Epidemiologic Evidence on Serum Adiponectin Level and Lipid Profile

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ABSTRACT

The concentration of adiponectin, a hormone which is secreted from adipose tissue, is inversely correlated with body fat mass. This hormone has anti inflammatory and anti atherogenic properties. Its concentration reduces in metabolic syndrome and cardiovascular diseases. This study reviews the evidence on the relationship between serum adiponectin concentration and lipid profile. In this study former clinical trials, cross sectional and prospective studies have been reviewed. The PubMed search engine has been used to find related research for the topic by considering dyslipidemia, total cholesterol (TC), high and low density protein (HDL and LDL), triglyceride (TG), lipid profile (LP) and adiponectin as the key words. Finally, 25 articles were recruited to review in the present article. Serum adiponectin level was positively correlated with plasma HDL cholestrol concentrations. There was a significant inverse relationship between plasma triglyceride and serum adiponectin. An inverse correlation between very low density lipoprotein (VLDL) and LDL levels and adiponectin was reported from the studies. So, Adiponectin has an important role in the metabolism of lipid profile including HDLc.

Keywords: Adiponectin, HDL, LDL, Lipid profile, TG, VLDL

Review Article

INTRODUCTION

Obesity, as a major health problem in all countries,[1] is influenced by environmental and genetic factors.[2] Obesity leads to insulin resistance, dyslipidemia and metabolic syndrome.[3] Furthermore, inflammatory markers are increased in metabolic syndrome.[4] Systemic inflammation is also associated with type 2 diabetes, atherosclerosis and cardiovascular disease (CVD).[5] On the other hand, as energy density increases, the risk of CVD[6] and metabolic syndrome[7] elevates. Increased waist circumference in obese patients is associated with increased levels of TG and inflammatory factors.[8] Adiponectin levels, as an anti inflammatory hormone, are reduced in obese subjects.[3]

Adiponectin is a cytokine which is mainly secreted from adipose tissue,[9] and its concentration is inversely associated with body fat mass.[10] This hormone constitutes 10% of total plasma proteins.[11] The major form of this hormone in plasma is the oligomers with high molecular weight (HMW).[12]

Adiponectin receptors exist in two forms (AdipoR1 and AdipoR2), and both receptors expression is associated with insulin sensitivity.[13] The plasma adiponectin concentration is inversely associated with inflammation, serum glucose levels, atherosclerosis, hyperlipidemia, diabetes, CVD and hypertension.[14-20] It is shown that less than 4 μg/ml concentration of adiponectin is related to early incidence of coronary heart disease (CHD).[21] Consuming different diets could affect on adiponectin, s concentrations. Weight loss diets,[22] healthy dietary patterns,[23] more consumption of marine protein[24] and eggs[25] are effective in increasing plasma adiponectin levels. Healthy eating patterns can also be effective in improving insulin resistance and metabolic syndrome.[26] Soy protein also increases levels of this hormone[27] and improves blood lipids.[28] Studies have shown that difference the prevalence of low HDL_C and high TG in middle income countries and other countries is due to differences between their diets.[29]

Several studies have shown the relationship between adiponectin and plasma lipid levels.[15-20] In most studies, the level of this hormone indicates an inverse relationship with the low density lipoprotein (LDL), triglycerides (TG) serum cholesterol; and a positive correlation with high density lipoprotein (HDL).[15,20,30-32] Adiponectin level is associated with HDL, independent of abdominal fat and body mass index (BMI) and insulin sensitivity.[33] Dyslipidemia which is characterized by low concentrations of apolipoprotein A_I and high concentrations of TG-rich lipoproteins[31] has an inverse relationship with serum adiponectin concentrations.[20] It is also shown that plasma adiponectin regulates TG rich lipoprotein metabolism[34] and lipid metabolism regulatory enzymes.[35] According to a survey, elevation of serum TG/HDL, TC/HDL and LDL/HDL ratios reduces the plasma log of adiponectin level[32]. TG/HDL, TC/HDL and LDL/HDL ratios are predictive of insulin resistance,[36] CVD[37] and CHD,[38] respectively. Serum TG and HDL levels are two important constituents of metabolic syndrome[32] which are effective in incidence of CVD.[39] Because of the fundamental role of serum adiponectin level in chronic diseases and also the importance of dyslipidemia in cardiovascular disease and metabolic syndrome, the aim of present study is an overview of the relationship between serum adiponectin level and plasma lipid profile (LP).

METHODS

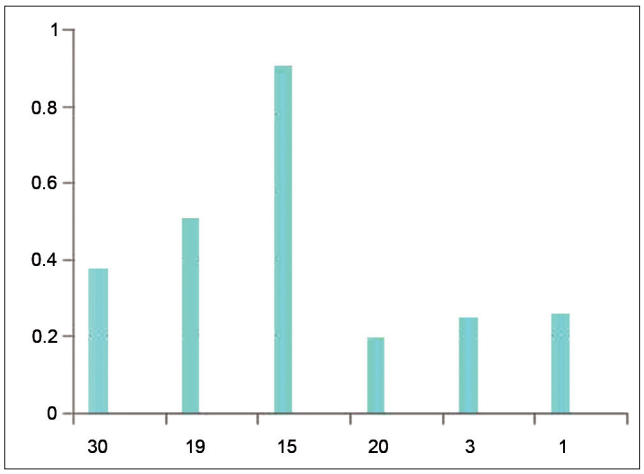
For assessing the association between adiponectin level and lipid profile, PubMed was searched from 2002 to October 2011, by using the following key words for the topic: Dyslipidemia, lipid profile, triglyceride, high or low density lipoprotein, total cholesterol and adiponectin. All 153 articles with design of clinical trials, cross sectional and prospective studies have been reviewed. 25 articles were recruited in this review and other duplicated and studies with no free access full text were excluded. We included any articles which mentioned about the association between serum/plasma adiponectin (total adiponectin and/or any type of HMW, MMW and/or receptors of adiponectin) with lipid profile (such as triglyceride, very low, low and high density lipoprotein and total cholesterol) among healthy/patients 'men and/or women. We also included the articles which have been discussed about the relationship between adiponectin with size of lipoproteins. Finally, the most relevant articles were included and others were excluded. Studies that investigated the association between levels of adiponectin and lipid profile are presented in [Table 1].

RESULTS

Relationship between serum adiponectin and plasma lipid levels

Various studies have shown a strong positive correlation between plasma adiponectin and HDL levels.[15,30,31,33,40-43] Correlation coefficients based on association between adiponectin and HDL resulted from the studies are shown in Graph 1.

In a study of 158 patients with familial hyperlipidemia, every 25% reduction in serum adiponectin, led to 7.3% reduction in HDL-c. Low level of the hormone was shown in patients with familial hyperlipidemia, which is associated with an increase in atherogenic lipids such as low HDL and high LDL and high TG.[17] The study investigated 1174 patients in the age range of 30-70 years, who were suffered from coronary heart disease (CHD). 31% of participants had features of metabolic syndrome. Serum adiponectin level had



Graph 1: Correction coefficient based on association between adiponection and HDL. 30. Matsubara M, *et al.* 19. Mantzoros CS, *et al.* 15. Geloneze B, *et al.* 20. Eynatten MV, *et al.* 3. Licenciature NH, *et al.* 1. Alitinova AE, *et al.*

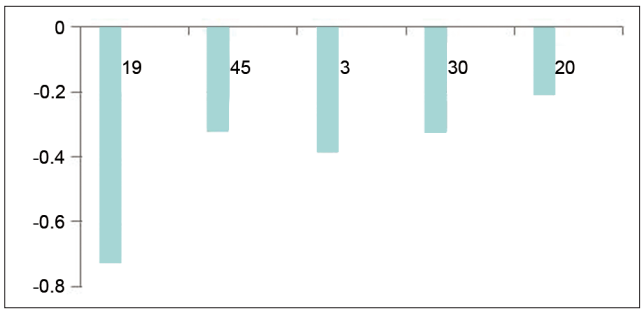
possitive association with HDL-c, after adjustment for possible confounding (r = 0.21, $P < 0.0001$).[20] In a cohort study on 138 obese children, there was a direct relationship between serum adiponectin and HDL (r = 0.26, $P = 0.002$).[3] This relationship elevated by an increasing the rate of obesity in adolescents.[44] Positive and significant association was observed between HDL cholesterol and plasma adiponectin level, after adjusting the effect of body fat mass, sexual maturation, waist circumference,[18] and BMI.[12,18] This relationship also was observed in overweight and obese adults (r = 0.27, $P < 0.009$).[1] According to a study on 925 diabetic women, in the age range of 30-55 years, increasing of 10 µg/ml in circulating adiponectin level elevated 4.11 µg/ml in plasma HDL levels (22%).[19]

Findings from some investigations showed

Table 1: Studies that investigated about association of adiponectin level and lipid profile

Study	Type of study	Study comments	Results
Wagner *et al.*[18]	Cross-sectional	647 overweight and obese adolescents, aged 12 years	Direct association between serum adiponectin concentration and HDL, inverse correlation with TG
Geloneze B *et al.*[15]	Cross-sectional	31 thin, overweight and obese subjects	Positive and strong correlation between adiponectin and HDL/inverse association with TG
Mantzoros CS *et al.*[19]	Cross-sectional	925 diabetic women, aged 30-55 years	Increasing 10 µg/ml of adiponectin lead to 22% elevation of HDL/25% reduction of TG/6% reduction of $ApoB_{100}$
Matsubara M *et al.*[30]	Cross-sectional	352 women suffered form dislipidemia	Positive correlation between adiponectin and HDL/ and inverse association with TG and LDL
van der Vleuten GM *et al.*[17]	Cross-sectional	647 hyperlipidemic and control subjects	25% reduction of plasma adiponectin level lead to 6.2% elevation of TG and 3.7% reduction of HDL/no relationship between adiponectin and TC, LDL-C and ApoB
Eynatten MV *et al.*[20]	Cross-sectional	1174 men with CHD disease	Positive correlation between the hormone and HDL/ and inverse association with TG and TC/HDL ratio
Chan DC *et al.*[31]	Cross-sectional	50 obese men and 37 non-obese men	Positive correlation between the hormone and HDL and Apo A_I/and inverse association with VLDL ApoB
Nascimento H *et al.*[3]	Prospective	138 obese children	Positive correlation between the hormone and HDL/ and inverse association with TG and TC/HDL ratio
Broedl UC *et al.*[13]	Cross-sectional	20 men and women with obesity and insulin resistance	Inverse association between aAdipo R_2 with VLDL-TG, VLDL-C and TG/positive relationship between adiponectin with catabolism of ApoB
Maruyama C *et al.*[16]	Clinical trial	24 diabetic patients and 17 healthy subjects, aged 18-49 years, consuming of 2 meals including of toast bread with or without butter before blood screening	Subjects with higher level of HMW had lower levels of TG and VLDL-C
Altinova AE *et al.*[1]	Cross-sectional	46 overweight and obese women and men	Positive correlation between adiponectin and HDL/no association with TC, LDL and TG

HDL=High density lipoprotein, TG=Triglyceride, CHD=Coronary heart disease, LDL=Low density lipoprotein, TC=Total cholesterol, VLDL=Very low density lipoprotein



Graph 2: Correction coefficient based on association between adiponection and TG. 19. Mantzoros CS, *et al.* 45. Chan DC, *et al.* 3. Licenciatura NH, *et al.* 30. Matsubara M, *et al.* 20. Eynatten MV, *et al.*

that adiponectin levels are inversely correlated with plasma TG concentration.[33,44-46] Correlation coefficients based on association between adiponectin and TG resulted from the studies are shown in Graph 2.

In a study on 37 non-obese men, an inverse relationship was shown between plasma adiponectin concentration and plasma TG levels (r = 0.327).[45] A 25% reduction in this hormone levels, increased TG concentration by 6.2%.[17] In an analysis on 138 obese children, a significant inverse correlation was observed between TG level and hormone levels ($r = -0.392$, $P < 0.001$).[3] A study on Japanese men and women, was shown that low concentration of HMW (less than 97.2 μg/ml) was associated with the TG/HDL cholesterol (r = 0.67, 95CI, 0.63-0.71).[40] In another study of patients with type 1 diabetes, patients with the higher level of HMW had TG levels less than those with lower HMW ($P < 0.01$).[16] In a study among 352 women with dyslipidemia, aged 18-86 years, plasma adiponectin concentrations were inversely associated with serum TG level ($r = -0.33$, $P < 0.0001$).[30] In multiple linear regressions, after adjusting for confounding, elevation of 10 μg/ml circulating adiponectin level caused to 25% reduction in TG levels (47.4 mg/dl).[19] In a cross-sectional study of 1174 patients with CHD, after adjustment for age and sex, there was an inverse relationship between serum adiponectin levels and plasma TG level ($r = -0.21$, $P < 0.0001$).[20]

Findings from some studies suggest an inverse relationship between serum adiponectin concentration and the concentration of TC,[33] VLDL[16,47] and LDL.[30,33,48,49] However some previous studies have reported contradictory findings.[1,19]

A study on 352 adult women with dyslipidemia, showed a significant inverse relationship between plasma adiponectin level and LDL cholesterol concentration, after adjusting for the effect of BMI ($P = 0.082$).[30] Adiponectin concentrations were inversely associated with LDL cholesterol level among girls.[50] In another study on 925 women with diabetes, no significant correlation between circulating adiponectin concentration, LDL cholesterol and TC was observed. While in the multiple linear regression, for each 10 μg/ml increase in adiponectin, the level of apo B_{100} decreased by 5.68 ng/dl (equivalent to 6%).[19] An inverse relationship between adiponectin and LDLox levels (LDL oxidized) was observed in people with diabetes, CAD and those with coronary heart failure (CHF).[51,52] While there was a positive relationship between hormone concentrations in pregnant women and LDLox,[53] no relationship were reported between hormone levels, TC and LDL apo B in the study of patients with familial hyperlipidemia[17] and overweight subjects.[1]

In studies on type 1 diabetic patients, people with higher levels of HMW had lower VLDL cholesterol levels than in healthy subjects and diabetic patients with low HMW.[16] On the other hand, adiponectin has been suggested as an independent predictive in apo B-VLDL catabolism.[47] Hormone R2 receptors are also linked directly with apo B-VLDL catabolism.[13] Based on the findings of a recent study, plasma adiponectin participates to change VLDL-apo B_{100} by regulating Apo A_{II} transfer.[45]

DISCUSSION

In general, adiponectin correlates with HDL independent of BMI and insulin resistance,[15] and this shows that the plasma concentration of adiponectin in obese patients, regulates plasma HDL cholesterol levels independently of BMI and insulin resistance.[1,15] Based on findings from several previous studies, adiponectin stimulates the activity of peroxisome proliferation activated receptor α ligand (PPARα) in both skeletal muscle and liver. Thus a possible reason for the positive association between increased concentrations of HDL serum and adiponectin concentrations is the effect of the related PPARα gene to the metabolism of HDL.[12,54] Adiponectin also acts as an important

component in the catabolism of apo A_I, independent of insulin sensitivity.[55] Increasing the concentration of adiponectin during a weight loss program is significantly related to reducing the catabolism of apo A_I.[56] On the other hand, HDL plays an intermediate role in the relationship between serum adiponectin and CHD. Thus treatment with PPARα agonists such as rosiglitazone increases adiponectin gene expression and levels of HDL can be improved.[10] Thus, the relationship between serum adiponectin and HDL probably is controlled by physiological/pathological mechanisms. Adiponectin regulates HDL concentration by reducing HDL catabolism and inhibiting hepatic lipase activity.[57]

According to studies, adiponectin may increase TG plasma concentrations through elevating skeletal muscle LPL and VLDL receptor expression and thus reduce VLDL catabolism.[58] Adiponectin reduces TG storage in skeletal muscle by increasing fatty acid oxidation through AMP kinase activity.[59] On the other hand, HMW is also able to increase the activity of TG metabolism.[16] The Adiponectin R2 receptor also plays an important role in the metabolism of VLDL and TG. Increasing of the R2 receptor is associated with reduced plasma TG.[13] The findings of a study on macrophage foam cells showed that cholesterol and TG accumulation in these cells is reduced by reduction of LDL_{ox} and elevation of the HDL-cholesterol flow by expression of adiponectin in macrophage foam cells.[60]

Observations suggest that adiponectin has been effective on pathology of lipid metabolism.[19] Based on the findings adiponectin reduces the secretion of hepatic apoE and apoB from the liver. The effect of ApoE on blood lipid levels is influenced by the BMI and adiponectin levels.[3] Adiponectin can increase the insulin activities, improve the glucose tolerance and plays an important role on fatty acid oxidation. It may also affect on lipid metabolism.[61, 62] On the other hand, adiponectin is significantly associated with both LDL and HDL size, so that it has an inverse relationship with small LDL cholesterol ($P < 0.006$) and is correlated with large LDL cholesterol ($P < 0.001$) and large HDL cholesterol ($P < 0.001$).[63]

According to the important role of adiponectin in preventing dyslipidemia and its inverse relationship of the hormone with the concentration of LDL cholesterol, TC and TG levels and also the positive relationship between circulating adiponectin and HDL cholesterol levels, the use of nutritional strategies such as diet and weight loss[16,22,64] and use of healthy eating patterns[23,65] to improve adiponectin levels is recommended.

CONCLUSION

Findings from various studies indicate a positive correlation between circulating adiponectin levels and HDL cholesterol concentrations.[30,31] It is possible that adiponectin regulates HDL cholesterol concentration, independent of BMI and insulin resistance.[15] There is an inverse relationship between hormone levels and TG levels.[33,44] TG is able to reduce adiponectin plasma concentrations.[58] R2 adiponectin receptors also play an important role in the metabolism of VLDL cholesterol and TG.[13] Our findings suggest that there is an inverse relationship between VLDL cholesterol, LDL cholesterol, TC, LDL_{OX} concentrations and serum adiponectin levels.[16,30,33]

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