perpetuation of inflammation. However, outside the context of diseases associated with obesity, an inflammatory status is not necessarily correlated with low adiponectin levels. Actually, the opposite is observed, with adiponectin levels increasing during inflammatory conditions that are unrelated to increased adipose tissue mass. This article discusses this apparent paradox, which is also summarized in Fig 1.

CONSENSUS

As mentioned, dozens of studies consistently reported low levels of adiponectin in obesity, T2D, and CVD.[1] *In vitro* studies demonstrated that proinflammatory factors—including cytokines such as TNF-α and IL-6—suppress adiponectin production by adipocytes. An inverse correlation between adiponectin and classic markers of inflammation, such as C-reactive protein (CRP) and IL-6, has been observed in obese and insulin-resistant subjects (particularly in the presence of visceral adiposity), in which chronic low-grade inflammation of adipose tissue, with macrophage infiltration, is commonly observed. In addition, several reports demonstrated that adiponectin exerts a variety of anti-inflammatory activities, ranging from inhibition of proinflammatory cytokine production, to induction of anti-inflammatory factors, to reduction of adhesion molecules expression, and others.[2]

A substantial amount of coherent data has thus generated the following paradigm:

1. Obesity is associated with inflammation in adipose tissue.
2. Proinflammatory factors suppress adiponectin production.
3. Low levels of adiponectin increase insulin resistance and risk of CVD.
4. Low levels of adiponectin promote inflammation, thus generating a self-sustaining inflammatory loop.

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Supported by National Institutes of Health grants DK061483 and DK068035.
Disclosure of potential conflict of interest: The author has declared that she has no conflict of interest.
Received for publication August 15, 2007; revised October 3, 2007; accepted for publication October 5, 2007.
Available online December 3, 2007.
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0091-6749/$34.00

doi:10.1016/j.jaci.2007.10.018

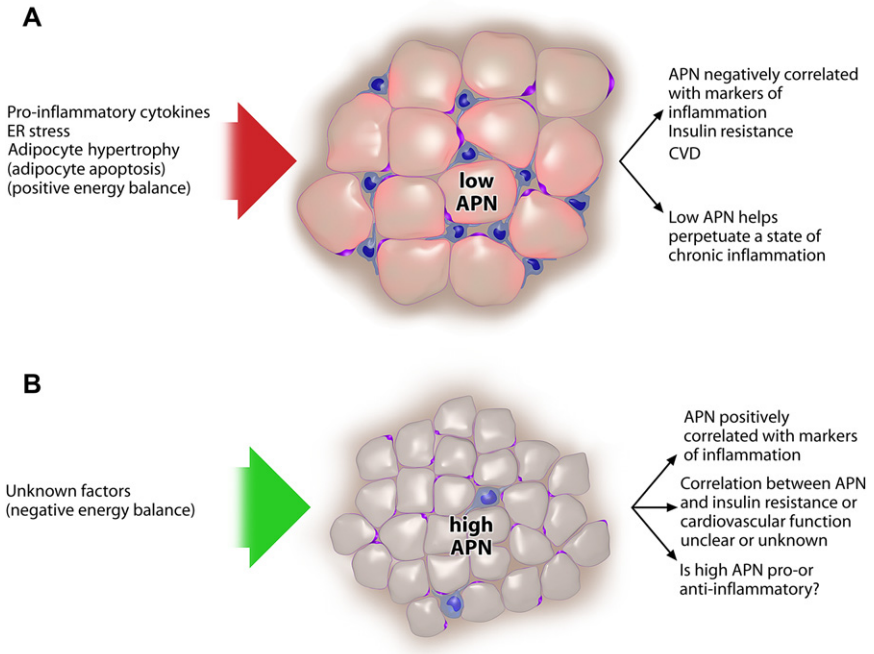

FIG 1. Role and regulation of adiponectin *(APN)* in metabolic versus autoimmune/chronic inflammatory disease. A variety of factors, including proinflammatory cytokines like TNF-α and IL-6, endothelial reticulum stress, and adipocyte hypertrophy have been demonstrated to inhibit APN production from adipocytes in the context of metabolic diseases such as T2D, CVD, and the metabolic syndrome **(A)**. Possible (although not demonstrated) factors also influencing APN production during metabolic disease include, among others, increased adipocyte apoptosis and positive energy balance. A combination of the aforementioned conditions leads to low APN levels, which tend to perpetuate the state of low-grade chronic inflammation typical of metabolic disease. On the background of metabolic disease, APN levels are negatively correlated with markers of inflammation, such as CRP and IL-6, as well as with indices of insulin resistance and CVD. In contrast, during autoimmune/chronic inflammatory conditions such as T1D, RA, SLE, inflammatory bowel disease, and CF **(B)**, an unknown range of factors, possibly including a tendency toward negative energy balance, leads to high levels of APN, either locally or systemically. These high levels of APN are positively rather than negatively correlated with markers of inflammation. The correlation between APN and insulin resistance or CVD in the context of autoimmune/chronic inflammatory diseases is still not completely clear. Furthermore, the issue of whether these high APN levels exert proinflammatory or anti-inflammatory effects remains open. *ER*, Endoplasmic reticulum.

Although the relationship is not necessarily linear and is certainly more complex than outlined, the scientific community appears to have reached a consensus on this issue, substantiated by robust experimental and clinical data.

CONTROVERSY

In contrast with reduced levels of adiponectin in metabolic conditions associated with excess adipose tissue, increased local and/or systemic adiponectin levels are present in chronic inflammatory and autoimmune diseases such as rheumatoid arthritis, SLE, type 1 diabetes (T1D), and inflammatory bowel disease. Thus, these conditions present the apparent paradox of being characterized by high levels of adiponectin in the presence of inflammation. It is important to note that, in the vast majority of studies, patients and controls have been matched by BMI; therefore, the observed differences are unlikely to be secondary to variations in the degree of adiposity, although in most of these studies, differences in the distribution of adipose tissue have generally not been taken into account. Furthermore, a growing number of studies also indicates that adiponectin can exert proinflammatory rather than anti-inflammatory activities.

Unfortunately, because of space limitations, only a selected number of reports describing the association between adiponectin and inflammatory diseases can be cited.

Rheumatoid arthritis

A letter to the *Journal of the American Medical Association* by Schaffler et al[3] was probably the first report indicating increased adiponectin concomitant with an inflammatory response. The authors described increased levels of adiponectin in synovial fluid of patients with rheumatoid arthritis (RA) compared with patients with osteoarthritis.[3] The observation of increased synovial adiponectin in RA was later confirmed by other investigators and extended to systemic levels.[4-6] Increased serum adiponectin levels in RA were observed despite high CRP levels, and CRP was positively correlated to serum adiponectin, the opposite of what was reported for metabolic diseases.[4,5]

In the context of RA, recombinant adiponectin selectively induced synthesis of IL-6 and matrix metalloproteinase inhibitor 1 in human synovial fibroblasts via a p38 mitogen-activated protein kinase pathway and induced expression of growth regulated oncogene α, monocyte chemoattractant protein 1, and tissue

inhibitor of metalloproteinase 1 in osteoarthritis chondrocytes.[6,7] Quite interestingly, neutralization of TNF-α activity resulted in inhibition of the ability of recombinant adiponectin to induce IL-6 and matrix metalloproteinase inhibitor 1, indicating that the proinflammatory effects of adiponectin in the synovium are likely mediated by TNF-α, which can be induced by adiponectin in macrophages.[7]

Thus, in RA high levels of local and systemic adiponectin are observed in the presence of concomitant chronic inflammation, and *in vitro* studies indicate that adiponectin exerts proinflammatory effects (likely TNF-mediated) in chondrocytes and synovial fibroblasts. However, a correlation between high adiponectin and reduced inflammation has been observed in patients with RA.[5] Thus, the question of whether adiponectin exerts proinflammatory or anti-inflammatory effects in the arthritic joint remains open and awaits the use of animal models for mechanistic investigations.

SLE

Increased serum adiponectin levels are present in patients with SLE compared with controls, particularly in patients with inflammatory renal flare.[8,9] High serum adiponectin in SLE was observed despite the simultaneous presence of high serum TNF-α, which is considered one of the major inhibitors of adiponectin production.[8] Despite higher adiponectin levels, patients with SLE were more insulin-resistant and had a higher prevalence of T2D and hypertension compared with controls, irrespective of BMI.[8] However, the expected negative correlation between serum adiponectin and indices of insulin resistance—widely reported in other populations—was also present in patients with SLE.[8] Thus, in SLE, the accepted negative correlation between adiponectin and insulin resistance has been confirmed, but this association is present on the background of increased adiponectin levels with significant systemic inflammation.

Inflammatory bowel disease

Increased adiponectin expression (at both the mRNA and the protein level) and release was observed in the fat wrapping—hypertrophic mesenteric adipose tissue that surrounds the inflamed segments of the intestine—in Crohn disease compared with mesenteric adipose tissue obtained from controls or from patients with ulcerative colitis, in which fat wrapping is typically not present.[10,11] Notably, in individual patients with Crohn disease, higher adiponectin expression was observed in inflamed compared with noninflamed adipose tissue, indicating the presence of an ongoing inflammatory reaction concomitant with high adiponectin expression.[10] In colonic epithelial cells, adiponectin exerted proinflammatory effects by inducing chemokine production.[12] In experimental models of colonic inflammation, adiponectin-deficient mice have been reported to be either protected or more susceptible.[13,14]

The available evidence thus indicates that in Crohn disease, local inflammation in mesenteric adipose tissue is associated with increased rather than decreased adiponectin production by adipocytes, that adiponectin exerts proinflammatory effects on colonic epithelial cells, and that adiponectin deficiency may result in reduced colonic inflammation in animal models, although this latter issue is still controversial.

T1D

In contrast with T2D, in which serum adiponectin is decreased, a significant increase in circulating adiponectin levels—irrespective of BMI—has been reported by several groups for adult patients with T1D.[15-17] Some investigators directly compared patients with T1D and T2D, confirming in the same setting the observation of increased adiponectin in T1D and decreased adiponectin in T2D.[15,16] High adiponectin levels in T1D were not correlated with length of insulin treatment or BMI and were observed in association with systemic markers of inflammation, such as increased levels of CRP and IL-6, which are negatively correlated with adiponectin in patients with T2D.[1,17] Furthermore, patients with T1D who developed nephropathy or retinopathy because of microvascular disease had significantly higher adiponectin levels compared with patients with T1D without microvascular complications,[18] a finding that appears to contradict the role of adiponectin as a protective factor in the vascular wall.

Although in T1D metabolic alterations and body composition may influence adiponectin levels irrespective of ongoing inflammation and autoimmunity, it is quite interesting to observe that inflammatory markers (CRP, IL-6) as well as microvascular disease are associated with increased, rather than decreased, serum adiponectin levels. The role and regulation of adiponectin in animal models of T1D has not been investigated as of this writing.

Allergy and asthma

Despite evidence for an association between obesity and asthma, very few studies evaluated the role and regulation of adiponectin in these conditions. In an animal model of ovalbumin-induced airway hyperresponsiveness, administration of exogenous adiponectin exerted a protective effect by reducing cellular infiltrate and cytokine levels.[19] Furthermore, ovalbumin challenge led to a 30% reduction in serum adiponectin levels as well as in the expression of adiponectin receptors in the lung. [19] In contrast, Rothenbacher et al[20] reported that elevated cord blood adiponectin levels are associated with an increased risk of asthma or obstructive bronchitis in children born from atopic mothers, whereas adiponectin levels in the lowest quintile confer protection against the same conditions. Thus, the current, very limited evidence on the role of adiponectin in allergy and asthma is contradictory, and further research is clearly needed in this field.

Other inflammatory conditions

"Unorthodox" levels of adiponectin have also been reported for other conditions characterized by chronic inflammation. In one report, patients with cystic fibrosis (CF) had increased adiponectin levels despite increased visceral adipose tissue mass, higher serum CRP levels, and similar levels of insulin resistance compared with a control population matched by BMI, age, and sex.[21] A second study in patients with CF demonstrated absence of alterations in systemic adiponectin levels despite the presence of insulin resistance, glucose intolerance, and subclinical chronic inflammation.[22] Finally, 2 groups evaluated the effect of LPS administration in healthy volunteers and reported that, contrary to expectations, adiponectin levels were not altered, despite the anticipated induction of proinflammatory cytokines and acute-phase response.[23,24] However, lack of modulation of adiponectin levels

in this setting may simply reflect the acute nature of the inflammatory response after a single administration of LPS.

OPEN QUESTIONS

The data discussed suggest that the paradigm

Inflammation → low adiponectin → more inflammation,

currently accepted in the context of obesity, metabolic syndrome, T2D, and CVD, does not apply to classic chronic inflammatory conditions in which increased adipose tissue mass does not likely play a pathogenetic role. In fact, a consistent pattern of elevated rather than decreased adiponectin levels is emerging for autoimmune/chronic inflammatory diseases, in which proinflammatory mediators should theoretically lead to reduced adiponectin production.

This apparent paradox raises a series of questions. (1) Are the low adiponectin levels of conditions associated with increased adipose tissue mass directly attributable to inflammation, or are they a result of other factors, with inflammation possibly playing a contributory role? A possible (nonexhaustive) list of alternative and/or complementary factors includes enlarged adipocyte size with concomitant endoplasmic reticulum stress,[25] hypoxia of adipose tissue,[26] high rates of adipocyte death and turnover, and positive energy balance, which are all usually increased in obesity and associated diseases but not in classic chronic inflammation.

The complementary question also needs to be asked: (2) is inflammation directly inducing increased adiponectin levels in RA, SLE, and T1D, or are other factors, such as metabolic alterations, responsible? As suggested by Behre[27] and more recently supported by data from Kubota et al,[28] adiponectin—together with leptin—has probably evolved to help survival during periods of catabolism secondary to malnutrition and starvation. For example, in mice, adiponectin decreases energy expenditure and limits the amount of adipose tissue loss during fasting.[28] Thus, the increased adiponectin of classic inflammation may be a result of inflammation-induced catabolic responses, which are not present in obesity-associated inflammation. Therefore, under this hypothesis, inflammation would secondarily increase adiponectin in classic inflammation through its effects on metabolism. However, a clear answer to what kind of process leads to increased adiponectin in autoimmunity and chronic inflammation is still lacking, and so is detailed information on the bioactivity of adiponectin in the context of inflammation.

(3) How is chronic inflammation secondary to increased adipose tissue mass different from chronic inflammation caused by autoimmunity, infection, or a dysregulated immune system? Is a different complement of mediators and/or cell populations involved in the 2 types of conditions, beside the obvious differences in the location of the primary inflammatory insult? Fat wrapping in Crohn disease, in which inflamed adipose tissue produces high levels of adiponectin, may be a useful model to attempt to answer these questions. In fact, both central obesity and Crohn disease are associated with inflammation of visceral adipose tissue, although the primary cause and characteristics of the inflammatory response are different. However, production of adiponectin is diametrically opposite in the 2 conditions, high in Crohn disease and low in visceral obesity.

(4) Is the role of adiponectin in regulating inflammation tissue-dependent and/or context-dependent? It has been hypothesized that low levels of adiponectin contribute to chronicity of inflammation in obesity, T2D, and CVD, whereas there are suggestions that the high adiponectin levels observed in chronic inflammatory diseases help dampen inflammation. However, data indicating possible proinflammatory roles for adiponectin question these assumptions. More research in this field is clearly necessary, particularly data clarifying the relative role and differential regulation of the various molecular forms of adiponectin (high versus low molecular weight versus globular adiponectin) and of adiponectin receptors.

(5) Why do adipocytes produce so much adiponectin? Circulating adiponectin levels are in the micrograms per milliliter range, about 2 to 5 orders of magnitude higher than is usually observed for other adipokines, cytokines, and growth factors. Receptor-dependent intracellular signaling cascades generally require concentrations that are 1000-fold to 10,000-fold lower than those commonly observed for adiponectin, indicating that receptor-independent interactions—such as binding to growth factors, chemokines, and/or extracellular matrix components—are likely critical in the function of adiponectin. Although both the insulin-sensitizing and appetite-regulating properties of adiponectin are receptor-dependent,[28,29] some activities of adiponectin more directly related to inflammation, such as facilitation of apoptotic cell clearance, are independent of adiponectin binding to its specific receptors.[30] It is still unclear how integration of adiponectin signals regulating metabolism and inflammation occurs and why the body produces so much adiponectin in conditions—such as starvation and catabolism—under which energy conservation would be expected.

More research on the role and regulation of adiponectin in inflammation and autoimmunity is clearly necessary to answer these and related questions. An open-minded approach to the likely pleiotropy of adiponectin and the complexity of its biological function and regulation will help generate meaningful data, and so will a close collaboration between researchers working in the fields of metabolic, inflammatory, and autoimmune diseases.

I thank Charles A. Dinarello and Britta Siegmund for their helpful comments.

REFERENCES

1. Lara-Castro C, Fu Y, Chung BH, Garvey WT. Adiponectin and the metabolic syndrome: mechanisms mediating risk for metabolic and cardiovascular disease. Curr Opin Lipidol 2007;18:263-70.
2. Ouchi N, Walsh K. Adiponectin as an anti-inflammatory factor. Clin Chim Acta 2007;380:24-30.
3. Schaffler A, Ehling A, Neumann E, Herfarth H, Tarner I, Scholmerich J, et al. Adipocytokines in synovial fluid. JAMA 2003;290:1709-10.
4. Otero M, Lago R, Gomez R, Lago F, Dieguez C, Gomez-Reino JJ, et al. Changes in plasma levels of fat-derived hormones adiponectin, leptin, resistin and visfatin in patients with rheumatoid arthritis. Ann Rheum Dis 2006;65:1198-201.
5. Senolt L, Pavelka K, Housa D, Huluzik M. Increased adiponectin is negatively linked to the local inflammatory process in patients with rheumatoid arthritis. Cytokine 2006;35:247-52.
6. Chen T-H, Chen L, Hsieh M-S, Chang C-P, Chou D-T, Tsai S-H. Evidence for a protective role for adiponectin in osteoarthritis. Biochim Biophys Acta 2006;1762:711-8.
7. Ehling A, Schaffler A, Herfarth H, Tarner I, Anders S, Distler O, et al. The potential of adiponectin in driving arthritis. J Immunol 2006;176:4468-78.
8. Sada KE, Yamasaki Y, Maruyama M, Sugiyama H, Yamamura M, Maeshima Y, et al. Altered levels of adipocytokines in association with insulin resistance in patients with systemic lupus erythematosus. J Rheumatol 2006;33:1545-52.
9. Rovin BH, Song H, Hebert LA, Nadasdy T, Nadasdy G, Birmingham DJ, et al. Plasma, urine, and renal expression of adiponectin in human systemic lupus erythematosus. Kidney Int 2005;68:1825-33.

10. Yamamoto K, Kiyohara T, Murayama Y, Kihara S, Okamoto Y, Funahashi T, et al. Production of adiponectin, an anti-inflammatory protein, in mesenteric adipose tissue in Crohn's disease. Gut 2005;54:789-96.
11. Paul G, Schaffler A, Neumeier M, Furst A, Bataille F, Buechler C, et al. Profiling adipocytokine secretion from creeping fat from Crohn's disease. Inflamm Bowel Dis 2006;12:471-7.
12. Ogunwobi OO, Beales IL. Adiponectin stimulates proliferation and cytokine secretion in colonic epithelial cells. Reg Peptides 2006;134:105-13.
13. Fayad R, Pini M, Sennello JA, Cabay RJ, Chan L, Xu A, et al. Adiponectin deficiency protects mice from chemically induced colonic inflammation. Gastroenterology 2007;132:601-14.
14. Nishihara T, Matsuda M, Araki H, Oshima K, Kihara S, Funahashi T, et al. Effect of adiponectin on murine colitis induced by dextran sulfate sodium. Gastroenterology 2006;131:853-61.
15. Perseghin G, Lattuada G, Danna M, Piceni Sereni L, Maffi P, De Cobelli F, et al. Insulin resistance, intramyocellular lipid content, and plasma adiponectin in patients with type 1 diabetes. Am J Physiol Endocrinol Metab 2003;285:E1174-81.
16. Furuta M, Tamai M, Hanabusa T, Yamamoto Y, Nanjo K, Sanke T. Serum adiponectin is associated with fasting serum C-peptide in non-obese diabetic patients. Diabetes Res Clin Pract 2006;72:302-7.
17. Heliovaara MK, Teppo AM, Karonen SL, Tuominen JA, Ebeling P. Improved glycaemia in type 1 diabetes results in decreased levels of soluble adhesion molecules with no change in serum adiponectin or most acute phase proteins. Exp Clin Endocrinol Diabetes 2006;114:295-300.
18. Hadjadj S, Aubert R, Fumeron F, Pean F, Tichet J, Roussel R, et al. Increased plasma adiponectin concentrations are associated with microangiopathy in type 1 diabetic subjects. Diabetologia 2005;48:1088-92.
19. Shore SA, Terry RD, Flynt L, Xu A, Hug C. Adiponectin attenuates allergen-induced airway inflammation and hyperresponsiveness in mice. J Allergy Clin Immunol 2006;118:389-95.
20. Rothenbacher D, Weyermann M, Fantuzzi G, Brenner H. Adipokines in cord blood and risk of wheezing disorders within the first two years of life. Clin Exp Allergy 2007;37:1143-9.
21. Moriconi N, Kraenzlin M, Muller B, Keller U, Nusbaumer CP, Stohr S, et al. Body composition and adiponectin serum concentrations in adult patients with cystic fibrosis. J Clin Endocrinol Metab 2006;91:1586-90.
22. Hammana I, Malet A, Costa M, Brochiero E, Berthiaume Y, Potvin S, et al. Normal adiponectin levels despite abnormal glucose tolerance (or diabetes) and inflammation in adult patients with cystic fibrosis. Diabetes Metab 2007;33:213-9.
23. Anderson PD, Mehta NN, Wolfe ML, Hinkle CC, Pruscino L, Comiskey LL, et al. Innate immunity modulates adipokines in humans. J Clin Endocrinol Metab 2007; 92:2272-9.
24. Keller P, Moller K, Krabbe KS, Pedersen BK. Circulating adiponectin levels during human endotoxaemia. Clin Exp Immunol 2003;134:107-10.
25. Skurk T, Alberti-Huber C, Herder C, Hauner H. Relationship between adipocyte size and adipokine expression and secretion. J Clin Endocrinol Metab 2007;92:1023-33.
26. Ye J, Gao Z, Yin J, He Q. Hypoxia is a potential risk factor for chronic inflammation and adiponectin reduction in adipose tissue of ob/ob and dietary obese mice. Am J Physiol Endocrinol Metab 2007;293:E1118-E1128.
27. Behre CJ. Adiponectin: saving the starved and the overfed. Med Hypotheses 2007; 69:1290-2.
28. Kubota N, Yano W, Kubota T, Yamauchi T, Itoh S, Kumagai H, et al. Adiponectin stimulates AMP-activated protein kinase in the hypothalamus and increases food intake. Cell Metab 2007;6:55-68.
29. Yamauchi T, Ni Y, Maki T, Kobayashi M, Takazawa T, Iwabu M, et al. Targeted disruption of AdipoR1 and AdipoR2 causes abrogation of adiponectin binding and metabolic actions. Nat Med 2007;13:332-9.
30. Takemura Y, Ouchi N, Shibata R, Aprahamian T, Kirber MT, Summer RS, et al. Adiponectin modulates inflammatory reactions via calreticulin receptor-dependent clearance of early apoptotic bodies. J Clin Invest 2007;117:375-86.