The effects of exercise on adipokines
-Focus on circulating adiponectin level in human studies-

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Abstract Adipose tissue is an important site for energy storage and energy homeostasis. In addition, it has been recognized as an endocrine organ that produces and secretes a number of bioactive peptides or proteins called “adipokines”. These molecules are directly and indirectly involved in the pathogenesis of metabolic disorders, such as obesity, type 2 diabetes, cardiovascular diseases, and metabolic syndrome. Until now, a number of adipokines (e.g. adiponectin, leptin, tumor necrosis factor-α, interleukin-6, and retinol-binding protein-4) have been identified and their functions have been elucidated. Among these, adiponectin is known to be involved in improvement in insulin sensitivity and endothelial function, and promotion of fat oxidation. Aerobic exercise also has the same effects. The benefits of aerobic exercise could be induced through changes in adiponectin levels. In this short-review, focus is given to the effects of aerobic exercise on circulating adiponectin levels in humans.

Keywords: adiponectin, adiponectin oligomers, aerobic exercise

Structure and function of adiponectin

Adiponectin was first identified in 1995, and is also referred to as Acrp30\(^1\), AdipoQ\(^2\), apM1\(^3\) or GBP28\(^4\). Adiponectin comprises of 244 amino acids, and is mainly composed of a carboxyl-terminal globular domain and an amino-terminal collagen domain\(^5\). Adiponectin exists in blood as a proteolytic cleavage fragment of the globular C-terminal domain (globular adiponectin) as well as a full-length form (full-length adiponectin). Globular adiponectin mainly exists as a trimer, whereas full-length adiponectin occurs as a low-molecular weight (LMW) trimer, a middle-molecular weight (MMW) hexamer, and high-molecular weight (HMW) 12- to 18-mer adiponectin\(^6,7\). In particular, HMW adiponectin is believed to be the most biologically active form of the 3 oligomers\(^7\). AdipoR1 and AdipoR2 receptors have been identified as adiponectin receptors; AdipoR1 is highly expressed in skeletal muscle, whereas adipor2 is expressed in the liver\(^8\).

Adiponectin levels are low in obese humans\(^9\), and lower adiponectin levels are associated with a higher incidence of diabetes\(^10\). Furthermore, adiponectin levels are inversely correlated with insulin resistance\(^9\). Hypoadiponectinemia is independently associated with metabolic syndrome\(^11\); it is also reportedly associated with cardiovascular disease\(^12\) and hypertension\(^13\). HMW adiponectin levels and the ratio of HMW to total adiponectin levels are associated with metabolic syndrome\(^14\), insulin resistance\(^15\) and cardiovascular diseases\(^16\) to a greater extent than total adiponectin levels.

Adiponectin has direct and indirect functions that are primarily related to the promotion of insulin sensitivity and endothelial function, and the inhibition of inflammatory mediators. It also inhibits hepatic glucose production\(^17,18\) and stimulates glucose uptake and fat oxidation in skeletal muscle and other tissues\(^18\). Furthermore, it directly increases nitric oxide\(^19\), reduces the expression of adhesion molecules in endothelial cells\(^20\), and elicits anti-inflammatory properties by decreasing cytokine production\(^21\).

The effects of aerobic exercise on circulating total adiponectin and adiponectin oligomer levels

As mentioned above, adiponectin improves insulin sensitivity and endothelial function, and stimulates fat oxidation. Aerobic exercise increases insulin sensitivity\(^22\), enhances vascular endothelial function\(^23\), and accelerates fat oxidation\(^24\). It is hypothesized that the benefits of aerobic exercise are induced through changes in adiponectin levels.

1. The effects of acute aerobic exercise

It seems quite probable that the change in circulating total adiponectin levels is minor in response to acute
aerobic exercise. Strenuous intermittent exercise at 60% (10 min), 75% (10 min), 90% (5 min), and 100% maximal oxygen consumption (V\textsubscript{O2max}) (5 min) did not change total adiponectin levels\textsuperscript{25}. A two-hour cycling exercise at 50% V\textsubscript{O2max} under normal, fasting conditions, and after the pharmacological inhibition of adipose tissue lipolysis, also did not change total adiponectin levels during and after the exercise\textsuperscript{26}. Moreover, Højbjerre et al.\textsuperscript{27} investigated the change in circulating total adiponectin levels during and after 60-min acute aerobic exercise at 55% V\textsubscript{O2max} in lean and obese males. Despite the increase and decrease in interstitial adiponectin levels and adiponectin mRNA in subcutaneous abdominal adipose tissue respectively, circulating total adiponectin levels did not change during and after the exercise. In contrast, Jurimae et al.\textsuperscript{28} reported that circulating total adiponectin levels decreased slightly immediately after rowing exercise; however, the levels returned to baseline at 30 min after the exercise. To our best knowledge, however, no study has reported an increase in circulating total adiponectin levels in response to acute aerobic exercise.

HMW adiponectin represents the most biologically active form of the 3 adiponectin oligomers\textsuperscript{7}. Therefore, we investigated the continuous change in total and HMW adiponectin levels during moderate-exercise (50% V\textsubscript{O2peak}, 60 min) and after the exercise (30 min) in healthy young males. HMW and total adiponectin levels during and after the exercise were not significantly different from those during a 90-min rest period\textsuperscript{29}. In addition, we recently reported the effects of exercise intensity on adiponectin oligomer levels in abdominally obese men\textsuperscript{30}. Nine untrained abdominally obese men performed 60-min moderate-intensity (50% V\textsubscript{O2max}) and high-intensity aerobic exercise (70% V\textsubscript{O2peak}). Unexpectedly, total adiponectin levels decreased only during the high-intensity aerobic exercise. Furthermore, HMW adiponectin levels remained unchanged in both trials, whereas MMW + LMW adiponectin levels decreased, and the ratio of HMW to total adiponectin levels increased during the high-intensity aerobic exercise. The decrease in total and MMW + LMW adiponectin levels correlated with a change in epinephrine levels. These findings suggest that high-intensity acute aerobic exercise modulates adiponectin by changing adiponectin oligomer levels; and a change in epinephrine levels during exercise is associated with alterations in circulating adiponectin levels. In addition, a reduction in MMW and/or LMW adiponectin levels may lead to reduced competition between adiponectin oligomers for binding to the adiponectin receptor; and fluctuations in the levels of MMW and/or LMW adiponectin levels indirectly reinforce the function of HMW adiponectin\textsuperscript{31}. However, since data on the effects of acute exercise on adiponectin oligomer levels is limited, further studies are needed.

2. Chronic aerobic exercise training

Data on the effects of chronic aerobic exercise training on circulating total adiponectin is inconsistent. Circulating total adiponectin levels did not change in the population with type 2 diabetes\textsuperscript{32} and obesity\textsuperscript{33} during a 12-week aerobic exercise intervention. In other long-term (6 to 12 month) aerobic exercise training studies, circulating total adiponectin levels did not change in an overweight/obese population\textsuperscript{34} or metabolic disorders population\textsuperscript{35} during the intervention. In contrast, Weiss et al.\textsuperscript{36} reported that circulating total adiponectin levels increased (~17%) dur-

![Fig. 1](image-url) Changes in total (A), high-molecular weight (HMW) (B) and middle- plus low-molecular weight (MLWM) (C) adiponectin levels during moderate-intensity aerobic exercise and high-intensity aerobic exercise. *A significant difference between rest and 60 min of high-intensity aerobic exercise (P < 0.05). Values are means ± SE.\textsuperscript{30}
ing a 12-month aerobic exercise intervention in a normal/overweight population. Moreover, another study found that a 16-week aerobic exercise intervention increased circulating total adiponectin levels (~5-7%)\(^3\). This discrepancy in results between studies can be explained, at least, by the amount of weight loss. The former studies observed a slight weight loss (~1-3.5%), whereas the latter studies observed substantial weight loss (~5-9%). Therefore, chronic aerobic exercise training itself may have only a minor impact on circulating total adiponectin levels. Aerobic exercise training, accompanied by weight loss, may be effective for achieving an increase in total adiponectin levels. Nevertheless, Balducci et al.\(^3\) reported that, despite weight remaining unchanged, 6-month aerobic exercise training increased total adiponectin levels (36%) in patients with type 2 diabetes. In that study, participants performed aerobic exercise at 70-80% Vo\(_{\text{peak}}\) intensity, which was relatively higher than that reported in other studies with no change in total adiponectin levels\(^{22-30}\). Therefore, it is possible that high-intensity aerobic exercise training may have a potential effect on improvements in circulating total adiponectin levels.

Few studies have reported the effects of aerobic exercise training on adiponectin oligomer levels. O’Leary et al.\(^3\) investigated changes in adiponectin oligomer levels in older insulin-resistant adults during 12 weeks of exercise alone or exercise with caloric restrictions. Total adiponectin and adiponectin oligomer levels did not change, but the ratio of HMW to total adiponectin levels increased during both interventions. The changes in the ratio of HMW to total adiponectin levels positively correlated with the changes in insulin sensitivity. In a recent study\(^3\), a 7-day aerobic exercise training routine increased HMW adiponectin levels in parallel with an improvement in insulin sensitivity. We observed that 12 weeks of aerobic exercise improved insulin sensitivity, but did not increase HMW adiponectin in obese males (unpublished data). Additional studies are required to determine whether aerobic exercise training alters adiponectin oligomer levels.

**Conclusion**

Aerobic exercise can have a minor effect on circulating adiponectin levels in humans. Aerobic exercise may contribute to an improvement in metabolic disorders by modulation of interstitial adiponectin levels\(^7\) and number of adiponectin receptors\(^4\), but not by circulating total adiponectin levels. However, it is quite likely that intensity and duration of aerobic exercise affect circulating adiponectin levels. Further studies are expected to clarify whether aerobic exercise alters adiponectin oligomer levels and can help for elucidating exercise-induced improvements in metabolic disorders.

**References**

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