

Effects of Exercise on Adiponectin: A Systematic Review

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Secreted from white adipose tissue, circulating concentrations of adiponectin are reduced in the presence of metabolic and cardiovascular disease such as obesity and type 2 diabetes. The aim of this systematic review is to assess the body of evidence critically for the effects of exercise on adiponectin levels. Literature searches using the Medline, CINAHL, Cochrane Controlled Trials registry, EMBASE, and SportDiscus databases were conducted from 1966 to September 2006 using keywords pertaining to “adiponectin” and “exercise.” Thirty-three trials met the inclusion criteria. Study designs consisted of 5 cross-sectional studies, 7 trials of acute exercise, 11 uncontrolled trials, 2 non-randomized controlled trials, and 8 randomized controlled trials (RCTs). Exercise of varying prescription has been shown to increase serum adiponectin in 38% of RCTs, demonstrating small-to-moderate effect sizes (ESs). One study reported a dose–response effect of resistance training intensity and the augmentation of adiponectin. Inconsistent support in the literature exists for increasing adiponectin levels after short-term exposure to robust aerobic or resistance training of moderate-to-high intensities. Particular attention should be directed toward high-risk cohorts, in whom augmentation of the anti-inflammatory cytokine adiponectin may assume critical importance.

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Adiponectin characteristics

Adipose tissue functions as an endocrine organ (1–4), in addition to its role in fuel storage, thermal insulation, and mechanical protection, releasing biologically active and diverse cytokines, termed adipokines (1,5). Adiponectin, first identified in 1995 (6) and also known as AdipoQ and ACRP30, is a serum protein hormone secreted from white adipose tissue into the circulation, where it is found in high concentrations (7–9). Adiponectin plays a significant role in metabolic disorders, such as obesity, type 2 diabetes, coronary heart disease, and metabolic syndrome (7,10,11) due to its insulin sensitizing (12), anti-inflammatory, and anti-atherogenic properties (13). Structurally, adiponectin contains three distinguishable domains: an N-terminal sequence, a collagenous region, and a globular domain (14).

Functions of adiponectin

Table 1 details the major known functions of adiponectin as they are currently

established, acknowledging the rapidly changing developments in this field. Adiponectin has known direct and indirect functions primarily related to endothelial function, the promotion of insulin sensitivity and inhibition of inflammatory mediators (15). Full-length adiponectin acts with insulin to inhibit hepatic glucose production whereas the globular domain stimulates fatty acid oxidation in skeletal muscle and other tissues in both animal and human models (16–18), with receptor expression up-regulated in obesity, impaired glucose tolerance, and type 2 diabetes (19). Adiponectin acts directly to increase nitric oxide (NO) production (20–22) and adenosine monophosphate-activated kinase (17) and indirectly decreases levels of C-reactive protein and interleukin-6 through the dose-dependent, reciprocal inhibition of tumor necrosis factor- α (10). In addition, adiponectin reduces expression of adhesion molecules in endothelial cells (10) and elicits its anti-

inflammatory properties by decreasing cytokine production from macrophages (via inhibition of nuclear transcription factor kappa signaling) (10,23).

Levels of adiponectin in healthy adults

An *in vitro* study (10) showed that plasma adiponectin levels of 5–25 $\mu\text{g}/\text{ml}$ had significant inhibitory effects on tumor necrosis factor- α -induced monocyte adhesion and adhesion molecule expression, suggesting an increased risk of adverse health effects at serum concentrations below this level. Consistent with these findings, circulating adiponectin levels in normal subjects has been reported as 5–20 $\mu\text{g}/\text{ml}$ (24). The primary characteristic found to be closely related with adiponectin concentration in humans is level of obesity. Other adipokines are generally secreted at above normal levels in obesity (25). However, in both animal and human studies, circulating levels of adiponectin decrease significantly in the presence of obesity (26,27),

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Table 1 Reported functions of adiponectin

Citation	Species	Function
Ouchi <i>et al.</i> (1999) (10)	Human	Inhibits TNF- α induced monocyte adhesion Inhibits adhesion molecule expression
Fruebis <i>et al.</i> (2001) (16)	Mice	Regulates plasma FFAs, glucose and triglyceride
Yamauchi <i>et al.</i> (2002) (17)	Mice	Stimulates β -oxidation in myocytes Stimulates glucose uptake in myocytes Stimulates phosphorylation of AMPK in myocytes Stimulates phosphorylation of ACC in myocytes Activates AMPK and phosphorylates ACC in liver <i>in vivo</i> Glucose-lowering effect through liver AMPK activation
Tsao <i>et al.</i> (2002) (8)	Human, mice	Activates NF- κ B (hexameric and HMW isoforms)
Chen <i>et al.</i> (2003) (20)	Human	Stimulates NO production in vascular endothelium Adiponectin stimulates phosphorylation of eNOS via AMPK
Hattori <i>et al.</i> (2003) (21)	Cow Human	Up-regulation of endothelial NO production (globular Ad) Up-regulation of eNOS activity (globular Ad) Up-regulation of eNOS mRNA and protein expression (globular Ad)
Onay-Besikci, Altarejos, and Lopaschuk (2004) (18)	Rabbits	Increases fatty acid oxidation (globular Ad)
Salmenniemi <i>et al.</i> (2004) (11)	Human	Low levels responsible for endothelial damage and a low-grade systemic chronic inflammatory state
Ajuwon & Spurlock (2005) (13)	Pig	Suppresses LPS-induced IL-6 and TNF- α mRNA expression Up-regulates PPAR γ 2 expression in adipocytes Regulates inflammation through partial inhibition of NF- κ B transcription factor
Xi <i>et al.</i> (2005) (22)	Cow	Vasorelaxation
Kim <i>et al.</i> (2006) (9)	Human	Suppresses IL-2-mediated NK cytotoxicity Inhibits IL-2 function
Lara-Castro <i>et al.</i> (2006) (12)	Human	Increases insulin sensitivity Increases basal lipid oxidation Increases number and size of HDL (HMW form) Decreases VLDL and LDL concentrations

ACC, acetyl coenzyme A carboxylase; AMPK, adenosine monophosphate kinase; eNOS, endothelial nitric oxide synthase; FFAs, free fatty acids; HDL, high density lipoprotein; HMW, high molecular weight; IL-2, interleukin-2; IL-6, interleukin-6; LDL, low density lipoprotein; LPS, lipo-polysaccharide; NF- κ B, nuclear factor- κ B; NK, natural killer; NO, nitric oxide; PPAR γ 2, peroxisome proliferator activated receptor-gamma 2; TNF- α , tumor necrosis factor- α ; VLDL, very low density lipoprotein.

which may reflect lower secretion of the protein. An inverse relationship has been shown to exist between BMI and adiponectin (7,19,25,28). Adiponectin levels are consistently reported as <6 μ g/ml in obese subjects (25,29–31).

On the other hand, exercise, alone (19,32) or in combination with diet-induced weight loss (30), significantly increases plasma adiponectin levels in both obese and insulin-resistant subjects, leading to improved insulin sensitivity and reductions of inflammatory markers. Calorie-restricted weight loss has been shown to be effective in increasing plasma adiponectin concentrations (7,33). However some of the most dramatic changes have been achieved through gastric bypass surgery where adiponectin levels increased by 50 and 281% (31,34), accompanied by significant weight loss. Although exercise alone has been reported to increase circulating adiponectin levels significantly (29,35,36), studies have not generally controlled for caloric intake or dietary

composition, compromising the validity of attributing changes in adiponectin concentrations to exercise alone. Moreover, diet interventions in combination with exercise have been shown to increase adiponectin robustly (30,37), suggesting the importance of overall fat mass reduction associated with these combined interventions. Distinction between the roles of visceral and subcutaneous adipose stores is unclear.

Adiponectin and chronic disease

Diseases associated with lower than normal circulating adiponectin are type 2 diabetes (7), coronary artery disease (28), and dyslipidemia (12). Where diseases are associated with increased adiposity, it is not clear whether these differences in adiponectin would remain after adjustment for visceral adiposity or physical activity levels, which has typically not been done. Thus, adiponectin is affected by, and is itself involved in, the regulatory pathway of many factors including tumor necrosis factor- α , interleukin-6, C-reactive protein, insulin,

weight loss/gain, body composition, and disease. Although exercise in combination with weight loss diets has been shown to increase adiponectin levels (30,37), it is not clear whether exercise in the absence of weight loss or dietary interventions can modify adiponectin levels. Furthermore, the effects of acute vs. chronic exercise training on adiponectin present inconsistencies, and the effect of aerobic versus resistance training on adiponectin levels, or dose-response characteristics of such relationships are largely unknown. Therefore, the purpose of this review is to review the published evidence systematically for exercise as a modifier of circulating adiponectin concentrations. To our knowledge, such a systematic review has not been published previously.

METHODS AND PROCEDURES

A systematic review of all published literature, regardless of study design, investigating the relationship between physical activity and adiponectin level in any tissue was conducted. Given the

novelty of the subject, the heterogeneity of the exercise modalities and cohorts studied, and the paucity of robust randomized controlled trials (RCTs), pooling of effect sizes (ESs) across studies in a meta-analysis was not considered appropriate at this stage.

Literature search

A literature review was conducted from 1966 to 2006 using computerized databases including Medline, CINAHL, Cochrane Controlled Trials Registry, EMBASE, and SportDiscus, with the last search being conducted in September 2006. The search utilized keywords pertaining to adiponectin and exercise as follows: The terms “adiponectin,” or “AdipoQ,” or “ACRP30” were combined using AND with the terms “exercise,” or “physical activity,” or “training,” or “aerobic,” or “resistance.” Reference lists of retrieved papers and review articles were hand-searched for additional relevant citations. Unpublished theses were not included in the literature search.

Inclusion criteria

Articles were selected from the initial search according to the following criteria: the study design was a RCT, non-RCT, uncontrolled trial, acute exposure to an exercise bout, or cross-sectional investigation measuring either exercise or physical activity and adiponectin levels in any tissue; human subjects were used; the full-length article was published in a peer-reviewed journal.

Exclusion criteria

Studies were excluded for the following reasons: only animal data was presented, exercise exposure or physical activity assessment was not included in the study design; they were non-English language papers; or the articles were reviews or abstracts. Articles were also excluded if the effects of exercise were confounded by other factors such as diet or pharmacological intervention.

Data extraction and analysis

Data were extracted for the assessment of study quality, as well as the description of methodology and primary and secondary outcomes of each trial by

two authors. From this data, values reported as s.e.m. were converted to s.d. The weighted mean difference between group means and 95% confidence intervals (CIs) assuming equal variances were calculated using a CI calculator (version 4.1, 26 January 2004) (38) where appropriate (controlled or comparison studies). Relative ES (mean change_{treatment} – mean change_{control}) / s.d._{pooled baseline} and 95% CIs (s.d._{pooled baseline} × bias correction factor (Hedges) ± z value × s.e. of ES estimate) were calculated for controlled trials (39). ES for each of the controlled trials were interpreted according to the method of Cohen (40). Scores for insulin sensitivity were calculated using the homeostasis model assessment calculator (HOMA Calculator Version 2.2) (41) when fasting insulin and glucose values were available, if the authors had not already reported these values.

Research quality

Study quality was assessed based on the Delphi list (42) for assessing the quality of RCTs and was extended to non-randomized controlled and uncontrolled trials. Additional quality variables considered were supervision of exercise training, adequacy of reporting of exercise modality, dose, and intensity, and precision of adiponectin assay reported.

RESULTS

Studies retrieved

Figure 1 displays the research results. The search generated 70 relevant citations. Thirty-two trials (31 publications) were accepted according to the inclusion/exclusion criteria. Observational and experimental studies were included which consisted of 5 cross-sectional studies, 7 studies on the acute effects of exercise, 11 uncontrolled trials, 2 non-RCTs, and 8 RCTs.

Study quality assessment

Study quality is summarized in Table 2. None of the RCTs met all of the Delphi list quality criteria, and the most common deficiencies were in the areas of blinded outcome assessors, concealment of randomization, reporting of dropouts, and statistical methods. The most important deficiency among the controlled trials was the lack of statistical inter-group comparisons. Fifty percent of these studies reported on only intra-group ANOVAs or *t*-tests, rather than appropriate tests of between-group ESs. Exercise interventions in these trials were generally not described adequately (35,43,44), particularly the resistance training protocols (45–47) and/or were of low intensity (19,47–49). Cohorts were generally described adequately and similar at baseline in the controlled trials.

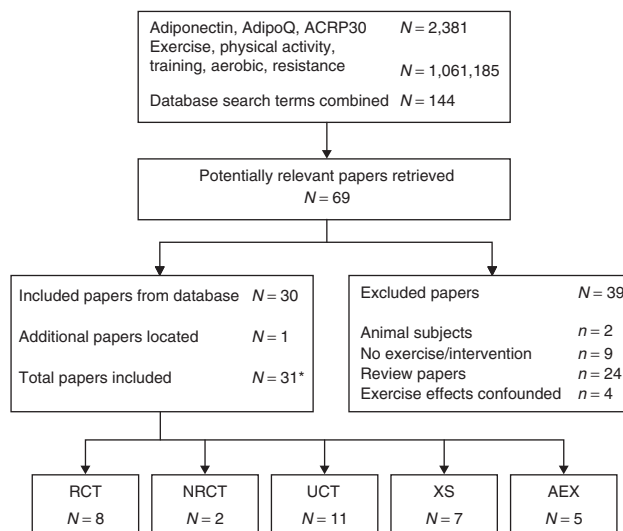


Figure 1 Summary of search results. AEX, Acute exercise study; NRCT, non-randomized controlled trial; RCT, randomized controlled trial; UCT, Uncontrolled trial; XS, Cross-sectional analysis. Asterisk denotes 33 trials were included from 31 publications.

Table 2 Summary of research quality

Citation	Randomization performed?	Treatment allocation concealed?	Groups/ subjects similar at baseline regarding important prognostic values?	Eligibility criteria specified?	Blinded outcome assessors?	Compliance reported?	Supervision of exercise sessions?	Dropouts reported?	Did the analysis include an intention-to-treat analysis?	Were point estimates and measures of variability presented for the primary outcome measures?	Were between groups statistics reported?
Uncontrolled trials											
Hulver <i>et al.</i> (2002) (34)	No	n/a	n/a	No	Not reported	No	Yes	No	Yes	Yes	No
Ryan <i>et al.</i> (2003) (44)	No	n/a	n/a	Yes	Not reported	No	Yes	No	No	Yes	Yes
Yatagai <i>et al.</i> (2003) (61)	No	n/a	n/a	No	Not reported	No	No	No	Yes	Yes (baseline)	No
Hsieh and Wang (2005) (63)	No	n/a	n/a	Yes	Not reported	Yes	No	No	No	Yes	No
Nassis <i>et al.</i> (2005) (52)	No	n/a	n/a	No	Not reported	No	Yes	No	No	Yes	No
O'Leary <i>et al.</i> (2005) (65)	No	n/a	n/a	Yes	Not reported	Yes	Yes	Yes	Yes	Yes	No
Polak <i>et al.</i> (2006) (53)	No	n/a	n/a	Yes	Not reported	No	Yes	No	Yes	Yes	No
Bluhner <i>et al.</i> (2006) (19)	No	n/a	n/a	No	Not reported	No	Yes	No	Yes	Yes	No
Oberbach <i>et al.</i> (2006) (32)	No	n/a	n/a	Yes	Not reported	Yes	Yes	No	Yes	Yes	No
Jurimae <i>et al.</i> (2006) (57)	No	n/a	n/a	No	Not reported	No	Yes	No	Yes	Yes	No
Jurimae <i>et al.</i> (2006) (58)	No	n/a	n/a	No	Not reported	No	Yes	No	Yes	Yes	Yes
Non-randomized controlled trials											
Yokoyama <i>et al.</i> (2004) (66)	No	No	Yes	No	Not reported	No	Yes	No	Yes	Yes	No
Kondo <i>et al.</i> (2006) (51)	No	No	Yes	Yes	Not reported	No	Yes	No	Yes	Yes	No
Randomized controlled trials											
Boudou <i>et al.</i> (2003) (54)	Yes	Yes	Yes	No	Not reported	No	Yes	No	Yes	Yes	Yes
Marcell <i>et al.</i> (2004) (64)	Yes	No	Yes	No	Not reported	No	Yes	No	Yes	Yes	No
Balagopal <i>et al.</i> (2005) (29)	Yes	No	Yes	Yes	Not reported	No	Yes	No	Yes	Yes	No
Brekke <i>et al.</i> (2005) (62)	Yes	Yes	Yes	Yes	Not reported	Yes	No	Yes	No	Yes	Yes
Fatouros <i>et al.</i> (2005) (35)	Yes	No	Yes	Yes	Not reported	Yes	Yes	Yes	No	Yes	Yes
Giannopoulou <i>et al.</i> (2005) (36)	Yes	No	Yes	Yes	Not reported	No	Yes	Yes	No	Yes	No
Hara <i>et al.</i> (2005) (46)	Yes	Yes	No	Yes	Not reported	No	Yes	No	Yes	Yes	Yes
Troseid <i>et al.</i> (2005) (43)	Yes	No	Yes	Yes	Not reported	No	Yes	No	No	Yes	Yes

Sample size

A total of 2,031 subjects were enrolled across 31 trials. One thousand two hundred and thirty-nine subjects were included in observational studies while 792 participants were involved in experimental studies. Sample sizes ranged from 63 to 738 subjects in observational studies and from 7 to 120 subjects in experimental study designs. For experimental trials, <20 subjects were enrolled in 42% of trials, 50% of studies had enrolled 20–75 participants, and 8% of studies enrolled >75 subjects.

Gender

Ninety percent of trials provided a gender breakdown (19,32). The sample consisted of a total of 1,316 men and 512 women; 13 trials included men only, 7 trials involved women only, and 11 studies involved both men and women. Observational studies included 940 men and 159 women with 2 studies including only women (47,50), 2 studies including men only (48,49), and another study including men and women but not providing a gender breakdown (19).

Experimental studies included 379 men and 353 women with 5 studies including women only (36,44,51–53) and 11 studies including men only (35,43,46,54–61). Ten studies included both men and women (19,29,32,34,45,62–66). One interventional study did not provide a gender breakdown (32).

Age

Mean age was 40.6 ± 17.5 years in studies providing this information. One trial presented an age range in which the youngest

and eldest patients enrolled were 18 and 33 years, respectively. Additionally, two trials used subjects under the age of 16 years with the sample age being 13.05 ± 1.75 years in one study (52) and 15.8 ± 0.4 years in the other (29).

Health status

A broad spectrum of subjects were studied and included cohorts with obesity (29,34,44,45,51,53,55,64); insulin resistance (19,32,36); type 2 diabetes (19,32,54,63,66); first-degree relatives of people with type 2 diabetes (62); metabolic syndrome (43); employees (48,49); sedentary and healthy subjects (35,45,47,50,60,61,65); and trained athletes (56–59).

Relationship between physical activity/exercise and adiponectin levels

Cross-sectional studies. All five cross-sectional studies obtained a fasting blood sample to assess plasma adiponectin and evaluated physical activity using questionnaire or accelerometer (47). **Table 3** summarizes the results of these studies, all of which support a significant direct relationship between physical activity and adiponectin levels in serum. For example, exercise two or more times per week was associated with adiponectin levels of $>4 \mu\text{g/ml}$ (odds ratio (OR) = 0.21, 95% CI = 0.06–0.74) (49). St-Pierre *et al.* (50) also reported a positive correlation of adiponectin and physical activity ($r = 0.31$, $P < 0.019$). Adiponectin levels in subjects with impaired glucose tolerance ($4.34 \pm 0.28 \mu\text{g/ml}$) and type 2 diabetes ($3.42 \pm 0.38 \mu\text{g/ml}$) were significantly lower than in those with normal glucose tolerance ($8.88 \pm 0.39 \mu\text{g/ml}$; $P < 0.001$), who were also found to have significantly higher levels of physical activity (19). Thus, the adiponectin difference may have been due to either physical activity level or disease state.

Acute exposure exercise studies. Seven acute bout studies have reported the effects of various modes of aerobic exercise (running, cycling, rowing) on circulating adiponectin with two uncontrolled trials also reporting these effects. These trials are summarized in **Table 4**. Only 2 of these 7 studies reported an

increase in adiponectin after exercise (57,59) (**Table 4**). A graded treadmill walk/run protocol in which subjects exercised at 60, 75, 90, and 100% $\text{VO}_{2\text{max}}$ elicited significant increases in adiponectin from $7.45 \pm 1.10 \mu\text{g/ml}$ to $8.18 \pm 1.20 \mu\text{g/ml}$ ($P < 0.05$) post-exercise in trained runners (59). By contrast, Jurimae *et al.* (56) found a significant reduction in adiponectin levels after-high intensity rowing exercise and correcting for plasma volume expansion ($6.2 \pm 9.5 \mu\text{g/ml}$ pre- to $5.5 \pm 8.5 \mu\text{g/ml}$ post-exercise; $P < 0.05$). No other studies corrected for plasma volume expansion. In another study by the same authors, the acute effects of volume-extended rowing training produced significantly greater adiponectin levels in the athletes selected for a national team immediately and 30 min post-exercise, and by contrast significant reductions identified in less-elite athletes who were not selected (57). Mean adiponectin levels decreased by $0.37 \pm 2.39 \mu\text{g/ml}$ as a result of exposure to acute exercise in this study (58). The three studies that showed no change in circulating adiponectin set protocol exercise intensities at low-moderate ($<65\% \text{VO}_{2\text{max}}$) for the duration of the test (45,55,60), suggesting the possibility that high-intensity exercise is required for modulation of adiponectin levels. However, the inconsistent results suggest the need for further study.

Chronic exposure (exercise training) studies

Uncontrolled trials. Eleven trials had average trial durations of 19.6 ± 13.4 weeks consisting of 3.1 ± 1.2 h/week. The results of these studies are summarized in **Table 5**. All trials incorporated aerobic exercise with one study utilizing power training (32) and another using resistance training in addition (44). However, for the resistance-training portion, the total number of repetitions performed and the number of sets per exercise were not described. Aerobic exercise activities included treadmill walking/running, cycling, swimming, jump rope, and group activities. Frequency of exercise sessions ranged from 3 to 6 times per week. The intensity of aerobic exercise varied across studies with most (7) studies using moderate-to-high-intensity exercise

prescriptions and four studies utilizing low-to-moderate intensities (19,32,53,63). Intensity for the resistance training protocol was set at 3–4 repetitions at 90% RM and then at 15RM and the power training protocol was not specified (32). Most trials (9) incorporated supervised training sessions (see **Table 2**).

Significant increases in adiponectin following the exercise intervention ranging from 12.6 to 97.1% were observed in only 3 of the 11 trials. All three positive trials enrolled subjects with varying degrees of glucose intolerance, including those with type 2 diabetes (19,32,63). An average increase in adiponectin of $1.33 \pm 2.83 \mu\text{g/ml}$ was seen in pre- and post-training adiponectin levels across all studies.

Non-randomized controlled trials. Two trials were identified and are summarized in **Table 6**. In the trial by Yokoyama *et al.* (66), study duration was only 3 weeks and involved supervised cycle ergometer exercise for 40 min/day, 5 days/week as well as walking 10,000 steps per day as measured using a pedometer. The cycling exercise was of low-moderate intensity ($50.6 \pm 8.6\% \text{HR}_{\text{max}}$) and there were negligible changes in adiponectin levels. The study by Kondo *et al.* (51) utilized a variety of aerobic activities at slightly higher exercise intensity (60–70% HR reserve) and involved a longer study duration, but also did not yield significant increases in adiponectin levels.

RCTs. The results from these eight studies are summarized in **Table 7**. Study durations averaged 15.3 ± 5 weeks with a mean exercise session time of 2.2 ± 0.5 h/week. Aerobic exercise was used as the sole exercise intervention in 5 (62.5%) trials. One study used resistance training only (35) while two studies used combinations of aerobic and resistance exercise (43,46). Overall, exercise frequency ranged from 3 to 5 days/week. Moderate–high intensity aerobic exercise averaged 70% $\text{VO}_{2\text{peak}}$ in two trials (36,54); 80–90% HR_{max} in one study (64) and also qualitatively in the same study, specified as an increase in physical activity based on current health promotion guidelines (64). An intensity based dose–response effect using resistance training only (35)

Table 3 Cross-sectional studies of physical activity and adiponectin

Citation	n, gender	Study groups	Cohort	Physical activity assessment method	Adiponectin measurement site, assay, CV	Adiponectin (µg/ml)	Physical activity category	P value	Analysis adjusted for body or fat mass?
Conus <i>et al.</i> (2004) (47)	96, f	MONW (n = 12) Non-MONW (n = 84)	Normal weight young women	Energy expenditure (tri-axial accelerometer) Minnesota leisure-time physical activity questionnaire	Plasma RIA CV not reported	9.18 ± 3.31 (n = 9) 10.70 ± 5.54 (n = 63)	1,335 ± 517 kJ/day 2,141 ± 1,457 kJ/day	-	No
Yokoyama <i>et al.</i> (2004) (48)	738, m	Grouped according to Breslow's index: Gp 1 (n = 3) Gp 2 (n = 13) Gp 3 (n = 86) Gp 4 (n = 196) Gp 5 (n = 234) Gp 6 (n = 159) Gp 7 (n = 47)	Employees of a Japanese corporation	Questionnaire (based on Breslow's lifestyle index; seven questions regarding breakfast, exercise, sleeping, control of body weight, drinking, snacks between meals, smoking)	Plasma ELISA CV not reported	>0.522 µg/dl	Sport >3x/week	NS NS	No
Tsukinoki, <i>et al.</i> (2005) (49)	202, m	Adiponectin <4 µg/ml (n = 77) Adiponectin >4 µg/ml (n = 125)	Workers at a metal plant	Lifestyle questionnaire (not specified)	Plasma ELISA CV not reported	2.9 ± 0.8	Ex <2x/week	P < 0.05	Yes
Blüher <i>et al.</i> (2006) (19)	140, m/f	NGT (n = 45) IGT (n = 69) T2D (n = 26)	Varying degrees of glucose tolerance	Not specified	Plasma RIA CV not reported	6.1 ± 1.9 8.88 ± 0.39 4.34 ± 0.28 3.42 ± 0.38	Ex ≥2x/week Low PA = 11% (n = 5) Mod PA = 47% (n = 21) High PA = 42% (n = 19) Low PA = 32% (n = 22) Mod PA = 51% (n = 51) High PA = 17% (n = 17) Low PA = 81% (n = 21) Mod PA = 15% (n = 4) High PA = 4% (n = 1)	NS P < 0.001 vs. NGT P < 0.001 vs. NGT + IGT	Yes
St-Pierre <i>et al.</i> (2006) (50)	63, f	n = 63	Non-obese	Energy expenditure (tri-axial accelerometer)	Plasma RIA Inter-assay CV = <15% Intra-assay CV = <10%	10.1 ± 4.2	2673 ± 806 kJ/day	P < 0.05	Yes

Results reported as mean ± s.d. unless otherwise stated; P values reported for pre vs. post unless otherwise stated; "-" Denotes value not reported by author; CV, coefficient of variance; ELISA, enzyme-linked immunosorbent assay; f, female; IGT, impaired glucose tolerance; m, male; MONW, metabolically obese normal weight; NGT, normal glucose tolerance; NS, not significant; RIA, radioimmunoassay; T2D, type 2 diabetes.

Table 4 Acute studies of exercise and adiponectin

Citation	n, gender	Study groups	Cohort	Acute exercise bout			Adiponectin measurement site, assay, CV	Adiponectin (µg/ml)			Analysis adjusted for body or fat mass?	
				Modality	Protocol	Duration		Pre	Post	P value		Adjusted mean difference (CI) ^a
Kraemer <i>et al.</i> (2003) (59)	7 m	Exercise (n = 7) Control (n = 7)	Trained runners	AER	TM walk/run 60% VO _{2max} (10 min) 75% VO _{2max} (10 min) 90% VO _{2max} (5 min) 100% VO _{2max} (2 min)	27 min	Plasma RIA	7.45 ± 1.10	0 min 8.18 ± 1.20 30 min 7.40 ± 1.05	P < 0.05 NS	0.73 (-0.61, 2.07) 0.05 (-1.30, 1.2)	No
Yatagai <i>et al.</i> (2003) (61)	12 m	Exercise (n = 12)	Healthy	AER	60 min/day Cycle ergometer 5x/week Lactate threshold	24 weeks	Plasma RIA	20.94 ± 7.4	17.2 ± 6.6	P < 0.05	3.74 (-9.68, 2.2)	No
Ferguson <i>et al.</i> (2004) (45)	8 m 8 f	Exercise (n = 16)	Healthy, moderately active	AER	Cycle ergometer 60% VO _{2max}	60 min	Plasma RIA	m: 16.4 ± 4.5 m: f: 19.3 ± 6.8	18.8 ± 9.9 20.5 ± 7.9	NS NS	0.2 (7.49, -7.09) 1.1 (-1.7, -3.9)	No
Punyadeera <i>et al.</i> (2005) (60) ^b	10 m	Exercise (LFA) (n = 10) Control (HFA) (n = 10)	Active	AER	Cycle ergometer 50% W _{max}	120 min	Plasma RIA	0 min 6.63 ± 0.8	30 min 6.2 ± 0.7	NS	Exercise vs. control Pre: 0.06 Post: 0.1 (-0.65, 0.77) (-0.56, 0.76)	No
Jurimae <i>et al.</i> (2005) (56)	10 m	Exercise (n = 10)	Elite rowers	AER	Rowing ergometer 6,000 m time trial	n/a	Plasma RIA	6.2 ± 9.5	5.7 ± 8.9	NS	0.5 (-9.15, 8.15)	No
Jurimae <i>et al.</i> (2006) (57)	11 m	Selected for national team (n = 6) Not selected for national team (n = 5)	Elite rowers (post 6-month volume-extended training) training was mainly performed on single sculls	AER	High-volume, low-intensity strength training On-water rowing	24 weeks	Plasma RIA	6.2 ± 9.5	5.5 ± 8.5	P < 0.05	0.7 (-9.17, 7.77)	No
Jamurtas <i>et al.</i> (2006) (55)	9 m	Exercise (n = 9)	Overweight/obese	AER	Cycle ergometer 65% VO _{2max}	45 min	Plasma ELISA	22.9 ± 9.4	0 min 17.5 ± 7.0 30 min 17.4 ± 7.6	P < 0.05 P < 0.05	5.4 (-17.49, 6.69) 5.5 (-17.97, 6.97)	No
								3.6 ± 0.7	3.2 ± 0.45	NS	0.4 (-0.99, 0.19)	No

Results reported as mean ± s.d.; P values reported for pre vs. post unless otherwise stated. AER, aerobic training; CI, confidence interval; CV, coefficient of variance; ELISA, enzyme-linked immunosorbent assay; f, female; HFA, high fatty acid; HFA trial, fasting conditions; LFA, low fatty acid; LFA trial, lipolysis inhibited (nicotinic acid analogue given (Acipimox)); m, male; NS, not significant; RIA, radioimmunoassay; TM, Treadmill. ^aAdjusted mean difference (CI) calculated using pre and post intervention values (48). ^bResults extrapolated from graph.

Table 5 Uncontrolled trials of exercise and adiponectin

Citation	n, Gender groups	Study	Cohort	Exercise intervention			Adiponectin measurement			Adjusted mean difference (CI) ^a	P value	Analysis adjusted for body or fat mass?
				Modality	Prescription	Duration	site, assay, CV	Pre	Post			
Hulver <i>et al.</i> (2002) (34)	11 m 14 f	Exercise (n = 8 m, 3 f) Weight loss (n = 3 m, 11 f)	Sedentary/obese	AER	45 min, TM walk/run, stair climbing, cycle 4x/week 65–80% VO _{2peak} Weight loss: gastric bypass surgery	24 weeks	Plasma RIA CV not reported	6.3 ± 7.5 4.4 ± 4.0	6.6 ± 9.0 13.6 ± 11.0	NS P < 0.05	0.3 (–6.69, 7.29) 9.2 (–1.97, 16.43)	No
Ryan <i>et al.</i> (2003) (44)	40 f	WL + AER (n = 16) WL + RT (n = 9) Weight loss (n = 15)	Overweight/obese/postmenopausal	AER + RT	45 min, TM, cycle ergometer, track 3x/week 60% VO _{2max} 8 exercises 1 set/upper body 2 sets/lower body Reps 3–4: 5RM or 90% 3RM Reps 4+: resistance ↓ so 15 reps could be performed	24 weeks	Plasma RIA Intra-assay Inter-assay CV = <10% CV = <10%	4.06 ± 1.68 3.78 ± 1.69 4.51 ± 1.23	Not reported Not reported Not reported	NS NS NS	All groups (n = 40): 0.24 (–0.2, 0.68)	No
Yatagai <i>et al.</i> (2003) (61)	12 m	Exercise (n = 12)	Healthy	AER	60 min/day Cycle ergometer 5x/week Lactate threshold	24 weeks	Plasma RIA Intra-assay Inter-assay CV = <5%	20.94 ± 7.4	20.9 ± 9.0	NS	0.04 (–7.02, 6.94)	No
Hsieh and Wang (2005) (63)	42 m 60 f	Older gp (n = 20 m, 30 f) Younger gp (n = 22 m, 30 f)	T2D	AER	20 min/day Moderate intensity (50–74% heart rate increase) (ACSM guidelines)	52 weeks	Plasma RIA Intra-assay Inter-assay CV = <9.5% CV = <9.4% Sensitivity = 1 µg/ml	4.26 ± 0.97 4.13 ± 0.88	6.56 ± 0.86 5.47 ± 0.59 Older vs. younger Older vs. younger (Corrected for body fat % & weight Δ)	P = 0.03 P = 0.04 P = 0.03 NS	2.3 (–1.94, 2.66) 1.34 (–1.05, 1.63)	Yes
Nassis <i>et al.</i> (2005) (52)	21 f	Exercise (n = 21)	Overweight/obese children	AER	40 min (total) 10 min, running, step benching, stair climbing, and jump rope 30 min, group activities (basketball, volleyball,	12 weeks	Plasma RIA Intra-assay CV = <3.6%	9.57 ± 3.01 (n = 11)	9.08 ± 2.32 (n = 11)	NS	0.49 (–2.88, 1.90)	No

Author (Year)	Age	Sex	Exercise	Intervention	Assessment	Assay	Mean	SE	Significance	CI	Notes
O'Leary <i>et al.</i> (2005) (65)	5 m 11 f		Exercise (n = 16)	Sedentary	AER	Plasma ELISA CV not reported	6.32 ± 3.6	6.05 ± 4.9	NS	0.27 (-3.37, 2.83)	No
Oberbach <i>et al.</i> (2006) (32)	60 m/f	NGT (n = 20)	Varying degrees of glucose tolerance	AER + PT	Plasma RIA CV not reported	8.6 ± 2.3	8.6 ± 2.8	NS	0 (-1.64, 1.64)	Yes	
		IGT (n = 20)				3.7 ± 0.9	5.8 ± 2.2	P < 0.001	2.1 (-1.02, -3.18)		
		T2D (n = 20)				3.75 ± 1.35	6.2 ± 2.1	P < 0.001	2.45 (-1.32, -3.58)		
Bluhner <i>et al.</i> (2006) (19)	29 m 30 f	NGT (n = 20); 9 m, 11 f	Varying degrees of glucose tolerance	AER	Plasma RIA CV not reported	8.7 ± 0.6	9.8 ± 0.6	P < 0.01	1.1 (-0.72, -1.48)	Yes	
		IGT (n = 20); 9 m, 11 f				3.4 ± 0.26	6.7 ± 0.7	P < 0.001	3.3 (-2.96, -3.64)		
		T2D (n = 20); 11 m, 9 f				3.5 ± 0.4	6.5 ± 0.6	P < 0.001	3.0 (-2.67, -3.33)		
Jurimae <i>et al.</i> (2006) (57)	11 m	Selected for national team (n = 6)	Elite rowers (post 6-month volume-extended training)	AER	Plasma RIA Intra-assay CV = <7.6% Inter-assay CV = <7.6%	22.5 ± 9.4	25.5 ± 7.5	NS	-3.0 (-7.94, 13.94)	No	
		Not selected for national team (n = 5)				15.1 ± 5.1	22.9 ± 9.4	NS	-7.8 (-3.23, 18.83)		
Jurimae <i>et al.</i> (2006) (58)	12 m	Exercise (n = 12)	Elite rowers	AER	Plasma RIA Intra-assay CV = <7.6%	25.38 ± 9.89	26.28 ± 6.29	NS	-0.9 (-6.12, 7.92)	No	
Polak <i>et al.</i> (2006) (53)	25 f	Exercise (n = 25)	Obese	AER	Plasma RIA CV = 9.3%	10.9 ± 6.1	10.0 ± 4.4	NS	0.9 (-3.92, 2.12)	Yes	

Results reported as mean ± s.d.; P values reported for pre vs. post unless otherwise stated. AER, aerobic training; CI, confidence interval; CV, coefficient of variance; ELISA, enzyme-linked immunosorbent assay; f, female; IGT, impaired glucose tolerance; m, male; NGT, normal glucose tolerance; NS, not significant; PT, power training; RIA, radioimmunoassay; RT, resistance training; TM, treadmill; T2D, type 2 diabetes; WL, weight loss.
^aAdjusted mean difference (CI) calculated using pre and post intervention values (48).

Table 6 Non-randomized controlled trials of exercise and adiponectin

Citation	n, gender	Study groups	Cohort	Exercise intervention			Adiponectin measurement site, assay CV	Adiponectin (µg/ml)			Relative effect size (CI) ^a	Analysis adjusted for body or fat mass?
				Modality	Prescription	Duration		Pre	Post	P value		
Yokoyama <i>et al.</i> (2004) (66)	14 m	Diet + Exercise	T2D	AER	40 min Cycle ergometer + walking	3 weeks	Plasma ELISA CV not reported	3.55 ± 1.32	3.65 ± 1.54	NS	0.13 (-0.56, 0.83)	No
	26 f	Diet (n = 4 m, 7 f)			10,000 steps/day (pedometer) 5x/week 50.6 ± 8.6% HR _{max}			4.28 ± 1.92	4.18 ± 1.72	NS		
Kondo <i>et al.</i> (2006) (51)	16 f	Exercise (n = 8)	Obese	AER	30–60 min Fast slope walk/jog, dumbbells, stretching, cycling, jump rope	21 weeks	Plasma ELISA CV not reported	2.4 ± 1.3	4.2 ± 1.2	NS	1.28 (0.2, 2.36)	No
		Control (n = 8)			60–70% HRreserve 4–5x/week			8.3 ± 1.5	8.2 ± 2.3	NS		

Results reported as mean ± s.d. unless otherwise stated; P values reported for pre vs. post unless otherwise stated.

AER, aerobic training; CI, confidence interval; CV, coefficient of variation; ELISA, enzyme-linked immunosorbent assay; f, female; m, male; NS, not significant.

^aEffect size (CI) calculated from pre and post values of intervention vs. control group (49).

was demonstrated using a training volume of 2–3 sets of 8 different exercises (repetitions not reported), 3 times/week at intensities ranging from 45% (low intensity) to 60–65% (moderate intensity) to 85% (high intensity) peak strength. Of the two trials using both modalities, one used high-intensity potentially randomized trials (PRT) (46) while the other study (43) did not provide an adequate report of the exercise prescription used. One study did not comment on supervision of exercise sessions (62).

Significant increases in plasma adiponectin ranged from 4.7 to 34.0% across 3 of the 8 trials in obese (29,64) and sedentary subjects (35,64), averaging an increase of 16.3% in response to differing exercise modalities ranging from moderate to high intensities. Of these studies, two used an aerobic exercise intervention (29,64) consisting of multi-modal aerobic activities and reported an average increase of 15.4% in adiponectin. A minimum exercise duration and frequency of 90 min/week of aerobic exercise elicited significant augmentations in adiponectin levels in these studies. The possibility of a dose–response effect was raised by one study (64) in which high-intensity aerobic exercise (80–90% maximum heart rate) was associated with an increase in adiponectin of 0.9 µg/ml; whereas mod-

erate intensity aerobic exercise (following current public health guidelines) elicited an increase of only 0.7 µg/ml. In similar to that, progressive resistance training (35) was found to improve adiponectin levels significantly by 21.7 and 61.4% using moderate and high intensities, respectively. The low-intensity resistance training did not significantly augment adiponectin levels. Neither study provided statistical inter-group comparisons however.

Effect size. Of the 10 controlled trials, only two interventions produced large ESs (35,51) at the 95% confidence level (Tables 7 and 8). Fatouros *et al.* (35) reported a significant increase of 4.32 µg/ml in the post-training adiponectin level of the high-intensity resistance-training group with the largest reported effect size of 1.59 at the 95% confidence level. Two studies generated moderate ESs (29,40) and five produced trivial to small ESs (36,46,54,64,66).

Other outcomes related to adiponectin
Insulin sensitivity and glucose homeostasis. Insulin sensitivity and/or glucose homeostasis was measured by means of an oral glucose tolerance test (19,52,64,65), intravenous glucose tolerance (34,61,62) or insulin tolerance (54,62), or by euglycemic

hyperinsulinemic clamp (19,64,66). Insulin resistance was also calculated from fasting insulin and glucose samples using the homeostasis model assessment by some studies (29,46–48,50–52,55,66) and was calculated by us in 13 others (19, 32,34,36,44,45,54,59,62,65). Most studies (n = 10) demonstrated increased insulin sensitivity in the absence of changes in adiponectin (34,36,52,53,55,61,62,64,66). Four studies did not report insulin sensitivity (43,57,58,63) while others reported insulin or glucose concentration or did not find a relationship (44–46,56,60). Most studies of acute exercise reported no significant relationship between adiponectin level changes and insulin sensitivity (45,56,60) and insulin sensitivity was shown to improve independently of adiponectin (55,61) and vice versa (59).

Weight loss. Weight loss was a stated goal in only 3 of the 21 intervention studies; however, 16 studies targeted overweight, obese, or diabetic cohorts. The interventions used to achieve this goal included diet plus aerobic exercise (34,44), aerobic exercise only (34) or resistance training plus diet (44). Of the 21 interventional studies, 6 trials did not report changes in weight. Three trials reported baseline weight characteristics only (44,62,63) and 15

Table 7 Randomized controlled trials of exercise and adiponectin

Citation	n, gender	Study groups	Cohort	Exercise intervention			Adiponectin measurement			Adiponectin (µg/ml)		Relative effect size (CI) ^a	Analysis adjusted for body or fat mass?
				Modality	Prescription	Duration	site, assay	CV	Pre	Post	P value		
Boudou <i>et al.</i> (2003) (54)	16 m	Exercise (n = 8) Control (n = 8)	T2D	AER	45 min Continuous exercise 2x/week 75% VO _{2peak} + 25 min total (repeated 5 times) Intermittent exercise 1x/week 85% VO _{2peak} (2 min) 50% VO _{2peak} (3 min)	8 weeks	Plasma RIA Intra-assay CV = 3.5–5.0%		6.30 ± 2.75	6.00 ± 3.50	NS	-0.04 (-1.02, 0.95)	No
Marcell <i>et al.</i> (2005) (64)	20 m 31 f	High intensity (n = 20) Mod intensity (n = 17) Control (n = 14)	Sedentary, overweight/ obese	AER	30 min Walking, jogging outdoors, TM 5x/week HI: 80–90% HR _{max} MI: current health promotion recommendations	16 weeks	Plasma RIA Intra-assay CV = < 8% Inter-assay CV = < 8% Sensitivity = 0.1 µg/ml		12.3 ± 4.8	13.2 ± 5.8	P < 0.05	0.47 (-0.22, 1.16) 0.46 (-0.26, 1.18)	No
Balagopal <i>et al.</i> (2005) (29)	11 m 10 f	Ex + obese (n = 8; 4 m, 4 f) Lean (n = 6; 3 m, 3 f) Control + obese (n = 7; 4 m, 3 f)	Healthy or obese adolescents	AER	45 min Physical activity 3 x/week	12 weeks	Plasma RIA Intra-assay CV = < 3% Inter-assay CV = < 10% Sensitivity = 1 ng/ml		4.44 ± 2.2	5.95 ± 2.2	P = 0.0002	0.62 (-0.42, 1.66)	No
Brekke <i>et al.</i> (2005) (62) ^b	49 m 28 f	Diet + exercise (n = 30) Diet (n = 25) Control (n = 22)	First degree relatives of patients with T2D	AER	≥30 min Walking or more intensive activities 4–5 times per week	16 weeks	Plasma ELISA CV not reported		5.70 ± 3.08	6.33 (0.17, 1.09)	-	0.75 (-0.3, 1.79)	No
Fatouros <i>et al.</i> (2005) (35)	50 m	Low intensity (n = 10) Mod intensity (n = 14) High intensity (n = 12)	Sedentary	RT	2 sets/exercise (weeks 1–8), 3 sets/exercise (week 8+) (reps/set not reported) 3 x/week LI: 45–50% 1RM, 2 min rest MI: 60–65% 1RM, 4 min rest HI: 80–85% 1RM, 6 min rest	24 weeks training 24 weeks detraining	Plasma RIA Intra-assay CV = 6.9% Inter-assay CV = 7.8% Sensitivity = 0.5 ng/ml		7.45 ± 2.3	8.48 ± 2.16	NS	0.15 (-0.62, 0.93)	No

Table 7 continued on next page

Table 7 Randomized controlled trials of exercise and adiponectin (continued)

Citation	n, gender	Study groups	Cohort	Exercise intervention		Adiponectin measurement		Adiponectin (µg/ml)		Relative effect size (CI) ^a	Analysis adjusted for body or fat mass?		
				Modality	Prescription	Duration	site, assay CV	Pre	Post			P value	
Giannopoulos <i>et al.</i> (2005) (36)	33 f	Exercise (n = 11) Diet (n = 11) Diet + exercise (n = 11)	T2D/ sedentary	AER	60 min Walking 3–4 x/week 65–70% VO _{2peak} Normal diet Diet: 40% fat, 40% carbs, 20% protein, no exercise	14 weeks	Plasma ELISA Intra-assay CV = 8.5% Inter-assay CV = 6.5% Sensitivity = 0.08 pg/ml	7.22 ± 2.7	7.84 ± 3.5	NS	No significance between groups	0.35 (–4.9, 1.19) 0.58 (–0.28, 1.43)	Yes
Hara <i>et al.</i> (2005) (46)	21 m	AER+RT (n = 7) Control group (n = 7)	Overweight/ obese	AER + RT	30 min TM/cycle ergometer 3 x/week 40.8–54.8% VO _{2max} (VT point) 50–60 min (after AER) 3 sets/10 reps 2–3 x/week 80% 1RM	AER: 8 weeks AER+RT: 20 weeks	Plasma ELISA Intra-assay CV = 3.3% Inter-assay CV = 7.4%	6.2 ± 2.0	6.6 ± 2.5	NS	0.1 (–0.94, 1.15) 0.05 (–1, 1.1)	No	
Trosied <i>et al.</i> (2005) (43) ^c	32 m	Exercise + Pravastatin (n = 9) Exercise only (n = 9) Pravastatin only (n = 8) Control (n = 6)	Metabolic syndrome	AER + RT	45–60 min (total) TM walking/jogging 3 x/week 15–20 reps/cycle AER: 40% session RT: 60% session Pravastatin: 40mg/day	12 weeks	Plasma RIA CV not reported	Exercise (n = 17) 11.7 (10.5, 16.5) Non-exercise (n = 14) 12.3 (–0.9, 1.0) Pravastatin (n = 15) 10.7 (–3.4, 0.9) Non-pravastatin (n = 16) 10.6 (–2.2, 0.1)	Exercise (n = 17) 11.7 (10.5, 16.5) Non-exercise (n = 14) 12.3 (–0.9, 1.0) Pravastatin (n = 15) 10.7 (–3.4, 0.9) Non-pravastatin (n = 16) 10.6 (–2.2, 0.1)	NS NS NS NS	NS NS NS NS	No significance between groups	

Results reported as mean ± SD unless otherwise stated; P values reported for pre vs. post unless otherwise stated. AER, aerobic; CI, confidence interval; CV, coefficient of variation; ELISA, enzyme-linked immunosorbent assay; f, female; HI, high intensity; GT, impaired glucose tolerance; LI, low intensity; m, male; MI, moderate intensity; NGT, normal glucose tolerance; NS, not significant; RIA, radioimmunoassay; RM, repetition maximum; RT, resistance training; T2D, type 2 diabetes; TM, treadmill; VT, ventilatory threshold. ^aEffect size (CI) calculated from pre and post values of intervention vs. control group(49). ^bValues are mean (95% CI) as change scores were reported. ^cValues are median (25.75% interquartile range) as reported by the authors.

studies reported both baseline and post-interventional weight change. **Table 8** compares the changes in body weight with the changes in adiponectin levels for the intervention studies in which both outcomes were presented. Linear

regression analysis showed that there was no significant relationship between changes in body weight and changes in adiponectin in response to exercise training from 15 studies that presented this information ($r = 0.21$, P value = 0.47).

However, of the four studies reporting significant weight loss, 75% also reported significantly favorable changes in adiponectin (19,32,46). Visceral and subcutaneous adipose tissue was assessed using computed tomography in

Table 8 Comparison of changes in weight and adiponectin for intervention studies

Citation	Study groups	Baseline BMI (kg/m ²)	Body weight (kg)		P value	Weight change (kg)	Adiponectin change (µg/ml)
			Pre	Post			
Uncontrolled trials							
Hulver <i>et al.</i> (2002) (34)	Exercise	29.1 ± 3.0	91.9 ± 19	91.6 ± 19.5	NS	-0.3	0.3
	Weight Loss	46.8 ± 4.5	139.2 ± 31	82.6 ± 17	$P < 0.05$	-56.6	9.2
Ryan <i>et al.</i> (2003) (44)	Diet + RT	31.4 ± 3.0	85.9 ± 31.0	-	-	-	-
	Diet + AER	31.1 ± 4.8	85.0 ± 19.0	-	-	-	-
	Diet	33.6 ± 4.6	89.9 ± 24.0	-	-	-	-
	All groups	32.1 ± 4.4	87.1 ± 13.9	81.4 ± 12.6	$P < 0.001$	-5.7	0.2
Yatagai <i>et al.</i> (2003) (61)	Exercise	20.8 ± 2.1	-	-	-	-	0.0
Hsieh and Wang (2005) (63)	Diet + Exercise (older)	31.2 ± 2.4	79.82 ± 6.02	-	-	-	2.3
	Diet + Exercise (younger)	30.6 ± 2.1	79.24 ± 5.05	-	-	-	1.3
Nassis <i>et al.</i> (2005) (52)	Exercise	26.8 ± 3.9	67.9 ± 14.5	68.3 ± 14.0	NS	0.4	-0.5
O'Leary <i>et al.</i> (2005) (65)	Exercise	33.2 ± 5.6	94.1 ± 17.2	90.9 ± 9.7	$P < 0.0001$	-3.2	-0.3
Oberbach <i>et al.</i> (2006) (32)	Exercise (T2D)	31.3 ± 3.1	94.6 ± 19.6	93.0 ± 8.1	$P < 0.05$	-1.6	0.0
	Exercise (IGT)	29.8 ± 3.9	87.6 ± 16.4	84.4 ± 6.1	$P < 0.05$	-3.2	2.1
	Exercise (NGT)	24.2 ± 3.1	69.6 ± 14.0	68.2 ± 7.7	$P < 0.05$	-1.4	-1.7
	Exercise (T2D)	32.5 ± 0.8	94.6 ± 33.8	93.0 ± 30.7	$P < 0.05$	-1.6	1.1
Bluher <i>et al.</i> (2006) (19)	Exercise (IGT)	29.3 ± 0.7	87.6 ± 28.4	84.4 ± 27.7	$P < 0.001$	-3.2	3.3
	Exercise (NGT)	24.2 ± 0.2	69.6 ± 24.6	68.2 ± 23.8	$P < 0.01$	-1.4	3.0
	Selected	-	93.5 ± 7.1	93.5 ± 7.1	NS	0.0	3.0
Jurimae <i>et al.</i> (2006) (57)	Not selected	-	89.6 ± 4.0	90.6 ± 5.4	NS	1.0	7.8
Jurimae <i>et al.</i> (2006) (58)	Exercise	-	91.9 ± 5.3	92.4 ± 5.7	NS	0.5	0.9
Polak <i>et al.</i> (2006) (53)	Exercise	32.2 ± 2.2	88.5 ± 8.2	83.3 ± 7.7	$P < 0.001$	-5.2	-0.9
Non-randomized controlled trials							
Yokoyama <i>et al.</i> (2004) (66)	Diet + exercise	29.0 ± 6.0	-	-	-	-	0.1
	Diet	28.4 ± 5.7	-	-	-	-	-0.1
Kondo <i>et al.</i> (2006) (51)	Exercise	29.5 ± 2.7	72.5 ± 6.9	64.5 ± 4.1	$P < 0.05$	-8.0	1.8
	Control	21.9 ± 3.2	55.0 ± 2.3	53.2 ± 2.5	NS	-1.8	-0.1
Randomized controlled trials							
Boudou <i>et al.</i> (2003) (54)	Exercise	28.3 ± 3.9	86.90 ± 13.4	85.00 ± 13.75	NS	-1.9	-0.3
	Control	30.85 ± 5.2	90.40 ± 11.5	88.75 ± 11.3	NS	-1.7	-0.3
Marcell <i>et al.</i> (2005) (64)	High intensity	32.5 ± 5.3	92.1 ± 135.1	86.5 ± 128.9	-	-5.6	0.9
	Mod intensity	33.9 ± 4.9	97.5 ± 97.1	92.8 ± 91.4	-	-4.7	0.7
	Control	43.7 ± 6.4	102.3 ± 128.5	101.2 ± 122.1	-	-1.1	-1.9
Balagopal <i>et al.</i> (2005) (29)	Exercise	38.1 ± 8.8	105.7 ± 23.8	104.5 ± 24.3	NS	-1.2	1.5
	Lean	21.3 ± 2.9	-	-	-	-	-
	Control	41.2 ± 11.1	115.9 ± 58.7	117.3 ± 59.1	$P < 0.02$	1.4	-0.5
Brekke <i>et al.</i> (2005) (62)	Diet + exercise	26.0 ± 3.4	79.2 ± 10.4	-	-	-	-
	Diet	25.3 ± 3.6	79.2 ± 12.9	-	-	-	-
	Control	26.0 ± 2.7	78.3 ± 11.5	-	-	-	-
Fatouros <i>et al.</i> (2005) (35)	High intensity	29.9 ± 4.2	82.0 ± 10.1	79.7 ± 9.1	NS	-2.3	4.3
	Mod intensity	28.5 ± 2.9	80.1 ± 9.2	78.8 ± 7.1	NS	-1.3	1.7
	Low intensity	30.1 ± 3.5	81.2 ± 12.0	80.2 ± 9.8	NS	-1.0	1.0
	Control	28.7 ± 2.1	80.3 ± 9.8	80.3 ± 7.2	NS	0.0	0.6
Giannopoulou <i>et al.</i> (2005) (36)	Diet + exercise	33.7 ± 1.9	89.5 ± 33.9	84.1 ± 26.4	NS	-5.4	2.4
	Exercise	35.9 ± 1.9	92.9 ± 33.9	91.2 ± 29.3	NS	-1.7	1.8
Hara <i>et al.</i> (2005) (46)	Diet	34.3 ± 1.9	92.4 ± 33.9	87.8 ± 25.9	NS	-4.6	1.2
	AER + RT	29.9 ± 3.8	90.6 ± 12.5	86.6 ± 11.4	$P < 0.05$	-4.0	0.4
	AER	29.9 ± 1.8	91.3 ± 7.8	90.2 ± 7.0	NS	-1.1	0.3
Troseid <i>et al.</i> (2005) (43)	Control	33.5 ± 5.6	98.1 ± 20.2	96.0 ± 19.6	NS	-2.1	0.2
	Exercise + Pravastatin	-	-	-	-	-	-1.2
	Exercise only	-	-	-	-	-	-0.5
	Pravastatin only	-	-	-	-	-	-2.4
Control	-	-	-	-	-	-0.5	

Results reported as mean ± s.d. "-" Denotes value not reported by author.

AER; aerobic training; IGT; impaired glucose tolerance; NGT; normal glucose tolerance; NS; not significant; RT; resistance training; T2D; type 2 diabetes.

only one study (43) and did not significantly change.

DISCUSSION

Adiponectin plays an important role in the control of metabolic dysfunction and restoration to normal levels may potentially contribute to better health outcomes by improving glucose homeostasis, insulin sensitivity, and fatty acid oxidation, with further evidence needed to clarify its true effect in those with comorbid disease. Chronic disease or pathology can significantly decrease circulating adiponectin levels to concentrations of $<4 \mu\text{g/ml}$ (49) which serves as a potential risk factor for cardiovascular and metabolic disease (28). Exercise of moderate-to-high intensity appears to modify adiponectin concentrations positively, as indicated by the moderate to large ESs seen in most of these studies. By contrast, small ESs in the majority of studies utilizing low-intensity exercise suggest a possible dose–response relationship. Current data also suggest improvements in insulin sensitivity may occur acutely and independently of changes in adiponectin concentrations.

Cross-sectional studies

Review of the included cross-sectional studies shows a positive correlation between physical activity and plasma adiponectin (19,48,50). Most studies controlled for changes in body/fat mass. In those studies that did not report a significant association, adiponectin levels were not adjusted for these variables.

Acute exposure exercise studies

Acute exposure to a range of exercise intensities produced no overall effect on adiponectin levels and actually lowered adiponectin concentrations in some studies (56,57,61), suggesting that changes in body composition may be necessary for significant modifications in circulating adiponectin to occur. Studies also failed to adjust adiponectin values for body or fat mass. Additionally, increases in plasma volume may play a role in the acute effects of exercise or adiponectin concentration and may also explain the significantly lower values reported in some studies post-exercise. Future studies need to control

for these factors and also include modes other than aerobic exercise.

Chronic exercise studies

Uncontrolled trials. Changes in adiponectin concentration associated with chronic exercise were absent in the majority of uncontrolled trials. Notably, plasma adiponectin was improved in the three trials of subjects with impaired glucose tolerance or type 2 diabetes, in which adiponectin values were also adjusted for changes in body or fat mass (19,32,63). These studies reporting significant increases highlight the influence of body composition on adiponectin levels and therefore necessitate controlling for these variables if an effect of exercise is to be identified. In addition, insufficient sample sizes and type 2 errors may account for the negative results reported in many trials, with the majority of uncontrolled studies only incorporating small samples.

Non-randomized controlled trials. No significant effect of exercise was indicated from the included non-RCTs. Although a large effect size was reported in the intervention group of one of the trials incorporating moderate intensity exercise (51), these studies did not control for changes in weight and therefore it is inconclusive as to whether exercise can be considered a modifier of adiponectin. Moreover, one trial was only 3 weeks in duration (66), an insufficient time in which to modify body composition.

Randomized controlled trials. The RCTs included in this review are inconclusive regarding the utility of exercise as a potential modifier of adiponectin levels. Important factors that were not controlled for in the majority of studies, including weight/adipose tissue change, diet and the effects of other cytokines, may have contributed to the heterogeneous results. Both aerobic and resistance training improved plasma adiponectin levels in about one-third of trials, including sedentary (35), overweight (64) and obese or type 2 diabetic subjects (36). More studies directly comparing responses in healthy, sedentary, lean, obese, and clinical cohorts need to be conducted

so that it is clear whether subject characteristics define the exercise adaptation or not.

Fatouros *et al.* (35) employed a resistance-training protocol which differed in intensity between groups and produced a robust and positive dose–response relationship, as supported by the increases in effect size as intervention training intensity increased. Small ESs were produced by most aerobic exercise interventions (36,46,54,64) regardless of training intensity, suggesting that perhaps changes in body composition associated with resistance training (decreased fat, increased muscle) may be required for large effects on adiponectin. Regular physical activity in obese adolescents (29) significantly increased plasma adiponectin with a moderate effect size. Exercise intensity and modality and type of cohort varied between the RCTs that reported positive results making it difficult to draw conclusions without additional studies directly comparing these factors in healthy and clinical populations.

Exercise mode. It remains to be established whether the changes in adiponectin induced by exercise are better achieved by aerobic or resistance exercise as no studies have directly compared these two modalities to each other. In addition, the mechanism of the adaptation, and whether it differed according to training modality, is currently unknown.

Exercise intensity. Exercise programs of moderate-to-high intensity exercise may have the greatest impact on adiponectin levels; however, RCTs of higher quality are necessary before a true dose–response relationship can be identified. Moderate-to-large treatment effects were seen in both aerobic (51) and resistance training (35) modalities suggesting that exercise of adequate intensity may be the key to elicit change in adiponectin levels. The large increase in plasma adiponectin levels resulting from the high and moderate intensity resistance-training protocol employed by Fatouros *et al.* (35) suggests a dose–response effect; however, more studies of resistance training reporting consistent findings are needed.

Training frequency. There appeared to be no effect of session frequency on adiponectin response. Trials incorporating lower training frequencies more often reported greater improvements in adiponectin levels than those with higher frequency, which may be a function of higher training intensity in these studies. Explicit comparisons of differing prescriptions of exercise volume, frequency and intensity would be needed to explore these hypotheses.

Future research. Positive results were seen across most age groups with more evidence required for younger and older age groups. Dietary effects were monitored in only a few studies using exercise as the sole intervention, thereby potentially introducing threats to validity among the included studies by confounding the true effects of exercise. The distinction between alterations in visceral and subcutaneous fat vs. changes in body weight, which may also constitute changes in total body water or lean tissue, needs to be identified to clarify the effect of body composition change on adiponectin levels. Measuring changes in regional body fat using image analysis techniques may overcome this limitation of the published literature. Controlling for the effects of plasma volume expansion in plasma measurements following acute and chronic exercise should also be considered to improve the reliability of adiponectin measures.

The strength of the literature to date is modest, and necessitates more standardized and thorough reporting. Methodological limitations of some of the studies included the failure to use blinded outcome assessors, randomization or report compliance. Between-group statistical analysis was similarly not routinely performed. Furthermore, inadequately described training volumes in combination with a number of confounders, such as protocols employing both diet and exercise compromise the validity of these trials. The imprecision of the adiponectin assay may also explain the lack of significant changes seen in post-intervention adiponectin concentrations in some studies. Owing to the heterogeneity of the study populations with regard to age, body composition, insulin sensitivity, and

glucose tolerance, conclusions about the effect of exercise on adiponectin may not be generalizable across cohorts.

Conclusions

The fact that a relationship between exercise and increased adiponectin levels was not observed in the majority of RCTs to date does not indicate that exercise is ineffective in this regard, but highlights the necessity for more robustly designed studies. 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, as a means to augment circulating adiponectin. However, exercise cannot be recommended as a sole intervention at this time without further proof from well-designed trials. Further investigation is needed utilizing long term, well-designed RCTs, which measure and control for dietary intake and visceral adiposity and assess distal health outcomes. Particular attention should be directed toward high-risk cohorts including overweight children and adolescents, and adults with obesity, metabolic syndrome, type 2 diabetes, or cardiovascular disease, in whom augmentation of the anti-inflammatory cytokine adiponectin may assume critical importance for long-term health outcomes.

DISCLOSURE

The authors declared no conflict of interest.

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