Progress in Nutrition 2019; Vol. 21, Supplement 1: 16-24 DOI: 10.23751/pn.v21i1-S.6046 



# The effect of obesity and weight loss through calorie restriction on HDL function

*Masoumeh Moradi[1], Ehsan Alvandi[2], Fariba Koohdani[1,3]*

[1]Department of Cellular and Molecular Nutrition, School of Nutritional Sciences and Dietetics, International Campus, Tehran University of Medical Sciences, Tehran, Iran; [2]Department of Cellular and Molecular Nutrition, School of Nutritional Sciences and Dietetics, Tehran University of Medical Sciences, Tehran, Iran; [3]Diabetes Research Center, Endocrinology and Metabolism Clinical Sciences Institute, Tehran University of Medical Sciences, Tehran, Iran - Email: fkoohdan@tums.ac.ir

**Summary.** The aim of the present study is to conduct a literature review on the mechanisms responsible for altered high density lipoprotein (HDL) in obesity and the effect of weight loss by calorie restriction on HDL function. Obesity, as a major modifiable risk factor for coronary heart disease (CHD), can influence the concentration and function of lipoproteins in plasma. HDL is associated inversely with CHD and acts through its antioxidant and anti-inflammatory capacity, as well as stimulation of reverse cholesterol transport from extrahepatic tissues to the liver for excretion into the bile. HDL structure and function is linked to its major apolipoproteins (APO) including APO A-I and APO A-II, and its related enzymes such as paraoxonase (PON) that cotransport with HDL in plasma and lecithin: cholesterol acyltransferase (LCAT) which contributes to HDL maturation. Through production of various cytokines which leads to inflammation, obesity can affect these factors and changes their serum levels as well as their function. In this article, the mechanism responsible for altered HDL in obesity and the effect of weight loss by calorie restriction, as the most commonly used therapy for obesity, on HDL concentration and its function will be reviewed.

**Key words.** Obesity, Calorie Restriction, HDL Function, Apolipoprotein, Paraoxonase, LCAT

## Introduction

The inverse relationship between plasma concentration of high-density lipoprotein (HDL) and cardiovascular disease (CVD) was reported for the first time in 1970s and since then, several studies have been conducted to identify the mechanisms underlying this relationship (Rye and Barter, 2014). Based on several studies, HDL is the strongest predictor of CHD risk (Rader and Hovingh, 2014). HDL has antioxidant, anti-inflammatory and anti-thrombotic properties as well as a beneficial effect on the endothelium (Assmann and Gotto, 2004). The principal mechanism of HDL as a cardio–protective agent is reverse cholesterol transport (RCT) (Mooradian et al., 2008). Apart from RCT, HDL have some important roles in LDL reduction, lipoprotein protection from oxidation, inhibiting the production of cell adhesion and pro-inflammatory molecules, endothelial cells stimulation to prostacyclin synthesis, antithrombotic effect, inducing the expression and activation of endothelial nitric oxide synthase (eNOS) (Arora et al., 2016; Calabresi et al., 2015).

It has been revealed that HDL functions depend on the activity and concentration of HDL enzymes such as paraoxonase-1 (PON1) and Lecithin: cholesterol acyltransferase (LCAT), and its apolipoproteins, in particular APO A-I and APO A-II, the ratio of APO A-II/APO A-I, and HDL particle size (Navab et al., 2007). Genetic, environmental and lifestyle factors such as smoking, physical activity, obesity, composition of diet and nutrients, can affect HDL functions (Siri-Tarino, 2011). Among these factors, obesity as a global public health issue, could affect plasma HDL level and its functions, as well as increasing the risk of

chronic diseases (Rashid and Genest, 2007; Wang and Peng, 2011). Nowadays, adipose tissue is considered as an endocrine tissue due to production of various cytokines which leads to inflammation and chronic disease (Keramat et al., 2015). The primary target for overweight or obese individuals is losing weight. A variety of methods have been suggested for treating obesity, but caloric reduction as a major strategy for weight loss is the goal for the majority of cases (NIH et al., 2000) The main aim of the present review is to clarify the effects of obesity and weight loss through calorie restriction on HDL main enzymes, such as PON1 and LCAT as well as APO A-I and APO A-II, as the most abundant HDL apolipoproteins. Also the potential mechanisms which contribute to these changes will be explained.

*The interaction between obesity and calorie restriction with PON1 activity on HDL*

The paraoxonase family consists of three enzymes, PON1, PON2 and PON3, with anti-oxidative properties in blood circulation. All of these enzymes prevent oxidative stress and fight inflammation (Précourt et al., 2011). PON1 protects LDL against oxidation and reduces macrophage foam cell formation, thus prevents atherosclerosis. It also suppresses the differentiation of monocytes into macrophage, prevents accumulation of oxidized LDL and stimulates cholesterol efflux from macrophage (Aviram and Rosenblat, 2004; Kowalska et al., 2015). PON3 shows the same functions, but it is less efficient than PON1 (Liu et al., 2008).

The plasma concentration and activity rate of PON1 are modulated by many factors such as age, environmental chemicals, lifestyle, diet, physiological and pathological conditions (Costa et al., 2005). Regarding the relationship between this enzyme and obesity, Zaki *et al.* reported that PON1 activity was significantly lower in obese adolescent than controls, which is due to the increased oxidative stress and malondialdehyde and decreased nitric oxide level in obese adolescent (Zaki et al., 2014). The same results were reported by Ferretti *et al.* (Ferretti et al., 2005) and Krzystek-korpacka *et al.* (Krzystek-Korpacka et al., 2013).

It could be explained that obese subjects, in comparison with lean individuals, are more exposed to inflammatory factors and these factors could reduce the paraoxonase and subsequently PON1 activity (Abbott et al., 1995). Besides, low levels of HDL in obese individuals are related to low PON1 activity (Kota et al., 2013). These findings confirmed that obesity is correlated with lipoproteins oxidative damage which could describe the higher risk of cardiovascular diseases in obese individuals (Van Gaal et al., 2006). Figure 1.

There are some inconsistent reports about the interaction between PON1 activity and the strategy for obesity treatment. For example, it was shown that Orlistat or gastric banding treatment could significantly increase PON1 activity in morbidly patients (Audikovszky et al., 2007; Uzun et al., 2004). Regarding the effects of weight loss through calorie restriction, Liang et al. studied non-diabetic obese individuals with metabolic syndrome and they found that 3-month weight loss program with calorie restriction plus 2-3 light physical exercises per week could result in 9.9 ± 5.4% weight reduction and significant decrease of PON1 level, however, with significant increase of PON1 specific enzyme activity (Liang et al., 2011). This result was in accordance with Kotani et al. which showed that low calorie diet for two months in overweight and non-morbidly obese women could significantly decrease the enzyme activity of PON1 lactonase, aryl esterase and tri-esterase by 6.1, 7.3 and 7.8 percent, respectively (Kotani et al., 2009). Moreover, Moradi et al. showed that energy restriction and increasing fiber consumption could significantly reduce serum PON1 level (Moradi et al., 2017a). In contrast, Roberts et al. reported no changes in serum PON1 level and activity after short term course of weight loss by diet and exercise in obese subjects (Roberts et al., 2006). It was also shown that in 6-month diet, which

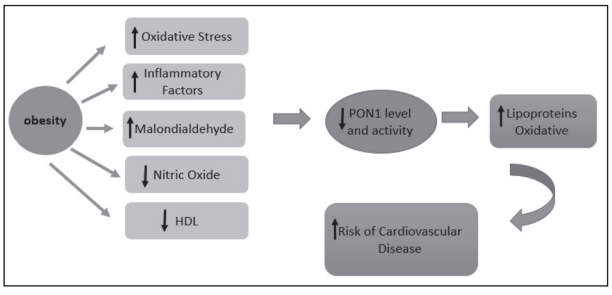


**Figure1.** Effect of obesity on plasma paraoxonase level and activity

resulted in average 2.2±3.9 kg weight loss, PON1 activity was altered, but not significantly (Aicher et al., 2012).

The interpretation of these inconsistent findings is complicated. Obesity, as well as metabolic syndrome (MetS), is associated with higher oxidative stress and pro-inflammatory status. These endogenous inhibitors could reduce paraoxonase activation in the circulation or disturbed the interaction of paraoxonase with HDL which could affect PON1 activity (Abbott et al., 1995). As a result, hepatic production increases to compensate the reduction of PON activity, and therefore reducing these inhibitors through weight loss could result in less need for hepatic synthesis (Rector et al., 2007).

Furthermore, higher oxidative stress in some diseases such as obesity and type 2 diabetes mellitus (T2DM) could lead to lower ratio of HDL-bound vs. free form of paraoxonase. It is important to note that free form of paraoxonase has a lower enzyme activity than HDL–bound form (Mackness et al., 1991). In weight loss, HDL-bound form of PON1 protein increases which results in higher enzyme activity (Liang et al., 2011).

Altogether, it seems that weight loss through calorie restriction could reduce PON1 activity. Since PON1 is a protective factor against coronary heart disease (CHD), the reduction in PON1 activity could be considered as a harmful effect of low calorie diet. This reduction might be explained as a consequence of the benefits of low calorie diet on CHD risk factors and the metabolic changes of HDL. As already mentioned, PON1 protects LDL against oxidation (Aviram and Rosenblat, 2004; Durrington et al., 2001) and calorie restriction diets lead to a noticeable reduction in LDL oxidation, thus with these diets, there is less need for LDL protection against oxidation (Shin et al., 2006). In addition, decreased HDL level and PON1 activity in response to low calorie diet may be a physiologically appropriate or adaptive phenomenon and therefore it may not be detrimental (Kotani et al., 2009).

*The effects of obesity and calorie restriction on APO A-I concentration and its function in HDL*

The major apolipoproteins of HDL are APO A-I and APO A-II, and the former is the most abundant apolipoprotein consisting 70% of the total HDL proteins. APO A-I is a single polypeptide chain with 28 KDa and 243 amino acids (Maïga et al., 2014). It is confirmed that plasma APO A-I level is inversely related to coronary heart disease (CHD) (Gotto and Brinton, 2004) and obesity, specially visceral obesity, impaired metabolism of HDL as well as APO A-I (Wang and Peng, 2012).

The plasma level of HDL could be determined by the APO A-I fractional catabolic rate (FCR) (Brinton et al., 1994). A meta-analysis of 13 studies demonstrated that overweight and obese individuals, compared with lean subjects, had significantly higher APO A-I FCR and production rate (PR). In these individuals, APO A-I FCR and PR were significantly associated with APO A-I level, however in the lean group, APO A-I level was only significantly associated with PR (Ooi et al., 2005).

Increasing the production of inflammatory cytokines, such as TNF-α and IL-1β, impaired insulin signaling, and carbohydrate intolerance have been shown to downregulate the expression of APO A-I gene in hepatocytes with a dose dependent manner (Haas et al., 2003). TNF-α could also suppress the APO A-I promotor activity through c-Jun N-terminal kinase (JNK) and MEK/ERK pathways (Beers et al., 2006). The promotor region of APO A-I contains several binding sites for orphan and nuclear hormone receptors such as TNF-α and NF-κB by which the expression of APO A-I gene is suppressed in hepatocytes (Haas et al., 2003; Morishima et al., 2003). Therefore, it could be assumed that APO A-I is a primary target for certain pro-inflammatory mediators. These cytokines can also negatively regulate the expression of APO A-I gene by decreasing the level of RXR and other nuclear hormone receptors, decreasing the glucocorticoid receptor activity, and interfering with coactivators such as Peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α) (Haas and Mooradian, 2010). Besides, two other important modulators of APO A-I production are glucose metabolism and insulin signaling. In fact, glucose decreases and insulin increases the expression of APO A-I protein (Murao et al., 1998).

Another mechanism for the reduction of APO A-I production is the higher plasma clearance of this molecule. In obese individuals, adipose tissue releases

more free fatty acids which are the substrate for VLDL formation in the liver. This process leads to higher rate of TG transfer from VLDL to HDL by cholesterol-ester transfer protein (CETP), thus CETP activity increases (Ginsberg, 2000). As a result, HDL particles become TG-rich which is hydrolyzed by hepatic lipase, resulting in the release of lipid-poor APO A-I and the formation of remnant HDL particles. Lipid-poor APOA-I is cleared more by kidney and HDL remnants is degraded by liver or kidney (Ginsberg, 2000; Guendouzi et al., 1999).

Calorie intake and the consumption of some nutrient such as glucose, fructose, protein, fatty acid have an important role in regulating the rate of both APO A-I fractional clearance and APO A-I gene expression (Mooradian et al., 2008). Regarding the effect of calorie restriction on APO A-I level, Aicher et al. revealed that after 6-month of calorie restriction and an average 2.2±3.9 Kg weight reduction, the APOA-I level increased but not significant (Aicher et al., 2012). In another study, weight loss through calorie restriction and exercise resulted in increased level of APO A-I and HDL2b. Since HDL2b contains APO A-I, but not APO A-II, increased level of HDL2b should be associated with a predominant increase in APO A-I level, without an increase in APO A-II concentration (Williams et al., 1992). According to Richard et al., 5-15% reduction in body weight through calorie restriction resulted in decreased APO A-IFCR, with no changes in APO A-II PR (Richard et al., 2013). However, in Theodore et al. study, hypocaloric, low-fat diet versus a weight maintenance diet resulted in decreased catabolic (-13%) and production (-13%) rates of HDL APO A-I, without altering the concentration of plasma HDL and APO A-I (Ng et al., 2007).
Weight loss leads to a reduction in VLDL-TG concentration. As already mentioned, TG in VLDL is a substrate for CEPT which exchanges TG between neutral lipids and HDL particles. This process results in the formation of triglyceride enriched HDL which is catabolized and cleared more rapidly in the circulation. Therefore, weight loss could lead to the reduction and delaying in APO A-I FCR (Lamarche et al., 1999; Richard et al., 2013). Moreover, weight loss results in increased plasma adiponectin level which subsequently can inhibit hepatic lipase activity which correlates with decreased HDL and APO A-I FCR (Ng et al., 2007). Furthermore, lowered directory fat, resulted from calorie restriction, can decrease the expression of APO A-I gene and its secretion from hepatic cells (Azrolan et al., 1995).

*The effects of obesity and calorie restriction on APO A-II concentration and function in HDL*

APO A-II is the second major apolipoprotein of HDL which represents the 20% of total HDL proteins and it contains 77 amino acids (Maïga et al., 2014). The effects of APOA-II level on atherogenesis in transgenic animals and humans are controversial. In several studies, increased plasma concentration of Apo A-II was considered to be pro-atherogenic (Castellani et al., 2001; Marzal-Casacuberta et al., 1998). In contrast, other studies showed that HDL enrichment of APOA-II considered as anti-atherogenic (Koohdani et al., 2016). It has demonstrated that HDL particles that contain only APO A-I are more efficient in RCT than those with both APO A-I and APO A-II (van't Hooft et al., 2001). Besides, it has proposed some beneficial effects for APO A-II such as increasing hepatic lipase (HL) activity and inhibition of CETP activity. Therefore, the role of apolipoprotein AII as an inhibitor or promoter of cholesterol efflux is yet to be discussed (Mooradian et al., 2008).

It has proposed that the body mass index (BMI) is correlated positively with APO A-II level and negatively with APO A-I level (Williams et al., 1992). Takahashi et al. revealed that overweight boys and girls, aged 10-15 years, had significantly higher plasma level of APO A-II than non-overweight children; and in non-overweight boys whose body fat mass was over 20%, the plasma level of APO A-II was higher than boys whose body fat mass was below 20% (Takahashi

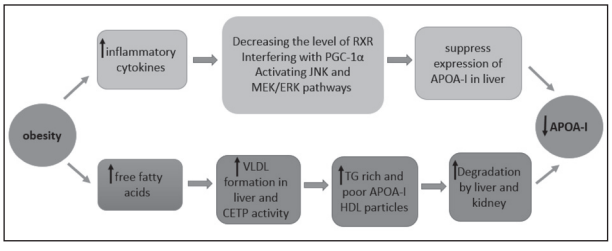


**Figure2.** Effect of obesity on APO A-I level and gene expression

et al., 1996). In another study, diabetic patients with CC genotype who had lower plasma APOA-II concentration consuming a high saturated fatty acids and had higher BMI and appear more prone to obesity and overweight than T-allele carriers who had upper plasma APOA-II level (Basiri et al., 2015).

Although the precise mechanism is unclear, but it was shown that increased level of APO A-II may have some effects on hypertriglyceridemia and HDL reduction which are the two main abnormalities in obese and T2DM patients. Based on in vitro studies, one possible mechanism is that APO A-II is more hydrophobic than APO A-I, and in higher APO A-II levels, it can replace APO A-I on the surface of HDL (Scanu and Edelstein, 2008). APO A-I activates LCAT, whereas APO A-II neither activates nor inhibits it. Therefore, by replacing APO A-I with APOA-II on the surface of HDL, it can inhibit LCAT activity indirectly and inhibits the nascent HDL maturation (Maïga et al., 2014). Besides, displaced APO A-I will be catabolized rapidly in kidney which might be the cause of decreasing plasma HDL (Julve et al., 2002).

In addition, increasing APO A-II in HDL inhibits Hepatic lipase (HL), endothelial lipase (EL) and LPL activities by hindering LPL lipase access to lipoprotein surface. By inhibiting HL and EL on the surface of HDL, APO A-II impairs remodeling of HDL and eliminates the synergistic action of lipase and scavenger receptor class B type I (SR-B1) (Dugué-Pujol et al., 2006; Weng et al., 1999).

Castellani et al. demonstrated that APO A-II could contribute to visceral obesity in transgenic mice. They hypothesized that overexpression of APO A-II changes the composition of HDL and thus impairs HDL interaction with skeletal muscle CD36. Therefore, the use of free fatty acids for energy production reduces and fat mass increases (Castellani et al., 2001). Another study on men with MetS showed that 16 weeks of low-caloric low-fat diet resulted in signification decrease of both the production rate (-23%) and FCR (-12%) of HDL-APO A-II, which together resulted i net reduction in APO A-II concentration (-9%) (Ng et al., 2010).

The mechanism responsible for decreased APO A-II through weight loss remains unclear. Weight loss could decrease the hepatic secretion of VLDL APOB100 which is significantly correlated with HDL-APO A-II. Therefore, lower production of VLDL-APOB positively correlates with reduced APOA-II production (Ng et al., 2010; Riches et al., 1999). Moreover, weight loss causes the reduction in plasma triglyceride levels and VLDL production, thus decreasing the VLDL-triacylglycerol pool and subsequent CETP activity leads to the delay in the liver uptake of HDL and subsequent increase in plasma HDL level (Ng et al., 2010).

*LCAT is influenced by obesity and weight loss through calorie restriction*

LCAT plays a critical role in HDL metabolism. It catalyzes the trans-esterification of free cholesterol and transferring cholesterol ester (CE) to the HDL core which results in the maturation of discoidal HDL to form spherical HDL (Kunnen and Van Eck, 2012).

Bajnok *et al*. reported that LCAT correlates inversely with obesity, BMI, wait circumferences and leptin levels. BMI is also an independent predictor of LCAT (Bajnok et al., 2007). However, Dullaart *et al*. showed that LCAT activity was not influenced by BMI (Dullaart et al., 1994). Based on Akanji *et al*. study on T2DM patients, the LCAT activity in plasma reduces significantly in obese individuals in comparison with non-obese population (Akanji and Agbedana, 1995). Yet Faidon Magkos *et al.* found higher plasma LCAT concentration (30%) in non-diabetic obese subjects than lean individuals (Magkos et al., 2009).

The molecular basis which could explain the lower LCAT activity in obese individuals is not yet clear. It may be due to the effect of obesity on APO A-I as the most potent activator of LCAT. In the state of obesity, residence time of APO A-I reduces, also its clearance and fractional catabolism increases which resulted in reduced levels of APO A-I, and as a consequence, plasma LCAT activity reduces (Akanji and Agbedana, 1995). Moreover, adipose tissue degrades HDL directly, and it may change the LCAT concentration and therefore its activity. McEneny *et al*. revealed that only HDL2-LCAT, but not HDL3-LCAT, is significantly related to the weight in overweight and obese children (McEneny et al., 2013). In addition, the obese subjects probably have more immature $HDL_2$ particles in comparison with lean individuals, because LCAT esteri-

fied free cholesterol within pre-B HDL and HDL3 to form HDL2 as a final mature product. Therefore, LCAT is found in former HDL particles and the level of LCAT in HDL2 is minimum (Magkos et al., 2009; McEneny et al., 2013). It was also showed that obese individuals have smaller HDL particles size compared with lean subjects (Magkos et al., 2008). Overall, plasma LCAT concentration positively correlates with the concentration of small HDL particles and negatively with the concentration of large HDL particles (Magkos et al., 2009).

Regarding the effect of weight loss through calorie restriction, Shoji *et al* indicated that LCAT concentration could decrease significantly after weight loss (Shoji et al., 1992), and Weisweiler *et al*. reported that during weight loss by low calorie diet (600 kcal/day), the LCAT activity did not change, but its activity was increased in the period of weight stabilization (WEISWEILER, 1987). However, in another study LCAT activity did not change after weight loss (Moradi et al., 2017b). They suggested that lower HL activity during weight loss and weight maintenance may explain the HDL cholesterol esterification that increases the capacity of HDL for RCT (Shoji et al., 1992; WEISWEILER, 1987). This result is in agreement with Hietane *et al*. study in which LCAT activity was decreased significantly during weight reduction period. They claimed that LCAT activity is positively correlated with changes in both cholesterol and triglyceride concentration and these parameters decrease after weight loss (Hietanen et al., 1982). Furthermore, another study revealed a strong correlation between total cholesterol levels and LCAT activity (Williams et al., 1990).

## Conclusion

It is obvious that obesity is linked to reduction in plasma HDL level and HDL-function is impaired in obese people. Initially, calorie restriction in individuals with obesity may reduce the HDL concentration, and it increases after weight stabilization, therefore, HDL reduction after weight loss is not a risk factor for CVD. Besides, the concentration of HDL in individuals with overweight and obesity can influence the HDL function by altering HDL major apolipoproteins and related enzymes. Also, lifestyle modification such as diet-induced weight loss leads to reduced enzymes and main HDL apolipoproteins, and since these factors are protective against CHD, the reductions in these parameters may be considered as a deleterious effects of low calorie diets. It could be explained as a consequence of the benefits of low calorie diets such as reduction in oxidized LDL, and therefore, less need to these factors. Only a few percent of overweight subjects can achieve and maintain weight loss for a prolonged period of time. Therefore, a combination of multiple strategies such as behavioral and lifestyle changes, diet and exercise interventions are needed to maintain the weight loss and improve the HDL-C concentration in individuals with obesity.

In the end, it should be noted that the diet composition such as protein, carbohydrate and fats, as well as the effects of these ingredients on the HDL component, such as apolipoproteins and its enzymes needs further investigations.

## References

1. Abbott, C.A., Mackness, M.I., Kumar, S., Boulton, A.J. and Durrington, P.N., 1995. Serum paraoxonase activity, concentration, and phenotype distribution in diabetes mellitus and its relationship to serum lipids and lipoproteins. Arteriosclerosis, thrombosis, and vascular biology, 15(11): 1812-1818.
2. Aicher, B.O. et al., 2012. Diet-Induced Weight Loss in Overweight or Obese Women and Changes in High-Density Lipoprotein Levels and Function. Obesity, 20(10): 2057-2062.
3. Akanji, A.O. and Agbedana, E.O., 1995. Glycaemia and body mass as determinants of plasma lecithin: cholesterol acyltransferase activity in Nigerian patients with non-insulin dependent diabetes mellitus. Clinica chimica acta, 238(1): 35-42.
4. Arora, S., Patra, S.K. and Saini, R., 2016. HDL—a molecule with a multi-faceted role in coronary artery disease. Clinica Chimica Acta, 452: 66-81.
5. Assmann, G. and Gotto, A.M., 2004. HDL cholesterol and protective factors in atherosclerosis. Circulation, 109(23 suppl 1): III-8-III-14.
6. Audikovszky, M. et al., 2007. Orlistat increases serum paraoxonase activity in obese patients. Nutrition, metabolism and cardiovascular diseases, 17(4): 268-273.
7. Aviram, M. and Rosenblat, M., 2004. Paraoxonases 1, 2, and 3, oxidative stress, and macrophage foam cell formation dur-

ing atherosclerosis development. Free Radical Biology and Medicine, 37(9): 1304-1316.
8. Azrolan, N., Odaka, H., Breslow, J.L. and Fisher, E.A., 1995. Dietary fat elevates hepatic apoA-I production by increasing the fraction of apolipoprotein AI mRNA in the translating pool. Journal of Biological Chemistry, 270(34): 19833-19838.
9. Bajnok, L. et al., 2007. Relationship of endogenous hyperleptinemia to serum paraoxonase 1, cholesteryl ester transfer protein, and lecithin cholesterol acyltransferase in obese individuals. Metabolism, 56(11): 1542-1549.
10. Basiri, M.G. et al., 2015. APOA2– 256T> C polymorphism interacts with saturated fatty acids intake to affect anthropometric and hormonal variables in type 2 diabetic patients. Genes & nutrition, 10(3): 1-7.
11. Beers, A., Haas, M.J., Wong, N.C. and Mooradian, A.D., 2006. Inhibition of apolipoprotein AI gene expression by tumor necrosis factor α: roles for MEK/ERK and JNK signaling. Biochemistry, 45(7): 2408-2413.
12. Brinton, E.A., Eisenberg, S. and Breslow, J.L., 1994. Human HDL cholesterol levels are determined by apoA-I fractional catabolic rate, which correlates inversely with estimates of HDL particle size. Effects of gender, hepatic and lipoprotein lipases, triglyceride and insulin levels, and body fat distribution. Arteriosclerosis, Thrombosis, and Vascular Biology, 14(5): 707-720.
13. Calabresi, L., Gomaraschi, M., Simonelli, S., Bernini, F. and Franceschini, G., 2015. HDL and atherosclerosis: Insights from inherited HDL disorders. Biochimica et Biophysica Acta (BBA)-Molecular and Cell Biology of Lipids, 1851(1): 13-18.
14. Castellani, L.W., Goto, A.M. and Lusis, A.J., 2001. Studies with apolipoprotein A-II transgenic mice indicate a role for HDLs in adiposity and insulin resistance. Diabetes, 50(3): 643-651.
15. Costa, L.G., Vitalone, A., Cole, T.B. and Furlong, C.E., 2005. Modulation of paraoxonase (PON1) activity. Biochemical pharmacology, 69(4): 541-550.
16. Dugué-Pujol, S. et al., 2006. Human apolipoprotein A-II associates with triglyceride-rich lipoproteins in plasma and impairs their catabolism. Journal of lipid research, 47(12): 2631-2639.
17. Dullaart, R., Sluiter, W., Dikkeschei, L., Hoogenberg, K. and Tol, A., 1994. Effect of adiposity on plasma lipid transfer protein activities: a possible link between insulin resistance and high density lipoprotein metabolism. European journal of clinical investigation, 24(3): 188-194.
18. Durrington, P., Mackness, B. and Mackness, M., 2001. Paraoxonase and atherosclerosis. Arteriosclerosis, thrombosis, and vascular biology, 21(4): 473-480.
19. Ferretti, G. et al., 2005. Paraoxonase activity in high-density lipoproteins: a comparison between healthy and obese females. The Journal of Clinical Endocrinology & Metabolism, 90(3): 1728-1733.
20. Ginsberg, H.N., 2000. Insulin resistance and cardiovascular disease. The Journal of clinical investigation, 106(4): 453-458.
21. Gotto, A.M. and Brinton, E.A., 2004. Assessing low levels of high-density lipoprotein cholesterol as a risk factor in coronary heart disease: a working group report and update. Journal of the American College of Cardiology, 43(5): 717-724.
22. Guendouzi, K. et al., 1999. Biochemical and physical properties of remnant-HDL2 and of preβ1-HDL produced by hepatic lipase. Biochemistry, 38(9): 2762-2768.
23. Haas, M.J. et al., 2003. Suppression of apolipoprotein AI gene expression in HepG2 cells by TNF α and IL-1β. Biochimica et Biophysica Acta (BBA)-General Subjects, 1623(2): 120-128.
24. Haas, M.J. and Mooradian, A.D., 2010. Regulation of high‐density lipoprotein by inflammatory cytokines: establishing links between immune dysfunction and cardiovascular disease. Diabetes/metabolism research and reviews, 26(2): 90-99.
25. Hietanen, E., Laitinen, M., Ahonen, E., Marniemi, J. and Nousiainen, U., 1982. Changes in serum lipids and lecithin: cholesterol acyltransferase enzyme during 1 week weight reduction of women on a low-calorie diet. Enzyme, 29(3): 160-166.
26. Julve, J. et al., 2002. Mechanisms of HDL deficiency in mice overexpressing human apoA-II. Journal of lipid research, 43(10): 1734-1742.
27. Keramat, L. et al., 2015. Does apolipoprotein A-II polymorphism interact with the association of obesity and serum inflammatory biomarkers in type 2 diabetes patients? Journal of Nutritional Sciences and Dietetics, 1(2): 107-113.
28. Koohdani, F. et al., 2016. APO A2-265T/C Polymorphism Is Associated with Increased Inflammatory Responses in Patients with Type 2 Diabetes Mellitus. Diabetes & Metabolism Journal, 40(3): 222-229.
29. Kota, S.K. et al., 2013. Implications of serum paraoxonase activity in obesity, diabetes mellitus, and dyslipidemia. Indian journal of endocrinology and metabolism, 17(3): 402.
30. Kotani, K. et al., 2009. Changes on the physiological lactonase activity of serum paraoxonase 1 by a diet intervention for weight loss in healthy overweight and obese women. Journal of clinical biochemistry and nutrition, 45(3): 329-334.
31. Kowalska, K., Socha, E. and Milnerowicz, H., 2015. Review: the role of paraoxonase in cardiovascular diseases. Annals of Clinical & Laboratory Science, 45(2): 226-233.
32. Krzystek-Korpacka, M. et al., 2013. Paraoxonase-1 activity in overweight and obese children and adolescents: association with obesity-related inflammation and oxidative stress. Adv Clin Exp Med, 22(2): 229-36.
33. Kunnen, S. and Van Eck, M., 2012. Lecithin: cholesterol acyltransferase: old friend or foe in atherosclerosis? Journal of lipid research, 53(9): 1783-1799.
34. Lamarche, B. et al., 1999. Triglyceride enrichment of HDL enhances in vivo metabolic clearance of HDL apo AI in healthy men. The Journal of clinical investigation, 103(8): 1191-1199.

35. Liang, K.-W. et al., 2011. Persistent elevation of paraoxonase-1 specific enzyme activity after weight reduction in obese non-diabetic men with metabolic syndrome. Clinica Chimica Acta, 412(19): 1835-1841.
36. Liu, Y., Mackness, B. and Mackness, M., 2008. Comparison of the ability of paraoxonases 1 and 3 to attenuate the in vitro oxidation of low-density lipoprotein and reduce macrophage oxidative stress. Free Radical Biology and Medicine, 45(6): 743-748.
37. Mackness, M.I. et al., 1991. Serum paraoxonase activity in familial hypercholesterolaemia and insulin-dependent diabetes mellitus. Atherosclerosis, 86(2-3): 193-199.
38. Magkos, F., Mohammed, B.S. and Mittendorfer, B., 2008. Effect of obesity on the plasma lipoprotein subclass profile in normoglycemic and normolipidemic men and women. International journal of obesity, 32(11): 1655-1664.
39. Magkos, F., Mohammed, B.S. and Mittendorfer, B., 2009. Plasma lipid transfer enzymes in non-diabetic lean and obese men and women. Lipids, 44(5): 459-464.
40. Maïga, S.F., Kalopissis, A.-D. and Chabert, M., 2014. Apolipoprotein A-II is a key regulatory factor of HDL metabolism as appears from studies with transgenic animals and clinical outcomes. Biochimie, 96: 56-66.
41. Marzal-Casacuberta, À. et al., 1998. Human apolipoprotein A-II is a pro-atherogenic molecule when it is expressed in transgenic mice at a level similar to that in humans: evidence of a potentially relevant species-specific interaction with diet. Journal of lipid research, 39(2): 457-462.
42. McEneny, J. et al., 2013. High-density lipoprotein subfractions display proatherogenic properties in overweight and obese children. Pediatric research, 74(3): 279-283.
43. Mooradian, A.D., Haas, M.J., Wehmeier, K.R. and Wong, N.C., 2008. Obesity-related Changes in High-density Lipoprotein Metabolism. Obesity, 16(6): 1152-1160.
44. Moradi, M. et al., 2017a. Study of the relationship between APOA-II- 265T> C polymorphism and HDL function in response to weight loss in overweight and obese type 2 diabetic patients. Clinical Nutrition.
45. Moradi, M., Mahmoudi, M., Saedisomeolia, A., Zahirihashemi, R. and Koohdani, F., 2017b. The effect of weight loss on HDL subfractions and LCAT activity in two genotypes of APOA-II-265T> C polymorphism. Nutrition Journal, 16(1): 34.
46. Morishima, A., Ohkubo, N., Maeda, N., Miki, T. and Mitsuda, N., 2003. NF-κB regulates plasma apolipoprotein AI and high density lipoprotein cholesterol through inhibition of peroxisome proliferator-activated receptor α. Journal of Biological Chemistry, 278(40): 38188-38193.
47. Murao, K. et al., 1998. Effects of glucose and insulin on rat apolipoprotein AI gene expression. Journal of Biological Chemistry, 273(30): 18959-18965.
48. Navab, M. et al., 2007. High-density lipoprotein: antioxidant and anti-inflammatory properties. Current atherosclerosis reports, 9(3): 244-248.
49. Ng, T.W., Chan, D.C., Barrett, P.H.R. and Watts, G.F., 2010. Effect of weight loss on HDL-apoA-II kinetics in the metabolic syndrome. Clinical Science, 118(1): 79-85.
50. Ng, T.W., Watts, G.F., Barrett, P.H.R., Rye, K.-A. and Chan, D.C., 2007. Effect of Weight Loss on LDL and HDL Kinetics in the Metabolic Syndrome Associations with changes in plasma retinol-binding protein-4 and adiponectin levels. Diabetes Care, 30(11): 2945-2950.
51. NIH, N., National Heart, L., Institute, B. and Obesity, N.A.A.f.t.S.o., 2000. The Practical Guide Identification, Evaluation, and Treatment of Overweight and Obesity in Adults.". NIH Publication Number DO-4084: 35-38.
52. Ooi, E.M. et al., 2005. High-density Lipoprotein Apolipoprotein AI Kinetics in Obesity. Obesity research, 13(6): 1008-1016.
53. Précourt, L.-P. et al., 2011. The three-gene paraoxonase family: physiologic roles, actions and regulation. Atherosclerosis, 214(1): 20-36.
54. Rader, D.J. and Hovingh, G.K., 2014. HDL and cardiovascular disease. The Lancet, 384(9943): 618-625.
55. Rashid, S. and Genest, J., 2007. Effect of Obesity on High-density Lipoprotein Metabolism. Obesity, 15(12): 2875-2888.
56. Rector, R.S. et al., 2007. Exercise and diet induced weight loss improves measures of oxidative stress and insulin sensitivity in adults with characteristics of the metabolic syndrome. American Journal of Physiology-Endocrinology and Metabolism, 293(2): E500-E506.
57. Richard, C., Couture, P., Desroches, S., Lichtenstein, A.H. and Lamarche, B., 2013. Effect of weight loss, independent of change in diet composition, on apolipoprotein AI kinetic in men with metabolic syndrome. Journal of lipid research, 54(1): 232-237.
58. Riches, F. et al., 1999. Reduction in Visceral Adipose Tissue Is Associated with Improvement in Apolipoprotein B-100 Metabolism in Obese Men 1. The Journal of Clinical Endocrinology & Metabolism, 84(8): 2854-2861.
59. Roberts, C.K., Ng, C., Hama, S., Eliseo, A.J. and Barnard, R.J., 2006. Effect of a short-term diet and exercise intervention on inflammatory/anti-inflammatory properties of HDL in overweight/obese men with cardiovascular risk factors. Journal of Applied Physiology, 101(6): 1727-1732.
60. Rye, K.-A. and Barter, P.J., 2014. Regulation of high-density lipoprotein metabolism. Circulation research, 114(1): 143-156.
61. Scanu, A.M. and Edelstein, C., 2008. HDL: bridging past and present with a look at the future. The FASEB Journal, 22(12): 4044-4054.
62. Shin, M.-J. et al., 2006. Weight loss effect on inflammation and LDL oxidation in metabolically healthy but obese (MHO) individuals: low inflammation and LDL oxidation in MHO women. International journal of obesity, 30(10): 1529-1534.
63. Shoji, T. et al., 1992. High-density-lipoprotein metabolism during a very-low-calorie diet. The American journal of clinical nutrition, 56(1): 297S-298S.
64. Siri-Tarino, P.W., 2011. Effects of diet on high-density lipoprotein cholesterol. Current atherosclerosis reports,

13(6): 453-460.
65. Takahashi, H., Hashimoto, N., Kawasaki, T., KIKUCHI, T. and UCHIYAMA, M., 1996. The usefulness of measuring body fat deposition for detecting obesity and atherogenesity in Japanese school children. Pediatrics International, 38(6): 634-639.
66. Uzun, H. et al., 2004. Changes in leptin, plasminogen activator factor and oxidative stress in morbidly obese patients following open and laparoscopic Swedish adjustable gastric banding. Obesity surgery, 14(5): 659-665.
67. Van Gaal, L.F., Mertens, I.L. and Christophe, E., 2006. Mechanisms linking obesity with cardiovascular disease. Nature, 444(7121): 875-880.
68. van't Hooft, F.M. et al., 2001. Human evidence that the apolipoprotein A-II gene is implicated in visceral fat accumulation and metabolism of triglyceride-rich lipoproteins. Circulation, 104(11): 1223-1228.
69. Wang, H. and Peng, D.-Q., 2011. New insights into the mechanism of low high-density lipoprotein cholesterol in obesity. Lipids in health and disease, 10(1): 1.
70. Wang, S. and Peng, D., 2012. Regulation of adipocyte autophagy—The potential anti-obesity mechanism of high density lipoprotein and ApolipoproteinA-I. Lipids in health and disease, 11(1): 1.
71. WEISWEILER, P., 1987. Plasma Lipoproteins and Lipase and LecithinrCholesterol Acyltransferase Activities in Obese Subjects Before and After Weight Reduction. The Journal of Clinical Endocrinology & Metabolism, 65(5): 969-973.
72. Weng, W. et al., 1999. ApoA-II maintains HDL levels in part by inhibition of hepatic lipase: studies in apoA-II and hepatic lipase double knockout mice. Journal of lipid research, 40(6): 1064-1070.
73. Williams, P.T., Albers, J.J., Krauss, R.M. and Wood, P.D., 1990. Associations of lecithin: cholesterol acyltransferase (LCAT) mass concentrations with exercise, weight loss, and plasma lipoprotein subfraction concentrations in men. Atherosclerosis, 82(1-2): 53-58.
74. Williams, P.T., Krauss, R.M., Vranizan, K.M., Albers, J.J. and Wood, P.D., 1992. Effects of weight-loss by exercise and by diet on apolipoproteins AI and A-II and the particle-size distribution of high-density lipoproteins in men. Metabolism, 41(4): 441-449.
75. Zaki, M.E., El-Bassyouni, H., Kamal, S., El-Gammal, M. and Youness, E., 2014. Association of serum paraoxonase enzyme activity and oxidative stress markers with dyslipidemia in obese adolescents. Indian journal of endocrinology and metabolism, 18(3): 340.

Correspondence:
Dr. Fariba Koohdani, Professor of Nutrition,
Department of Cellular and Molecular Nutrition, School of Nutritional Sciences and Dietetics,
Tehran University of Medical Sciences, Naderi St., Hojatdoost Ave., Keshavarz Blvd., Tehran, Iran
Tel: +982188955569
Fax: +982188974462
Email: fkoohdan@tums.ac.ir