بسم الله الرحمن الرحيم

((يَرْفَعِ اللَّهُ الَّذِينَ آمَنُوا مِنكُمْ وَالَّذِينَ أُوتُوا الْعِلْمَ دَرَجَاتٍ ۚ))

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Effect Of Adiponectin On Insulin Resistance In Type2 D.M

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BY

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Dedication.

To Hashd Allah Almuqadas

To our family , especially

Mom and Dad

For their help , love and support

We would like to express our thanks for our supervisor

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DIABETES MELLITUS

Introduction

Diabetes mellitus is a chronic endocrine disorder, characterized by hyperglycaemia resulting from absolute or relative insulin deficiency. There are a number of different causes of diabetes but by far the majority of cases are classified as either type 1 or type 2 diabetes. The pathophysiology of type 1 diabetes derives from the autoimmune destruction of insulin-secreting pancreatic β-cells, resulting in insulin deficiency and subsequent hyperglycaemia. Type 1 diabetes accounts for about 10-15% of all diabetics. Type 2 diabetes is characterized by abnormal insulin secretion due to peripheral resistance and accounts for 85-90% of all persons with diabetes. While type 1 diabetes usually manifests itself in childhood or adolescence and type 2 diabetes at a later stage, clinical manifestation and progression vary considerably and some patients might not be clearly classified as having either type 1 or 2 initially. Type 1 diabetes may occur at any age and with late onset usually shows slower progression, and type 2 manifests itself more and more often earlier in life, even in childhood and adolescence, sometimes allowing for accurate diagnosis only over time. In the uncontrolled state, both types of diabetes are characterized by increased hepatic glucose output and decreased glucose uptake in the muscles and adipose tissue. Patients with type 1 diabetes are at risk of severe lipolysis leading to diabetic ketoacidosis. The remaining insulin activity in type 2 diabetes usually inhibits lipolysis and ketone production such that these patients are less likely to develop ketoacidosis but are more likely to develop a hyperosmolar, non-ketotic state . (1)

Classification

Diabetes can be classified in to the following general categories

1- Type 1 diabetes (due to B-cell destruction ,usually leading to absolute insulin deficiency)

2- Type 2 diabetes (due to a progressive insulin secretory defect on the back ground of insulin resistance)

3- Gestational diabetes mellitus (GDM) (diabetes diagnosed in the second or third trimester of pregnancy that is not clearly overt diabetes)

4- Specific types of diabetes due to other causes ,e. g ,monogenic diabetes syndromes (such as neonatal diabetes and maturity-onset diabetes of the young [MODY]), diabetes of exocrine pancreas (such as cystic fibrosis) , and drug- or chemical- induced diabetes (such as in the treatment of HIV/ AIDS or after organ transplantation . (2,3 ,4,5)

Methods and criteria for diagnosing diabetes

1. Diabetes symptoms (e.g. polyuria, polydipsia and unexplained weight loss for Type 1) plus:
   - a random venous plasma glucose concentration ≥ 11.1 mmol/l or
   - a fasting plasma glucose concentration ≥ 7.0 mmol/l (whole blood ≥ 6.1 mmol/l) or
   - two hour plasma glucose concentration ≥ 11.1 mmol/l two hours after 75g anhydrous glucose in an oral glucose tolerance test (OGTT).
2. With no symptoms diagnosis should not be based on a single glucose determination but requires confirmatory plasma venous determination. At least one additional glucose test result on another day with a value in the diabetic range is essential, either fasting, from a random sample or from the two hour post glucose load. If the fasting random values are not diagnostic the two hour value should be used . (2,3,4,5,6)

Haemoglobin A1c (HbA1c) testing to diagnose diabetes

An HbA1c of 48mmol/mol (6.5%) is recommended as the cut off point for diagnosing diabetes. A value of less than 48mmol/mol (6.5%) does not exclude diabetes diagnosed using glucose tests . (2,3,4 ,5 ,6)

Gestational diabetes

The criteria for diagnosing gestational diabetes is different. Gestational diabetes should be diagnosed if the woman has either.

- a fasting plasma glucose level of 5.6mmol/l or above or
- a 2-hour plasma glucose level of 7.8mmol/l or above. (2,3,4,5,6)

Diabetes mellitus type1

Diabetes mellitus type1 (also known as type1 diabetes , or T1D; formerly insulin-dependent diabetes or juvenile diabetes) is a form of diabetes mellitus that results from the autoimmune destruction of the insulin-producing beta-cell in the pancrease subsequent lack of insulin leads to increase blood and urine glucose. The classical symptoms are polyuria (frequent urination) ,polydipsia(increased thirst) ,polyphagia (increased hunger). (2,3)

Type 2 diabetes

In T2D ,the body either produce inadequate amount of insulin to meet the demands of the body or insulin resistance has developed . Insulin resistance refer to when cells of the body such as the muscle, liver and fat cells fail to respond to insulin ,even when levels are high . In fat cells ,triglycerides are instead broken down to produce free fatty acids for energy ,muscle cells are deprived of an energy source and liver cells fail to build up glycogen stores .

This also leads to an overall rise in the level of glucose in the blood .glycogen stores become markedly reduced and there is less glucose available for release when it may be needed .Obesity and lack of physical activity are thought to be major causes of insulin resistance. (4,5)

Symptoms of type2 diabetes includes

1-tiredness and fatigue.

2-unexplained weight loss and muscle loss.

3-diabetics are prone to infection because the high blood sugar provides a favourable growth medium for microbes . Diabetics are also less able to defend against these infections . fungal infections of vulva in femals are common leading to itching and urinary tract infections may occurs in both in men and women .Diabetic individual may also develop non-healing ulcers or sores which can turn gangrenous if left untreated . (4,5)

Complication:

eventually ,serious complications of the disease may arise and affect various bodily systems. For example , the following may develop : (4,5,6,7)

Retinopathy

((floaters)) or floating dark spots in the field of vision may occur as a result of damage caused to the retina by an inadequate supply of nutrients and oxygen by blood vessels. This occurs due to the microvascular changes that diabetes causes in the eye.

Diabetic neuropathy

This refers to nerve damage caused by diabetes which may lead to tingling , pain or numbness is affected areas . Usually , the peripheries such as the toes and fingers are the first to be affected .

The autonomic nervous system may also be affected causing disorder of bodily systems such as the digestive , reproductive and urinary systems .

Cardiovascular disease

The risk of heart disease is also raised in diabetic individuals which increases the likelihood of heart attacks , heart failure , high blood pressure and strokes.

Role of inflammation in development of diabetes mellitus

Although it is plausible to accept diabetes as a trigger for vascular inflammation, the converse is also true, as substantial evidence has shown that low-grade inflammation is an important pathogenetic determinant of type 2 diabetes. In the West of Scotland Coronary Prevention Study, increased CRP levels significantly predicted the risk of later developing type 2 diabetes, and this risk was independent of body mass index, fasting triglyceride or glucose levels, or statin use (10). Moreover, a high white blood cell count was an independent predictor of a worsening insulin action and the development of type 2 diabetes in Pima Indians (11), as well as in U.S. adult women (12). Increased levels of other markers of inflammation, such as sialic and orosomucoid acid, are also associated with the later occurrence of diabetes (13).

More recently, an abundance of clinical evidence has confirmed the pathogenetic role of inflammation in the onset of diabetes, showing that anti-inflammatory agents, such as statins (14), PPAR agonists (15),and other drugs, including angiotensin-converting enzyme inhibitors (16), may prevent or delay the onset of diabetes in high-risk subjects. Trials are currently underway to further validate this exciting hypothesis.

Adiponectin : a hormone also known as adipoQ or adipocyte complement-related protein, is specifically and very highly expressed in adipose tissue. This hormone enhances insulin sensitivity in muscle and liver and increases FFA oxidation in several tissues, including muscle fibers (17-19). It also decreases serum FFA, glucose, and triacylglycerol concentrations. if normal, lean mice are given injections of adiponectin in conjunction with a meal high in fat and sugar, the normal postprandial increases in plasma glucose, FFA, and triacylglycerol concentrations are smaller as the result of an increased rate of clearance from the blood rather than a reduced rate of absorption from the gut (17). In contrast, if insulin-resistant mice are treated with physiologic concentrations of adiponectin, glucose tolerance is improved and insulin resistance is reduced (18).

In humans, plasma adiponectin concentrations fall with increasing obesity, and this effect is greater in men than in women (20). Reduced adiponectin concentrations correlate with insulin resistance and hyperinsulinemia (21, 22). In addition, several polymorphisms of the adiponectin gene (*APM1*, mapped to chromosome 3q27) have been identified that are associated with reduced plasma adiponectin concentration (23) and that increase the risk of type 2 diabetes, insulin resistance, or the metabolic syndrome (23, 24).

Interestingly, adiponectin appears to be implicated in the development of atherosclerosis. Adiponectin concentrations are reduced in patients with coronary artery disease (21), and adiponectin inhibits tumor necrosis factor α (TNF-α)-induced expression of adhesion molecules and the transformation of macrophages to foam cells, both of which are key components of atherogenesis .

Structure

Adiponectin is a 244-amino-acid-long polypeptide (protein). There are four distinct regions of adiponectin. The first is a short signal sequence that targets the hormone for secretion outside the cell; next is a short region that varies between species; the third is a 65-amino acid region with similarity to collagenous proteins; the last is a globular domain. Overall this gene shows similarity to the complement 1Q factors (C1Q). However, when the 3-dimensional structure of the globular region was determined, a striking similarity to TNFα was observed, despite unrelated protein sequences.(25)

Function

Adiponectin is a protein hormone that modulates a number of metabolic processes, including glucose regulation and fatty acid oxidation .(26) Adiponectin is exclusively secreted from adipose tissue (and also from the placenta in pregnancy(27)) into the bloodstream and is very abundant in plasma relative to many hormones. Levels of the hormone are inversely correlated with body fat percentage in adults; (28) however, a meta analysis was not able to confirm this association in healthy adults.(29) The association in infants and young children is less clear. Similarly, circulating adiponectin concentrations increase during caloric restriction in animals and humans, such as in patients with anorexia nervosa . This observation is surprising, given that adiponectin is produced by adipose tissue; however, a recent study suggests that adipose tissue within bone marrow, which increases during caloric restriction, contributes to elevated circulating adiponectin in this context.(30) Transgenic mice with increased adiponectin show impaired adipocyte differentiation and increased energy expenditure associated with protein uncoupling .(31) The hormone plays a role in the suppression of the metabolic derangements that may result in type 2 diabetes ,(28) obesity , atherosclerosis,(26) non-alcoholic fatty liver disease (NAFLD) and an independent risk factor for metabolic syndrome .(32) Adiponectin in combination with leptin has been shown to completely reverse insulin resistance in mice .(33)

Adiponectin is secreted into the bloodstream where it accounts for approximately 0.01% of all plasma protein at around 5–10 μg/mL. Plasma concentrations reveal a sexual dimorphism , with females having higher levels than males. Levels of adiponectin are reduced in diabetics compared to non-diabetics. Weight reduction significantly increases circulating levels.(34)

Adiponectin automatically self-associates into larger structures. Initially, three adiponectin molecules bind together to form a homotrimer. The trimers continue to self-associate and form hexamers or dodecamers. Like the plasma concentration, the relative levels of the higher-order structures are sexually dimorphic, where females have increased proportions of the high-molecular weight forms. Recent studies showed that the high-molecular weight form may be the most biologically active form regarding glucose homeostasis.(35) High-molecular-weight adiponectin was further found to be associated with a lower risk of diabetes with similar magnitude of association as total adiponectin.(36) However, coronary artery disease has been found to be positively associated with high molecular weight adiponectin, but not with low molecular weight adiponectin.(37)

Adiponectin exerts some of its weight reduction effects via the brain . This is similar to the action of leptin , (38)but the two hormones perform complementary actions, and can have synergistic effects.

Receptors

Adiponectin binds to a number of receptors. So far, two receptors have been identified with homology to G protein-coupled receptors , and one receptor similar to the cadherin family.

- adiponectin receptor 1 – ADIPOR1
- adiponectin receptor 2 – ADIPOR2
- T-cadherin –CDH13

These have distinct tissue specificities within the body and have different affinities to the various forms of adiponectin. The receptors affect the downstream target AMP kinase, an important cellular metabolic rate control point. Expression of the receptors is correlated with insulin levels, as well as reduced in mouse models of diabetes, particularly in skeletal muscle and adipose tissue.(39,40)

Adiponectin effects:

- glucose flux
- decreased gluconeogenesis
- increased glucose uptake (26 ,38 ,41)
- lipid catabolism(41)
- β –oxidation (38)

- triglyceride clearance (38)
- protection from endothelial dysfunction (important facet of atherosclerotic formation)
- insulin sensitivity
- weight loss
- control of energy metabolism.(41)
- upregulation of uncoupling proteins (31)
- reduction of TNF-alpha

Regulation of adiponectin

- Obesity is associated with decreased adiponectin.
- The exact mechanism of regulation is unknown, but adiponectin could be regulated by post-translational mechanisms in cells.
- Hypoadiponectinemia

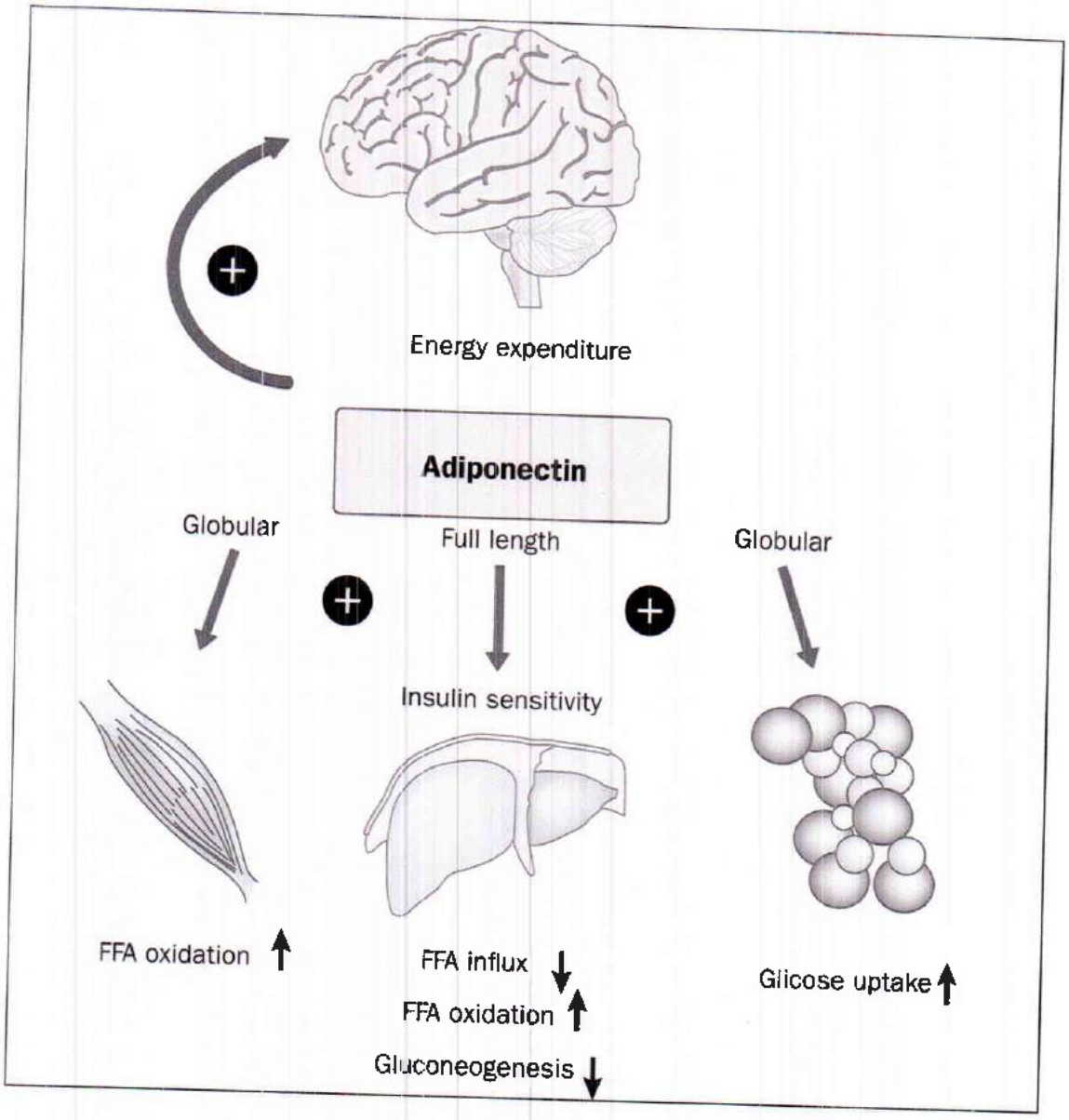
  A low level of adiponectin is an independent risk factor for developing:
- Metabolic syndrome (32)
- Diabetes mellitus (38,42,43,44,45)

Influence of obesity on adiponectin and insulin resistance

The term "diabesity" is used for *diabetes* occurring in the context of obesity . Insulin resistance has a genetic component not yet completely understood, which is often transmitted across generations. Moreover, obesity also has an important genetic component that invariably exacerbates insulin resistance.

As noted above, insulin resistance is often associated with increased body weight and cardiovascular dysfunction. In addition, various adipokines such as adiponectin, TNF-α, resistin and interleukins, are associated with this disease state.(49)

The first article indicating that adiponectin actively affects insulin sensitivity was published in 2001. A fragment of the C-terminal globular adiponectin is capable of reducing plasma glucose concentrations by increasing fatty acid oxidation in muscle (Figure 1).(50,51,52)



FFA: free fatty acids. Source: Fasshauer et al., 2004.(50)

FIGURE1 Hypothetical model for adiponectin action on insulin sensitivity and energy expenditure.

The Adipor1 receptor is predominantly found in skeletal muscle. Most studies have used globular adiponectin binding, which seems to have increased biological activity in skeletal muscle compared to the full-length form of the protein • In disease states, the effects of adiponectin in skeletal muscles are reduced. The binding of globular adiponectin and full-length adiponectin is reduced in obese rats and in insulin-resistant rats, which may be due to a lower density of adipon .(46,49 ,55,56)

The effect of drugs on adiponectine

•The relationship between insulin action and control of the adipocyte-derived factor adiponectin was studied in age- and weight-matched obese individuals with type 2 diabetes failing sulfonylurea therapy. After initial metabolic characterization, subjects were randomized to troglitazone or metformin treatment groups; all subjects received glyburide (10 mg BID) as well. Treatment was continued for 3 months. The extent of glycemic control after treatment was similar in both groups. However, the increase in maximal insulin-stimulated glucose disposal rate was greater following troglitazone therapy (_44%) compared with metformin treatment (_20%). Troglitazone treatment increased serum adiponectin levels nearly threefold. There was no change in serum adiponectin with metformin treatment. A positive correlation was found between increases in whole body glucose disposal rates and serum adiponectin levels after troglitazone; no such relationship was seen with metformin. The adiponectin protein content of subcutaneous abdominal adipocytes was increased following troglitazone treatment and unchanged after metformin. Adiponectin release from adipocytes was also augmented with troglitazone treatment. Adiponectin was present in adipocytes and plasma in several multimeric forms; a trimer was the major form secreted from adipocytes. These results indicate that increases in adiponectin content and secretion are associated with improved insulin action but are not directly related to glycemic control. Modulation of adipocyte function, including upregulation of adiponectin synthesis and secretion, may be an important mechanism by which thiazolidinediones influence insulin action.

Adipose tissue is now recognized as an important source of metabolically active secretory products (adipocytokines), including leptin, tumor necrosis factor (TNF)-_, interleukin (IL)-6, plasminogen activator inhibitor (PAI)-1, adipsin, and free fatty acids (FFAs), which are capable of affecting peripheral insulin action. Human adiponectin (also known as GBP28 or apM1) and its murine homolog acrp30 (also known as adipoQ) are novel fat cell secretory products recently independently identified by a number of investigators (56–59). Adiponectin is abundantly expressed; its levels in plasma account for 0.01–0.03% of total plasma protein (60). Circulating adiponectin levels have been shown to be negatively correlated with BMI (60), plasma glucose, triglyceride, and insulin levels (61). An involvement of adiponectin in regulation of metabolism has been suggested by studies in nonhuman obese primates (62) and an obese Pima Indian population (63), which has shown whole-body insulin sensitivity to be independently associated with reductions in circulating adiponectin levels. Consistent with this finding, two different interventions that improve insulin action, weight loss (64), and thiazolidinedione treatment (65–67) elevate circulating adiponectin Thiazolidinediones

(TZDs) are a new class of insulin sensitizing agents used in the treatment of type 2 diabetes. In clinical studies they have been shown to reduce plasma glucose and insulin levels and to improve lipid abnormalities (68). Recent studies have shown that TZDs dose dependently increase the mRNA expression and secretion of adiponectin (65). Metformin, a member of the biguanide class of compounds, is effective at lowering blood glucose in patients with type 2 diabetes (69). A number of studies have shown that metformin exerts its effects primarily on the liver, inhibiting gluconeogenesis and reducing hepatic glucose output (69,70). Metformin has also been reported to improve peripheral insulin sensitivity and increase insulin-mediated glucose uptake in skeletal muscle of patients with type 2 diabetes (71), possibly through stimulation of the AMP-activated protein kinase(72). To understand more about the potential relationships between adiponectin, glucose tolerance, and insulin action, we evaluated the effects of these two different pharmacologic interventions on adiponectin production in obese type 2 diabetic subjects failing sulfonylurea treatment. We report here that subjects with type 2 diabetes treated with TZDs had significantly greater fat cell content, release, and circulating levels of adiponectin as compared with those with matched glycemic control treated with metformin.

Foods and Adiponectin

almonds

The prevalence of diabetes continues to increase worldwide. Eating almonds helps people with diabetes manage their blood sugar, according to an April 2011 article in "Metabolism." Scientists do not yet understand how almonds control sugar levels. Almonds appear to trigger the release of substances from bodily tissues -- special hormones that lower blood sugar. A clinical trial described in the March 2011 edition of the "European Journal of Clinical Nutrition" tested this hypothesis in women with ovary disease. Patients received daily portions of almonds for six weeks. Relative to baseline, this regimen enhanced levels of adiponectin -- a hormone known to regulate sugar level and body weight. It also tended to reduce masculine hormones such as testosterone. The participants did not experience negative reactions from eating the almonds.(73,74 75).

Polyunsaturated fatty acid and omega-3

The results of studies involving animal models indicate that the consumption of hyperlipidemic dietsrich in saturated fat reduces the levels of adiponectin, while the diets rich in polyunsaturated fatty acids and supplementation with omega-3 increase both gene expression and plasma levels. In humans, the results corroborated the positive association between the levels of adiponectin and healthy feeding, with the intake of fruits and whole grains. Evidence also suggests that the Mediterranean diet is correlated with high concentrations of adiponectin in healthy and diabetic individuals although the mechanisms are not fully understood. The initial results demonstrate that the consumption of diets with omega-3 and EPA supplementation may improve the levels of adiponectin in humans. Moreover, omega-3 supplementation provided a non-significant increase in the levels of adiponectin (10%). Due to the importance of adiponectin in preventing and treating diseases such as type 2 diabetes, hypertension, dyslipidemia and atherosclerosis, and its capacity to reduce cardiovascular risk, more studies must be carried out, seeking to identify strategies for the control of its plasma levels. It is extremely important the conducting of randomized controlled trials to evaluate the response to different sources and rates of various diet components and the safety of the supplementation of specific nutrients.(76)

fish oil : increases in unsaturated fat by fish oil (79) or by Mediterranean diet (80) appeared to increase adiponectin.

Coffee

In the present study, we found that the amount of coffee consumption was associated positively with adiponectin and inversely with leptin levels. Although coffee consumption was not related to BMI, our finding was independent of BMI and potential confounding variables. These associations of coffee with adipocytokines explained most of its association with triglycerides and some of those with hs-CRP and liver enzymes. A positive association of coffee consumption with adiponectin levels is consistent with previous reports from smaller studies. As adiponectin is secreted from adipocytes, coffee may have effects on adipocytes. Indeed, one of the major substances that coffee contains among several hundred other substances, caffeine, in an experimental study led to the upregulation of peroxisome proliferator-activated receptor γ expression. which is an essential regulator of adipocyte differentiation and maintenance. As no association between decaffeinated coffee consumption and adiponectin was reported, caffeine contained in the coffee may have acted to increase adiponectin levels.(77,78)

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