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REVIEW ARTICLE

# Role of Exercise-induced Adiponectin Activation on Obese and Diabetic Individuals

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**PURPOSE:** The physiological role of adipocytokines on obesity, diabetes, and insulin resistance is not clearly understood yet. Furthermore, the mechanism of exercise-induced changes in plasma adiponectin in obesity and diabetes is not known well. The aim of this review is to describe the role of exercise on the adiponectin production in adipose tissue of the obesity and diabetes.

**METHODS:** This study reviews 46 previous studies focusing on the effect of exercise on adiponectin in obese and diabetic individuals.

**RESULTS:** Increasing adiponectin levels after long-term exercise training in obese and diabetic individuals have inconsistent support in the scientific literature. However, the present review summarized evidence that supports for exercise training as a viable strategy to increase adiponectin in obese and diabetic individuals.

**CONCLUSIONS:** Despite the importance of regular physical activity for the prevention of obesity and diabetes outlined in numerous guidelines and recommendations, previous studies showed inconsistent results regarding the effect of physical activity among obese and diabetic individuals. This review suggested that exercise training induces the augmentation of the anti-inflammatory cytokine adiponectin and in turn, it provides long-term health outcomes for obese and diabetic individuals.

**Key words:** Exercise, Adiponectin, Obesity, Diabetes

## INTRODUCTION

Obesity and insulin resistance have been recognized as leading causes of metabolic syndrome and type 2 diabetes. Obesity is defined as the accumulation of excessive body fat. While the obesity is known to induce insulin resistance, metabolic syndrome, diabetes and cardiovascular diseases, the molecular mechanism of the link between obesity and those metabolic diseases are still not clarified yet [1]. Adipose tissue expresses various secretory proteins which may be involved in the regulation of energy expenditure, lipid metabolism and insulin resistance. Adipocytokines appear to contribute to inflammation, atherosclerosis, and may be involved in the etiology of type 2 diabetes, possibly constituting the missing link between obesity and insulin resistance [2]. Abnormal levels of adipocytokines may contribute to insulin resistance. However, in human beings, the physiological role of adipocytokines on obesity, diabetes, and insulin resistance is not conclusive. Unlike other adipocytokines, adiponectin plasma levels [3] and mRNA expression [4] are reduced with obesity and diabetes. Adiponectin is a secretory protein of white adipose tissue. It has been shown to have insulin-sensitizing and anti-inflammatory properties [5,6]. It may play an important role in the pathogenesis of diabetes and may be an independent predictor of the development of diabetes in women [7]. Likewise, adiponectin has been linked to insulin resistance such that low adiponectin levels are found with obesity and may contribute to insulin resistance and atherogenesis [8]. Recent systematic reviews and meta-analyses have been conducted on the relationship between exercise training and plasma adiponectin level. In

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these studies, plasma adiponectin levels increased or remained constant with exercise regimen in both obese [9,10] and diabetic individuals [11,12]. However, another meta-analysis [13] and few studies [14-17] conducted on individuals with type 2 diabetes have provided conflicting results from those found on obese individuals, indicating that either this population does not respond in the same manner to lifestyle interventions or that more dramatic weight loss is necessary for changes to occur. Even though physical exercise has been found to affect adiponectin and other adipocytokines such as leptin in a favorable manner, the effect may be potentiated with dietary co-intervention. Furthermore, the mechanism of exercise induced plasma adiponectin level in individuals with obesity and diabetes is not known well. This review summarizes some of the recent findings on the physiological role of adiponectin in obesity and diabetes and how exercise may affect these changes.

## 1. Adiponectin

Adiponectin is a collagen like protein and adipocyte-derived hormone that is exclusively synthesized in white adipose tissue, is induced during adipocyte differentiation, and circulated at relatively high concentrations in the serum [18]. It has been shown to suppress proliferation and activation of immune cells and the secretion of inflammatory cytokines such as tumor necrosis α (TNF-α) in the atherogenic process [19]. It also downregulates vascular adhesion molecules in endothelial cells and inhibits foam cell formation and smooth muscle migration. In doing so, adiponectin influences pathogenic processes on the vascular wall in the way that the development of atherosclerotic plaques is inhibited [20]. Beyond these direct effects, adiponectin exerts further beneficial actions by lowering dyslipidemia and other risk factor of cardiovascular disease. Adiponectin has been postulated to play an important role in the modulation of glucose and lipid metabolism in insulin-sensitive tissues in both humans and animals. It also increases fatty acid oxidation, probably by activation of AMP kinase [21]. Adiponectin contrasts with most other adipocytokines, whose levels are increased in obesity in proportion to an increased total body fat mass. Decreased circulating adiponectin levels have been shown in genetic diet-induced murine model of obesity [22], as well as in diet-induced form of human obesity [3]. In clinical studies, low adiponectin levels have been associated with an atherogenic lipid profile [23,24]. The association of low adiponectin levels with obesity, insulin resistance, coronary artery disease and dyslipidemia indicates that this novel protein may be an important new marker of the metabolic syndrome.

## 2. Effects of exercise on body composition and adiponectin

It was observed increase in plasma adiponectin levels with -14.7% body weight loss in middle aged obese women with introduction of aerobic exercise training [25]. Hara et al. reported that plasma adiponectin levels are correlated with percent body fat and that changes of plasma adiponectin levels are negatively correlated with changes of body fat mass [26]. These training studies have shown that exercise might not be a significant factor towards adiponectin modifications [27,28]. It seems that modifications in body weight or body composition might be responsible for alterations in adiponectin levels. Subjects who had significant weight loss with diet alone or with exercise training and dietary modifications had an increase in adiponectin [29]. Similar results were found for adiponectin following gastric partition surgery that induced weight loss, and also no change in plasma adiponectin concentration after a 6-month exercise program when weight balance was maintained [30]. These data suggests that adiponectin was affected more by weight loss than by exercise and body weight/composition alterations are necessary to increase adiponectin concentrations. Thus, the decrease of body weight and/or body fat is probably necessary to increase adiponectin concentrations. It is also suggested that adiponectin level does not change due to small magnitude of weight reduction, and its levels are increased following an improvement of the body composition and this is more important than the way training is performed.

## 3. Effects of exercise on inflammatory markers and adiponectin

Epidemiologic studies have demonstrated that several well accepted markers of inflammation, such as TNF-α, interleukin-6 (IL-6) and C-reactive protein (CRP), are independent predictors of incident diabetes. In overweight and obese subjects, serum levels of inflammatory markers are significantly higher than those in lean subjects [31]. Plasma adiponectin levels may be negatively associated with levels of CRP and fibrinogen [29,32]. Elevated serum hs-CRP may play a role in the development of insulin resistance syndrome and type 2 diabetes. This elevation is accompanied by the opposite changes of adiponectin [33]. It indicates potential anti-inflammatory properties of adiponectin. Regular exercise reduces the circulating concentrations of CRP, IL-6, and TNF-α. Therefore, exercise-enhanced release of cytokines can be directly implicated in alteration of both CRP and adiponectin levels [34]. In contrast, there is one evidence suggesting that exercise training is not associated with improved levels of CRP or adiponectin [27]. They found that participation in moderate to intense exercise was not associated with improved mea-

sures of chronic inflammation markers. These results are in agreement with that improvements in insulin sensitivity resulting from exercise or modest weight loss did not appear to be related to changes in these markers [27,35]. Therefore, it is possible that if enough weight loss occurs with or without concurrent exercise, declines in CRP and changes in other inflammatory markers may occur. However, the severity of exercise required to elicit these inflammatory responses is not well established.

## 4. Effects of exercise on insulin resistance and adiponectin

Increasing adiponectin levels has been associated with a lower risk for developing diabetes across populations in a dose-response relationship [36]. Exercise increases insulin sensitivity through reduction of resting levels of TNF-α and CRP and augmentation of adiponectin levels [37]. Exercise is one preventive therapy that has been shown to improve insulin sensitivity both acutely and with chronic training [38]. However, less is known about the effects of exercise on adiponectin and insulin resistance, and results of many studies are inconsistent. Hulver et al. found that adiponectin is unaltered with exercise training despite enhanced insulin action, however, a group of subjects who lost weight, adiponectin concentrations increased significantly with a corresponding increase in insulin sensitivity [30]. Another study reported that supervised intensive training program did not induce significant changes in adiponectin levels despite a tremendous decrease in abdominal fat and improvement in insulin sensitivity in sedentary middle-aged type 2 diabetic men [14]. This study also demonstrated that in the trained group there was an inverse relationship between changes in body weight and changes in adiponectin levels whereas the improvement in insulin sensitivity was not associated with a significant change in adiponectin and leptin levels. A previous study [39] in moderately obese females 3 month's aerobic training suggested that adiponectin is not a factor which affects to insulin sensitivity related to exercise. Furthermore, contrasting with diet-induced weight loss, the improvement of insulin sensitivity by training is not related to adiponectin variations. Thus, the possibility that elevation of adiponectin levels may no longer be necessary to increase insulin sensitivity during exercise training has been emerged. Based on Yokoyama et al.'s finding, restoring insulin sensitivity by aerobic exercise is mainly mediated by mechanisms other than adiponectin, such as the AMP-activated protein kinase pathway [17]. However, adiponectin may play a central role in operating insulin action when an improvement of insulin sensitivity is achieved mainly by fat mass reduction even though it seems that the changes in insulin sensitivity by exercise training are independent of adiponectin alteration.

## 5. Effective strategy for increasing adiponectin

Recent meta-analysis [11] revealed that aerobic exercise, but not other exercise modalities, lead to significant increase in adiponectin levels. This was might be explained through greater negative energy balance induced by aerobic exercise as compared to other modalities. Another systematic review and meta-analysis [40] suggested that concurrent aerobic plus resistance exercise improves body composition, metabolic profiles, and inflammatory state in the obese population. Other meta-analysis in obese and patients with type 2 diabetes suggested that concurrent exercise is the most efficacious means to improve anthropometric indicators of adiposity [41], glycemic control, and blood lipids [42], as compared with aerobic or resistance training alone. However, it remains to be established whether the changes in adiponectin induced by exercise are better achieved by aerobic or resistance exercise. In addition, the mechanism of the adaptation, and whether it differed according to training modality, is currently unknown. There is at present some support for the use of moderate or high-intensity resistance or aerobic training of adequate duration to produce substantive changes in body composition, to augment circulating adiponectin. Exercise programs of moderate-to-high intensity exercise may have the greatest impact on adiponectin levels [43]. Moderate-to-large treatment effects were seen in both aerobic and resistance training modalities suggesting that exercise of adequate intensity may be the key to elicit change in adiponectin levels. Fatouros et al. suggested that the large increase in plasma adiponectin levels resulting from high and moderate intensity resistance-training protocol was in a dose-response effect [44]. However, more studies of resistance training reporting consistent findings are needed. Several previous studies reported increased adiponectin changes after caloric restriction. The findings of prior studies support that weight close to 10% or more is associated with increased adiponectin concentration [45]. However, Wang et al. recently reported that 12.7% weight loss induced by caloric restriction alone did not result in any change in adiponectin whereas an increase was observed in those with the addition of exercise with the same amount of weight loss [46]. It is suggested that exercise may "sensitize" the adiponectin response to weight loss. In addition, exercise and caloric restriction induced weight loss may function via different mechanisms to influence adiponectin concentration. Thus, further study is needed to examine the effects of caloric restriction and exercise on adipose tissue adiponectin production.

## CONCLUSIONS

In reviewing the information on the effects of exercise on adiponectin in obese and diabetic individuals, the present review shows that exercise training represents a viable strategy to increase adiponectin in obese and diabetic individuals. Even though the physiological benefits of regular physical activity, as well as guidelines and recommendations on the type and amount, are provided in different guidelines for prevention and treatment of diabetes and obesity, exercise training induced the augmentation of the anti-inflammatory cytokine adiponectin may assume critical importance for long-term health outcomes.

## CONFLICT OF INTEREST

The authors declare no conflict of interest.

## AUTHOR CONTRIBUTIONS

Writing–original draft: K Lim, K Kim; Writing – review & editing: K Lim, K Kim.

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