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Aerobic exercise reduces insulin resistance markers in obese youth: a meta-analysis of randomized controlled trials

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Abstract

Objective: The purpose of this meta-analysis was to examine the evidence for the effectiveness of aerobic exercise interventions on reducing insulin resistance markers in obese children and/or adolescents. A secondary outcome was change in percentage of body fat.

Methods: A computerized search was made from seven databases: CINAHL, Cochrane Central Register of Controlled Trials, EMBASE, ERIC, MEDLINE, PsycINFO, and Science Citation Index. The analysis was restricted to randomized controlled trials that examined the effect of aerobic exercise on insulin resistance markers in obese youth. Two independent reviewers screened studies and extracted data. Effect sizes (ES) and 95% confidence interval (CI) were calculated, and the heterogeneity of the studies was estimated using Cochran's Q-statistic.

Results: Nine studies were selected for meta-analysis as they fulfilled the inclusion criteria ($n=367$). Aerobic exercise interventions resulted in decreases in fasting glucose ($ES = -0.39$; low heterogeneity) and insulin ($ES = -0.40$; low heterogeneity) and in percentage of body fat ($ES = -0.35$; low heterogeneity). These improvements were specifically accentuated in adolescents (only in fasting insulin), or through programs lasting more than 12 weeks, three sessions per week, and over 60 min of aerobic exercise per session.

Conclusions: This meta-analysis provides insights into the effectiveness of aerobic exercise interventions on insulin resistance markers in the obese youth population.

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Introduction

Atherosclerotic cardiovascular disease is a pathological process that usually begins during childhood (1). Obesity plays a crucial role in the metabolic syndrome, which includes hyperinsulinemia, hypertension, dyslipidemia, and glucose intolerance (1). Hyperinsulinemia and glucose intolerance are precursors of type 2 diabetes (2). During the past two decades, an increasing frequency of type 2 diabetes has been reported (3), which seems to parallel the increase in the prevalence and severity of obesity in

children and adolescents (4), with the lack of physical activity identified as the main driver of the childhood obesity epidemic in industrialized countries (5). Likewise, previous controlled clinical trials have reported the effectiveness of exercise on improving levels of cardiometabolic risk factors (CRF), including insulin resistance (6, 7) but not glucose tolerance (6). In addition, two recent qualitative reviews have highlighted the influence of exercise on improving both adiposity and cardiometabolic

risk (8, 9), but both of them concluded that the role of physical activity alone in reducing the risk of type 2 diabetes and insulin resistance remained unclear. However, a recent meta-analysis has found a small-to-moderate improvement in fasting insulin levels and insulin resistance in children and adolescents with exercise training (10).

This meta-analytic approach has not been previously used to examine the effects of aerobic exercise on fasting glucose and insulin levels, specifically in obese children and adolescents. The purpose of this meta-analysis of randomized trials was to determine the effectiveness of aerobic exercise interventions on reducing insulin resistance markers in obese children and/or adolescents.

Methods

The review was performed according to the PRISMA statement for quality of reporting a meta-analysis (11).

Literature search

The electronic bibliographical databases screened included: CINAHL (1937–2nd September 2013), Cochrane Central Register of Controlled Trials (CENTRAL; 2002–2nd September 2013), EMBASE (1980–2nd September 2013), ERIC (1966–2nd September 2013), MEDLINE (1965–2nd September 2013), PsycINFO (1987–2nd September 2013), and Science Citation Index (1900–2nd September 2013). The search was conducted from 20th August to 2nd September 2013. First, four keyword categorical searches were conducted: i) ‘aerobic exercise’ NOT ‘physical activity’; ii) ‘child’ AND ‘adolescent’; iii) ‘obesity’ NOT ‘overweight’; and iv) ‘insulin’ OR ‘glucose’. All languages were accepted. In addition, the reference lists and related links of retrieved articles were examined to detect studies potentially eligible for inclusion.

Study selection

Studies were included in the meta-analysis if they met the following criteria: i) the subjects were children or adolescents (6–18 years old) diagnosed with obesity; ii) the type of study was randomized controlled trial (RCT), in which the control group received no physical exercise or dietary restriction intervention; iii) the type of intervention was aerobic exercise (excluding studies in which exercise was part of a multicomponent therapy involving a combination of aerobic exercise plus educational and/or nutritional therapy); and iv) evaluation of insulin

resistance markers, including fasting glucose and insulin levels. The four criteria for inclusion were restrictive in order to achieve a homogeneous sample of studies.

Assessment of risk of bias

Risk of bias was evaluated according to the PRISMA recommendation (11). For the quality assessment of RCTs, we used the Delphi list as described by Verhagen *et al.* (12), which includes eight questions with three response options ‘yes’, ‘no’, or ‘do not know’ depending on the compliance with key methodological components, and produces a quality score that provides an overall estimate of RCTs’ quality. Quality assessment was independently performed by two unblinded reviewers (A García-Hermoso and J M Saavedra) and disagreements were solved by consensus or by a third reviewer (Y Escalante).

Data abstraction

Two authors (A García-Hermoso and J M Saavedra) independently screened the titles and abstracts of potentially eligible studies identified by the search strategy. Later, the authors extracted the following data from each candidate’s selectable article: i) characteristics of subjects (number, age, sex, ethnicity, and obesity definition); ii) characteristics of exercise program (type, duration, frequency, and intensity); iii) assessment of primary outcome (fasting glucose and insulin) and secondary outcome (percentage of body fat (%BF)); and iv) results (before and after intervention). Discrepancies between the two reviewers about study conditions were resolved by consensus with the third author (Y Escalante).

Statistical analysis

The primary outcome in this meta-analysis was changes in fasting glucose (mg/dl) and insulin (μ U/ml) levels. Secondary outcome was changes in %BF. Effect sizes (ES) and 95% CI were calculated for each study by means of *t*-scores, number of subjects, and s.d. (13). When the s.d. was unavailable, it was calculated from the s.e.m. ($s.d. = s.e.m. \cdot \sqrt{n}$). Cohen’s categories were used to evaluate the magnitude of the ES (small if $0 \leq |d| \leq 0.5$; medium if $0.5 < |d| \leq 0.8$; and large if $|d| > 0.8$) (14). The heterogeneity of the studies was assessed using Cochran’s *Q*-statistic applied to the ES means (15). The percentage of total variation across the studies due to heterogeneity was determined using I^2 . Usually, I^2 values of <25, 25–50, and >50% are considered to represent small, medium, and

large amounts of heterogeneity (16). In order to analyze the influence of each study on the overall results, each study was deleted from the model once and the pooled analyses were conducted without this study in the model. The funnel plot and the Egger test were used to examine publication bias (17). A level of <0.05 was used to determine if statistically significant publication bias might be present.

Finally, the following subgroup analyses were pre-specified: ages (children or adolescents); duration of the study (≤ 12 or >12 weeks); frequency of exercise per week (≤ 3 or >3 times/week); and duration of session (<60 or ≥ 60 min/session). A similar grouping approach has been previously used in studies of obese children (18, 19, 20).

Results

Study selection

The literature search identified 2242 references (Fig. 1), and 36 full articles were retrieved. Of these, 27 were rejected: five for failing the subjects' profile criterion (overweight or obese children); 18 because of the type of intervention criterion (diet or/and drugs); and five did not determine insulin or glucose levels. Finally, nine articles met all inclusion criteria and were used for the meta-analysis.

Figure 1

Flowchart for identification of trials for inclusion in the meta-analysis.

Study characteristics and interventions (methodological quality)

Table 1 summarizes the study characteristics (21, 22, 23, 24, 25, 26, 27, 28, 29) ($n=191$ and $n=176$, in intervention and control groups respectively). Three studies were conducted in the USA (22, 23, 28), one in Germany (21), three in Korea (25, 27), one in Tunisia (26), and one in Turkey (24).

Subjects

The analysis included a total of 367 youths. Three studies included only boys (24, 27, 28) and two only girls (25, 29); the remaining studies included both boys and girls (21, 22, 23, 26). Participants were children (6–12 years old) in three studies (23, 24, 25), adolescents (12–18 years old) in another three studies (27, 28, 29), and participants of both age groups in the remaining studies (21, 22, 26). Several criteria were used to define obesity: four interventions used nation-specific criteria for the child population of Germany (21), Korea (25, 29), and USA (Centers for Disease Control Growth Charts) (28). One study used triceps skin-fold above the 85th percentile (23), and another used a criterion from a consensus in pediatrics (30) of BMI >30 kg/m² (24). Finally, one study (26) used the international criteria of the International Obesity Task Force (31). The remaining studies did not provide any reference for the criterion they used for the classification (22, 27) (Table 1).

Aerobic exercise program characteristics

The main content of the programs was based on treadmills, cycle ergometers, rowers (machines) (23, 28), sports games, such as soccer and basketball (21, 22, 26), running (21, 26), walking (22, 24, 25), cycling, snowshoeing (22), and skipping rope (27, 29). Finally, only four studies reported compliance (23, 25, 26, 28), and all of them showed above 80%.

Glucose and insulin assessments

When the information was provided, the lipid and lipoprotein evaluations were made in the morning after at least 8 h (28), 10 h (21), 11 h (29), and 12 h (23, 24, 25, 26, 27) overnight fasting. However, one study did not provide this information (22). Several techniques were employed to determine fasting glucose and insulin. Fasting glucose concentration was determined by

Table 1 Characteristics of the studies included in the meta-analysis.

References	EG			CG			Intervention characteristics					Delphi score	
	n	Age (years) ^a	Type	n	Age (years) ^a	Type	BMI (kg/m ²)	Duration (weeks)	Frequency (Se/W)	Se duration (min)	Intensity		Compliance (%)
Ben Ounis et al. (26)	16	13.4 (0.4)	Multi-sports walking + machines + multi-sports	16	13.2 (0.6)	None	≥ 97p	8	4	90	66% ^b	100	5
	27	12.5 (0.5)		23	12.5 (0.7)	None	≥ 95p	36	5	45	NR	NR	5
Ferguson et al. (23)	40	9.5 (1.0) ^c	Machines + multi-sports	37	9.5 (1.0) ^c	None	≥ 85p ^d	16	5	40	> 150 ^e	80	5
Karacabey (24)	20	11.8 (0.5)	Walking	20	11.2 (0.8)	None	> 30	12	3	30–65	60–65% ^f	NR	4
Kim et al. (27)	14	17.0 (0.11) ^c	Jump rope	12	17.0 (0.1) ^c	None	NR	6	5	40	NR	NR	4
Kim & Yang (25)	14	14.0 (0.5)	Walking	14	13.8 (0.3)	None	≥ 95p	12	6	30–60	55–75%	96.2	4
Lee et al. (28)	11	16.9 (0.9) ^c	Jump rope	7	16.9 (0.9) ^c	None	> 25	12	4	30–40	60–80% ^f	NR	4
Lee et al. (29)	16	15.2 (1.9)	Machines	13	14.8 (1.4)	None	≥ 95p	12	3	60	50–75% ^b	99	6
Meyer et al. (21)	33	13.7 (2.1)	Multi-sports	34	14.7 (2.2)	None	≥ 97p	24	3	60–90	NR	NR	4

EG, experimental group; CG, control group; Se, session; none, no intervention; p, percentile; NR, not reported; W, week; Delphi score = 9-item scale.

^aData were presented as the mean value (s.d.).^bMaximal oxygen consumption.^cAge of the experimental and the control groups together.^dPercentile of skin-fold thickness.^eBeats/min.^fMaximal heart rate.**Table 2** Pre- and post-test (mean and s.d.) values and effect sizes for fasting glucose and insulin. Data were presented as the mean value (s.d.). To convert glucose from millimoles per liter to milligrams per deciliter, divide by 0.0555.

References	Glucose (mg/dl)				Insulin (μU/ml)			
	Pre-test		Post-test		Pre-test		Post-test	
	EG	CG	EG	CG	EG	CG	EG	ES
Benounis <i>et al.</i> (26)	91.7 (11.60)	86.5 (9.50)	81.1 (1.70)	85.8 (8.60)	–	–	–	–
Carrel <i>et al.</i> (22)	83.0 (4.00)	86.0 (7.00)	87.0 (5.00)	93.0 (7.00)	25.7 (15.70)	22.9 (13.20)	21.9 (14.00)	–0.32
Ferguson <i>et al.</i> (23)	87.9 (6.48)	87.4 (6.48)	81.1 (6.48)	82.0 (6.48)	22.4 (6.82)	24.5 (6.82)	20.2 (6.82)	–0.13
Karacabey (24)	–	–	–	–	37.1 (4.30)	39.6 (5.20)	31.5 (6.10)	–0.31
Kim <i>et al.</i> (27)	82.3 (7.11)	86.8 (4.16)	85.0 (5.99)	85.1 (6.58)	13.0 (5.98)	13.6 (3.12)	8.9 (4.98)	–0.40
Kim & Yang (25)	97.1 (10.70)	98.6 (5.67)	85.1 (6.50)	89.1 (7.45)	–	–	–	–
Lee <i>et al.</i> (28)	79.5 (7.47)	71.3 (9.50)	84.4 (3.88)	84.6 (4.12)	19.4 (6.23)	13.1 (6.24)	12.7 (3.42)	–1.17
Lee <i>et al.</i> (29)	95.9 (4.20)	96.9 (5.00)	95.5 (4.41)	96.7 (5.33)	38.3 (21.20)	32.9 (13.60)	21.1 (26.50)	–0.68
Meyer <i>et al.</i> (21)	–	–	–	–	13.8 (5.20)	15.9 (6.47)	11.2 (4.61)	–0.54

EG, experimental group; CG, control group; ES, effect sizes.

enzymatic methods (22, 24, 26, 27) or using a glucose oxidase technique by using a radioimmunoassay (RIA) kit (25, 28, 29). Fasting insulin levels were determined using a chemiluminescent assay (22, 27), RIA (23, 26, 28, 29), or by an Immulite analyzer (24). One study did not provide the method for determining fasting glucose and insulin (21).

Primary outcomes (change in glucose and insulin levels)

Table 2 lists the values of each variable in all the studies pre- and post-intervention. Figure 2 summarizes these results. The ES and the 95% CI were estimated for each study. Decreases were observed in fasting glucose (ES = -0.39 ; 95% CI, -0.68 to -0.14 ; $P=0.002$; Fig. 2b) and insulin levels (ES = -0.40 ; 95% CI, -0.63 to -0.17 ; $P<0.001$) with medium ($I^2=19\%$) and low heterogeneity ($I^2=0\%$) respectively (16).

Subgroup analyses

Table 3 lists the subgroup analyses of post-treatment results. Regarding changes in fasting glucose, the analyses highlighted bigger increases in programs >12 weeks'

duration (ES = -0.42 ; $P=0.022$). Bigger decreases in fasting insulin were observed in adolescents (ES = -0.68 ; $P=0.005$), in programs >12 weeks, duration (ES = -0.54 ; $P=0.005$), >3 weekly sessions (ES = -0.50 ; $P=0.005$), and ≥ 60 min/session (ES = -0.58 ; $P=0.005$).

Secondary outcomes

The results showed a statistically significant reduction for %BF (ES = -0.35 ; 95% CI, -0.57 to -0.13 ; $P=0.002$; $n=8$ studies) and small heterogeneity ($I^2=0\%$) (21, 22, 23, 25, 26, 27, 28, 29).

Risk of bias, publication bias, and sensitivity analysis

Finally, all the included RCTs satisfied at least 50% of the quality criteria (four or more quality criteria; Table 1). For its parts, there was no significant publication bias, as evidenced by the funnel plot asymmetry or Egger test ($P=0.227$ and $P=0.562$ in fasting glucose and insulin parameters respectively). In addition, the results of the sensitivity analysis, with each study deleted from the model once, remained statistically significant across all deletions (Table 4).

Figure 2

Effects of the aerobic exercise programs on (a) fasting glucose and (b) insulin.

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Table 3 Subgroup analysis of the post-treatment results.

	Glucose					Insulin				
	Study (n)	Patient (n)	ES	P	I ²	Study (n)	Patient (n)	ES	P	I ²
Ages										
Children (6–12)	2	105	−0.25	0.201	0	2	117	−0.19	0.297	0
Adolescent (13–18)	3	73	−0.12	0.621	0	3	73	−0.68	0.005	0
Duration of study (weeks)										
≤ 12	5	133	−0.36	0.041	0	3	188	−0.32	0.030	0
> 12	2	121	−0.42	0.022	0	4	113	−0.54	0.005	0
Session frequency (times/week)										
≤ 3	–	–	–	–	–	4	165	−0.32	0.044	9
> 3	6	225	−0.41	0.002	31	3	136	−0.50	0.004	0
Duration of session (min)										
< 60	5	193	−0.35	0.016	36	5	205	−0.32	0.024	0
≥ 60	–	–	–	–	–	2	96	−0.58	0.005	0

ES, effect size; I², heterogeneity.

Discussion

As far as we know, the present study is the first meta-analysis to analyze the evidence for the effectiveness of aerobic exercise alone on the insulin resistance markers in children and adolescents with obesity. Interventions focusing only on aerobic exercise generated a small reduction in fasting glucose and insulin levels in obese youths. These findings remained true when each study was deleted from the model once (Table 4). The cumulative evidence from this meta-analysis supports recommendations on international exercise (32, 33) and highlights the notion that greater participation in aerobic exercise programs can result in greater reductions in CRF.

The results of several studies reporting the impact of aerobic exercise on insulin resistance in obese youths are controversial or inconsistent (8, 9, 34, 35). However, some controlled clinical trials (6, 7) or a meta-analysis in an other less-specific population (10) have reported a

decrease in both fasting glucose and/or insulin levels. Similar improvements in insulin resistance markers were found in the current meta-analysis (ES = −0.39 and −0.40 in fasting glucose and insulin respectively). Furthermore, these improvements were accompanied by a decrease in %BF in the participants (ES = −0.35; *P* = 0.002). Specifically, the study of Lee *et al.* (29) reported the greatest reduction in %BF (ES = −1.23) and showed a pronounced change in insulin levels (ES = −1.17) (Fig. 2). In accordance with these findings, another study has revealed that improvements in insulin resistance can be expected with reductions in BMI-S.D. score (≥0.5) (36). However, visceral fat seems to be a better predictor of insulin resistance independent of total body fat (7, 37). Unfortunately, abdominal fat values were not reported by all studies, which was why we could not investigate this in the current study. One possible reason for these inconsistencies might be participants' differences in pubertal

Table 4 Changes in fasting glucose and insulin with each study deleted once.

Study omitted	Glucose		Insulin	
	ES (95% CI)	P	ES (95% CI)	P
Ben Ounis <i>et al.</i> (26)	−0.34 (−0.61 to −0.07)	0.013	–	–
Carrel <i>et al.</i> (22)	−0.28 (−0.55 to −0.00)	0.046	−0.41 (−0.66 to −0.17)	0.001
Ferguson <i>et al.</i> (23)	−0.51 (−0.81 to −0.20)	0.001	−0.50 (−0.76 to −0.23)	<0.001
Karacabey (24)	–	–	−0.41 (−0.66 to −0.17)	0.001
Kim <i>et al.</i> (27)	−0.44 (−0.70 to −0.17)	0.001	−0.40 (−0.64 to −0.16)	0.001
Kim & Yang (25)	−0.37 (−0.64 to −0.10)	0.006	–	–
Lee <i>et al.</i> (28)	−0.42 (−0.68 to −0.16)	0.002	−0.36 (−0.60 to −0.12)	0.003
Lee <i>et al.</i> (29)	−0.41 (−0.68 to −0.14)	0.003	−0.37 (−0.61 to −0.13)	0.002
Meyer <i>et al.</i> (21)	–	–	−0.36 (−0.62 to −0.10)	0.006

ES, effect sizes.

stage (38). In this sense, a study has speculated that defective differentiation of subcutaneous fat and/or increased inflammation in visceral fat may be a better predictor of insulin resistance (39).

Regarding the subgroup analysis, improvements in insulin resistance markers were accentuated in studies that included only adolescents ($ES = -0.68$). In this sense, a longitudinal study revealed that during puberty, a decrease in insulin resistance occurred (7). However, the glucose disposition index was maintained via a compensatory increase in insulin secretion (7). Therefore, the present meta-analysis supports these results. Similarly, the duration of the program seems to be crucial in this regard. Those studies of more than 12 weeks of intervention and 3 weekly sessions favored an improvement in the two insulin resistance markers. Several meta-analyses in this population showed similar results for other CRFs, such as lipid levels (triglyceride and LDL cholesterol) (19) and blood pressure (20). As a consequence, the importance of good planning and optimization of aerobic exercise on CRF benefits (reductions in hypertension, triglyceride concentrations, LDL cholesterol concentrations, and insulin resistance markers) has been highlighted (37).

Limitations

The present meta-analysis has some limitations. First, the methods used to determine fasting insulin were different, and probably the CVs would be high. Second, many of the studies did not assess abdominal fat (%), a strong independent factor related to insulin and glucose levels (insulin resistance) (38). Third, the ethnicity of the subjects could affect changes in insulin resistance markers (40). Fifth, due to the short duration of the interventions, we cannot predict the long-term impact on the insulin resistance markers. Sixth, the heterogeneity in the development of maturational in children/adolescents in each study could influence the changes in insulin resistance (41). Finally, only four studies reported compliance, a substantial concern in the treatment of pediatric obesity (42).

Conclusions

In conclusion, the findings of this study suggest that aerobic exercise reduces insulin resistance in obese children and adolescents, although the magnitude of the impact on these parameters could be considered small. These improvements were accentuated in adolescents (only in fasting insulin) throughout programs more than

12 weeks' duration, three sessions per week, and 60 min of aerobic exercise per session (only in fasting insulin). Our results might have important health implications and provide support to effective strategies prescribed by health care professionals for the treatment of obesity and the reduction of metabolic risk in obese youths. Additional research on this topic is needed, including interventions with long-term follow-up in this population and other metabolic parameters commonly used in clinical practice. In addition, these interventions should identify socio-economical and built environmental barriers that need to be addressed in order to increase the potential benefits of the interventions, increasing the compliance of participants and also avoiding the feelings of failure for both the children and health care providers, thereby increasing the costs.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the review.

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Author contribution statement

A García-Hermoso conceptualized and designed the study, carried out the initial analyses, drafted the initial manuscript, and approved the final manuscript as submitted. J M Saavedra and Y Escalante supervised data collection, critically reviewed the manuscript and approved the final manuscript as submitted. M Sánchez-López drafted the initial manuscript, reviewed and revised the manuscript, and approved the final manuscript as submitted. V Martínez-Vizcainoa critically reviewed the manuscript and approved the final manuscript as submitted.

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