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Hypoadiponectinemia, Type 2 Diabetes, Ethnicity, and Exercise Training: A Meta-Analysis of Iranian Randomized Controlled Clinical Trials

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ABSTRACT

Background and objectives: Considering racial/ethnic differences is necessary when recommending lifestyle modifications for patients with diabetes. Racial/ethnic diversity may affect hypoadiponectinemia responses to exercise training among individuals with type 2 diabetes. This systematic review and meta-analysis is the first to investigate effects of exercise training on circulating adiponectin concentrations in Iranians with type 2 diabetes.

Methods: Literature searches of the Cochrane Central Register of Controlled Trials were carried out using the following search strategy: [exercise OR training OR physical activity OR Training] AND diabetes AND adiponectin. Next, RCTs were included and compared with each type of supervised exercise (aerobic training, resistance training, or combined training). Pooled intervention effects were evaluated and reported as standardized mean difference (MD) and 95% confidence intervals using a random effects model. Subgroup and sensitivity analysis was performed for study heterogeneity and following primary screening full text of the articles was evaluated.

Results: Fourteen studies with 444 individuals (236 men and 128 women) were included in the analysis. The age of the participants ranged between 18 and 60 years. The number of exercise sessions per week ranged between 3 and 5. The duration of interventions ranged between 6 and 12 weeks. The meta-analysis showed that adiponectin levels increased significantly in diabetic subjects after physical activity (MD: 0.72 ng/dl, $p<0.001$,), but the heterogeneity of the study remained significant ($I^2= 89\%$).

Conclusion: Overall, physical exercise, particularly aerobic exercise, increases adiponectin levels in Iranians with diabetes. However, this effect of exercise may be influenced by race/ethnic differences, type of training, frequency, type of adiponectin measurement, and complex and heterogeneous exercise responses of individual with diabetes.

Keywords: Exercise, Diabetes Mellitus, Hypoadiponectinemia.

INTRODUCTION

Diabetes is associated with abdominal fat accumulation (visceral/hepatic) (1). This, along with secretion of inflammatory adipokines such as leptin, adiponectin, interleukin-6, tumor necrosis factor-α (TNF-α), and resistin are important risk factors for insulin resistance (2). It has been shown that there are significant race-ethnic related differences in the secretory profile of adipocytes and circulating adipokines (3). Adiponectin, the most abundant anti-inflammatory adipocytokine (accounting for 0.01% of total serum protein), is secreted by adipocytes. It is involved in energy hemostasis (4), inflammation, vascular physiology (5), insulin sensitivity, and glucose and lipid metabolism (6). It also has cardioprotective and anti-atherogenic properties (7). In fact, it has been shown that hypoadiponectinemia is associated with severity of atherosclerosis and coronary artery disease in people with type 2 diabetes (8). Evidence indicates racial/ethnic differences in hypoadiponectinemia in different metabolic syndromes (9-11).

As exercise training intervention reduces the risk of developing type 2 diabetes complications (12); therefore, it may be interesting to evaluate effects of exercise on hypoadiponectinemia. Physical activity and exercise training also act as potent facilitators for the maintenance of health outcomes in patients with diabetes (13). Considering the racial-ethnic differences is crucial when recommending lifestyle modifications for patients with diabetes (14). Studies have also reported racial/ethnic differences in cardiac responses to submaximal exercise (15, 16), physical activity, dietary behaviors (17), and leisure-time physical activity levels among individuals with diabetes (18). The magnitude of responses of adiponectin to exercise training may also be influenced by race-ethnic characteristics and adiponectin gene polymorphism (19). For example, individuals with the genotype GT + TT at SNP276 (G/T) have a greater adiponectin response to exercise training compared to those with the GG genotype (20). However, some studies demonstrated that polymorphisms of the adiponectin gene are not associated with the effect of exercise training on adiponectin levels (19, 21). Recently, Sellami et al. illustrated the role of racial differences in anaerobic capacity, hematological parameters, and lactate levels during recovery in women (22). On the one hand, such racial/ethnic differences may affect adiponectin level changes in response to exercise training in metabolic syndrome. For example, Arslanian and colleagues showed that race/ethnicity alone has a significant effect, beyond the intervention effect, on adiponectin levels, insulin sensitivity, and β-cell function (9). In addition, there is no difference in the recommended guidelines for exercise training modalities across different racial groups. It has been shown that African-American individuals are generally more likely to follow exercise training recommendations. Hispanic men also have higher physical activity levels than other racial groups. Furthermore, racial/ethnic heterogeneity was found in responses to weight loss interventions. Caucasian and Hispanic individuals show more interest to lose weight (23).

Based on a review of existing literature, we hypothesized that there would be significant racial/ethnic differences in response of hypoadiponectinemia to different types of exercise training in Iranians with diabetes. We further hypothesized that racial differences have been overlooked in some systematic reviews and meta-analysis of randomized controlled trials (RCTs) that evaluated effectiveness of different exercise trainings on diabetes risk factors such as adipokines, especially adiponectin. Finally, we hypothesized that racial/ethnic characteristics should be considered when designing exercise training interventions for diabetic patients. The results related to other races may not be generalized to the Iranian population of diabetics. For example, a systematic review and meta-analysis of RCTs showed that aerobic exercise increased adiponectin levels in non-Iranian people with prediabetes and diabetes (24). Another meta-analysis of RCTs showed that aerobic training did not change adiponectin levels in non-Iranian patients with type 2 diabetes (25). The aim of this study was to conduct a systematic review and meta-analysis on RCTs to evaluate effects of different exercise trainings on hypoadiponectinemia in patients with diabetes, to help better application and generalization of data in Iranian diabetics.

MATERIALS AND METHODS

Literature searches of the Cochrane Central Register of Controlled Trials were carried out using the following search strategy: [exercise OR training OR physical activity OR Training] AND diabetes AND adiponectin. Next, RCTs were included and compared with each type of supervised exercise (aerobic training, resistance training, or combined training).
Inclusion criteria were studies involving 4 weeks of exercise intervention on diabetics and clinical trials on a human population. Exclusion criteria were as follows: having type 2 diabetes, RCTs that did not report enough data to complete meta-analysis, double-release or subgroup analysis of trials, and trials with less than 6 weeks of follow-up.
Two examiners extracted all data separately. For the variables of interest, we extracted baseline and post-intervention mean and standard deviation and sample sizes, for intervention and control groups (26). Two authors separately evaluated the methodological quality of the trials, and the Cochrane risk-of-bias tool was used to evaluate the risk of bias in each study.

Data analysis was carried out using random effect models (27), and the results were expressed as the weighted mean difference (WMD). The effect size was estimated based on the parameters that existed between the control group and the training group. Heterogeneity was evaluated by using the I^2 index (28).
The funnel plot and the *Egger's test* were used to assess publication bias (29). The trim and fill methods were used to estimate the potential impact of unpublished studies on our results (21). All analyses were conducted using the Stata statistical software (version 12.0, Stata, College Station, USA).

RESULTS

Fourteen studies with 444 individuals (236 men and 128 women) were included in the analysis. Figure 1 provides an overview of the search strategy. The age of the participants ranged between 18 and 60 years. The number of exercise sessions per week ranged between 3 and 5. The duration of interventions ranged between 6 and 12 weeks (Table 1).

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

Author(s), year of publication, reference number	Age (years, +C22:J38Mean ± SD)	Medical condition	Training sessions per week	Duration of intervention (weeks)
Ilkhani et al. [2017](30)	I: 63.12 ± 1.98, C: 63.12 ± 1.98	T2D	5	8
Mohamadzadeh salamat [2018] (31)	I: 21.9 ± 1.7, C: 21.8 ± 2	T2D	3	8
Abolfathi et al. [2015](32)	I: 47.85 ± 4.52, C: 45.25 ± 6.86	T2D	3	8
Hosseini et al [2018] (33)	I: 28.92 ± 3.6, C: 29.18 ± 4.33	T2D	3	6
Hosseini et al. [2018](33)	I: 30.27 ± 4.149, C: 29.18 ± 4.33	T2D	3	6
Begzade et al. [2019] (34)	I: 46.22 ± 7.28, C: 47.38 ± 7.08	T2D	3	8
Abedi (2016) (35)	I: ±, C: ±	T2D	3	8
Parsian et al. (2013) (36)	I: 45 ± 7, C: 43 ± 8	T2D	3	12
Moradi et al. [2013](37)	I: 20.9 ± 3.6, C: 21.5 ± 3.2	T2D	3	12
Atashak et al. [2011] (38)	I: 23.71 ± 3.81, C: 24.38 ± 2.33	T2D	3	10
Rashidlamir and Saadatnia [2010] (39)	I: 40.06 ± 4.04, C: 37.06 ± 5.1	T2D	4	8
Ghasemnian et al. [2013](40)	I: ±, C: ±	T2D	4	8
Rashidlamir et al. [2013] (41)	I: 22.54 ± 2.54, C: 22.3 ± 1.56	T2D	4	8
Shavandi et al. [2011](42)	I: 58.8 ± 6.65, C: 53.5 ± 4.5	T2D	3	8
Zarei et al. [2015](43)	I: 47.9 ± 3, C: 46.9 ± 1.2	T2D	3	12
Zarei et al. [2015] (43)	I: 45.8 ± 6.3, C: 46.9 ± 1.2	T2D	3	12
Zarei et al. [2017](43)	I: 47.5 ± 0.9, C: 46.9 ± 1.2	T2D	3	12

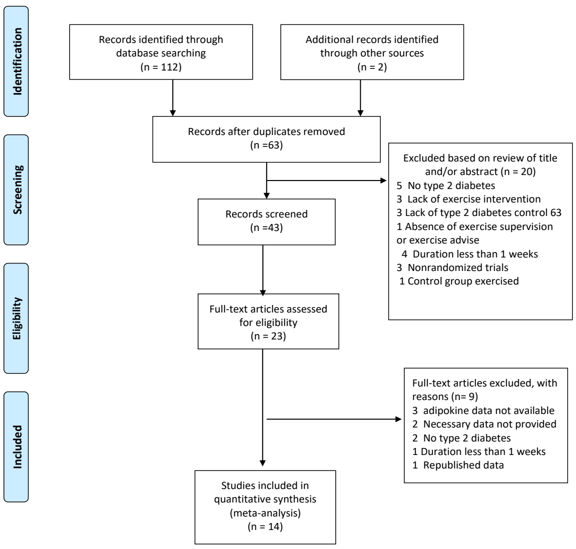

Figure 1. The overview of the search strategy

Effects of training on adiponectin

The meta-analysis showed that adiponectin levels increased significantly in diabetic subjects after physical activity (MD: 0.72 ng/dl, p<0.001,), but the heterogeneity of the study remained significant (I^2= 89%) . As shown in figure 2, different aerobic training modalities significantly increased adiponectin levels (MD: 0.84 ng/dl, p<0.001,), but neither interval training nor concurrent-resistance training significantly altered adiponectin levels (MD: 0.36 ng/dl; p=0.48).

Study name	Comparison	Statistics for each study						
		Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Begh zade et al[1397]	Aerobic Training	1.530	0.196	0.039	1.145	1.915	7.790	0.000
Ghasem nian et al[1392]	Aerobic Training	0.250	0.989	0.979	-1.689	2.189	0.253	0.801
Hosseini et al[1397]	Aerobic Training	0.185	0.114	0.013	-0.037	0.408	1.631	0.103
Parsiyan et al (1392)	Aerobic Training	1.890	0.577	0.333	0.759	3.021	3.276	0.001
Rashidl amir et al[1389]	Aerobic Training	1.360	0.583	0.340	0.218	2.502	2.334	0.020
Rashidl amir et al[1392]	Aerobic Training	1.050	0.613	0.375	-0.151	2.251	1.714	0.087
Shavandi et al[1390]	Aerobic Training	0.190	0.052	0.003	0.089	0.291	3.674	0.000
Zarei et al[1396]	Concurrent Training	0.400	0.952	0.907	-1.467	2.267	0.420	0.675
Zarei et al [1396]	Concurrent Training	0.600	0.860	0.740	-1.086	2.286	0.698	0.485
Zarei et al [1396]	Concurrent Training	0.100	0.837	0.701	-1.541	1.741	0.119	0.905
Abedi et al (1395)	Interval Training	7.920	2.304	5.307	3.405	12.435	3.438	0.001
Abolfathi et al [1394]	Interval Training	0.100	0.057	0.003	-0.012	0.212	1.746	0.081
Ilkhani et al[1396]	Interval Training	0.140	0.053	0.003	0.036	0.244	2.646	0.008
Mohammad zade [1397]	Interval Training	3.500	0.536	0.287	2.450	4.550	6.531	0.000
Atashak et al[1390]	Resistant training	1.660	0.243	0.059	1.184	2.136	6.836	0.000
Hosseini et al [1397]	Resistant training	0.157	0.093	0.009	-0.025	0.339	1.692	0.091
Moradi et al[1392]	Resistant training	0.100	1.061	1.126	-1.980	2.180	0.094	0.925
		0.715	0.129	0.017	0.463	0.968	5.551	0.000

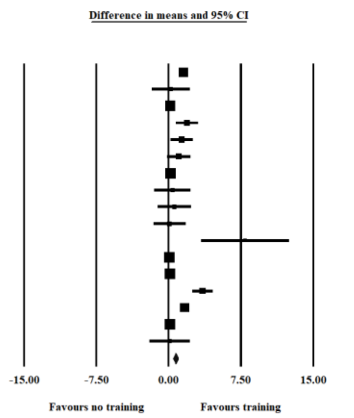

Figure 2- Effects of physical activity on adiponectin levels (ng/dl). The forest plot shows pooled mean differences with 95% confidence intervals (CI) for 14 effect sizes pooled from 17 trials. The effect sizes were merged due to the different training methods used in studies by Zarei (43) and Hosseini (33).

Subgroup analysis

Subgroup analysis was performed for a training method (Figure 3). Based on the results, heterogeneity remained high and adiponectin levels significantly increased across all subgroups.

Sensitivity analysis

No significant change in the effect size was found, which indicates robustness of the data in the initial analysis (Figure 4).

Group by Comparison	Study name	Comparison	Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
	Begh zade et al[1397]	Aerobic Training	1.530	0.196	0.039	1.145	1.915	7.790	0.000
	Ghasem nian et al[1392]	Aerobic Training	0.250	0.989	0.979	-1.689	2.189	0.253	0.801
	Hosseini et al[1397]	Aerobic Training	0.185	0.114	0.013	-0.037	0.408	1.631	0.103
	Parsiyan et al (1392)	Aerobic Training	1.890	0.577	0.333	0.759	3.021	3.276	0.001
	Rashidl amir et al[1389]	Aerobic Training	1.360	0.583	0.340	0.218	2.502	2.334	0.020
	Rashidl amir et al[1392]	Aerobic Training	1.050	0.613	0.375	-0.151	2.251	1.714	0.087
	Shavandi et al[1390]	Aerobic Training	0.190	0.052	0.003	0.089	0.291	3.674	0.000
Aerobic Training			0.840	0.251	0.063	0.349	1.332	3.352	0.001
	Zarei et al[1396]	Concurrent Training	0.400	0.952	0.907	-1.467	2.267	0.420	0.675
	Zarei et al [1396]	Concurrent Training	0.600	0.860	0.740	-1.086	2.286	0.698	0.485
	Zarei et al [1396]	Concurrent Training	0.100	0.837	0.701	-1.541	1.741	0.119	0.905
Concurrent Training			0.359	0.508	0.258	-0.636	1.354	0.708	0.479
	Abedi et al (1395)	Interval Training	7.920	2.304	5.307	3.405	12.435	3.438	0.001
	Abolfathi et al [1394]	Interval Training	0.100	0.057	0.003	-0.012	0.212	1.746	0.081
	Ilkhani et al[1396]	Interval Training	0.140	0.053	0.003	0.036	0.244	2.646	0.008
	Mohammad zade [1397]	Interval Training	3.500	0.536	0.287	2.450	4.550	6.531	0.000
Interval Training			0.696	0.249	0.062	0.207	1.185	2.792	0.005
	Atashak et al[1390]	Resistant training	1.660	0.243	0.059	1.184	2.136	6.836	0.000
	Hosseini et al [1397]	Resistant training	0.157	0.093	0.009	-0.025	0.339	1.692	0.091
	Moradi et al[1392]	Resistant training	0.100	1.061	1.126	-1.980	2.180	0.094	0.925
Resistant training			0.735	0.647	0.419	-0.534	2.004	1.136	0.256
Overall			0.724	0.162	0.026	0.407	1.041	4.481	0.000

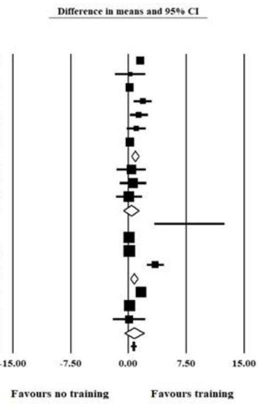

Figure 3.- Effects of different methods of physical activity on adiponectin levels (ng/dl). The forest plot shows pooled mean differences with 95% confidence intervals (CI) for 14 effect sizes pooled from 17 trials (tree separate effect sizes were pooled for different training modalities from Zarei (43), and two from Hosseini (33)).

Study name	Comparison	Point	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Begh zade et al[1397]	Aerobic Training	0.190	0.028	0.001	0.135	0.245	6.754	0.000
Ghasem nian et al[1392]	Aerobic Training	0.217	0.028	0.001	0.162	0.271	7.786	0.000
Hosseini et al[1397]	Aerobic Training	0.219	0.029	0.001	0.163	0.275	7.623	0.000
Parsiyan et al (1392)	Aerobic Training	0.213	0.028	0.001	0.158	0.268	7.641	0.000
Rashidl amir et al[1389]	Aerobic Training	0.214	0.028	0.001	0.160	0.269	7.687	0.000
Rashidl amir et al[1392]	Aerobic Training	0.215	0.028	0.001	0.161	0.270	7.720	0.000
Shavandi et al[1390]	Aerobic Training	0.228	0.033	0.001	0.163	0.293	6.897	0.000
Zarei et al[1396]	Concurrent Training	0.217	0.028	0.001	0.162	0.271	7.781	0.000
Zarei et al [1396]	Concurrent Training	0.216	0.028	0.001	0.162	0.271	7.771	0.000
Zarei et al [1396]	Concurrent Training	0.217	0.028	0.001	0.162	0.272	7.790	0.000
Abedi et al (1395)	Interval Training	0.216	0.028	0.001	0.161	0.270	7.749	0.000
Abolfathi et al [1394]	Interval Training	0.253	0.032	0.001	0.191	0.315	7.943	0.000
Ilkhani et al[1396]	Interval Training	0.246	0.033	0.001	0.182	0.310	7.523	0.000
Mohammad zade [1397]	Interval Training	0.208	0.028	0.001	0.153	0.263	7.461	0.000
Atashak et al[1390]	Resistant training	0.198	0.028	0.001	0.143	0.253	7.053	0.000
Hosseini et al [1397]	Resistant training	0.223	0.029	0.001	0.166	0.280	7.634	0.000
Moradi et al[1392]	Resistant training	0.217	0.028	0.001	0.162	0.272	7.790	0.000

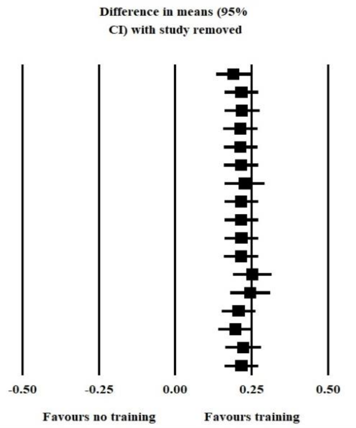

Figure 4. Sensitivity analysis of the studies. In sensitivity analyses, we recalculated the combined results by excluding one study per iteration.

Publication Bias

The funnel plots for adiponectin showed a moderate asymmetry. Publication bias, such as not publishing indecisive data, could have affected the results of the present meta-analysis (Figure 5).

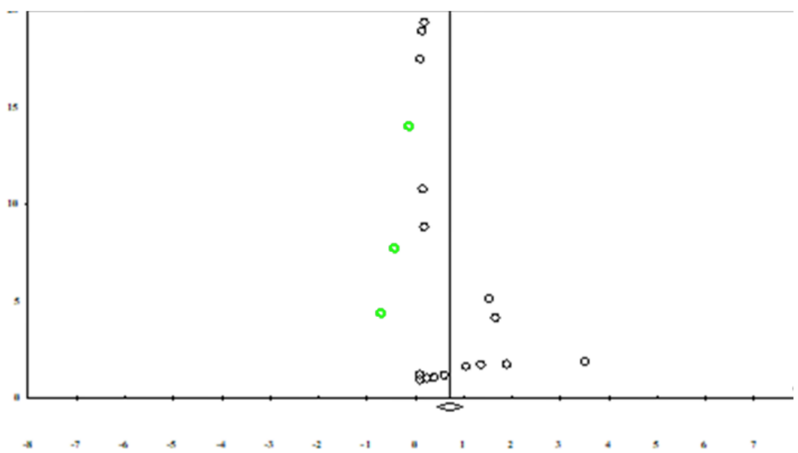

Figure 5- The funnel plot showing study precision against the mean difference effect estimate with 95% confidence interval for adiponectin

DISCUSSION

To our knowledge, this is the first systematic review and meta-analysis of RCTs to have investigated the effects of different exercise trainings on hypoadiponectinemia among Iranian diabetics. This is important because there is evidence that the benefits of exercise training interventions for people with diabetes may be influenced by racial and ethnic differences (44). In addition, no previous systematic review and meta-analysis has evaluated effects of exercise training on specific domains of adiponectin levels while considering ethnic differences in Iranian people. Since the prevalence of diabetes in Iran is increasing and background conditions such as ethnicity and race may be involved, it is crucial to identify strategies for successful management of diabetes in Iranians. Although numerous non-pharmacological options are available for treatment diabetes, exercise training always forms an integral part of a diabetes management program. A growing body of evidence demonstrates the benefits of exercise training, and adipocytokines might represent a possible explanation when it comes to the mechanisms mediating the beneficial effects of exercise training on impaired glucose metabolism.

Hypoadiponectinemia is closely related to insulin resistance, hyperinsulinemia, impaired glucose metabolism, inflammation, obesity, type 2 diabetes (45-48), and atherosclerosis (49, 50). Increased circulating adiponectin concentrations have been shown to be associated with a reduced risk of diabetes, even among different races (9, 51). It has been reported that exercise training interventions exert greater effects on circulating adiponectin compared with glucose/lipid-lowering medicines (52), anti-hypertensive drugs, anti-atherosclerotic agents, and nutritional interventions (53). Our study illustrated that circulating adiponectin levels increased in response to exercise training in adults Iranians with prediabetes and diabetes. This is in line with results of a previous meta-analysis on overweight and obese individuals of different races (54). A meta-analysis by Becic el al. (24) reported that physical exercise, particularly aerobic exercise, significantly changes adiponectin levels in diabetics; however, this meta-analysis did not include studies on Iranians. In contrast to our results, Hayashino and colleagues (25) did not find any significant changes in circulating adiponectin levels in response to exercise training in individuals with type 2 diabetes; however, this meta-analysis included studies that had been performed on racial groups different from ours.

Our meta-analysis confirms that adiponectin levels significantly increase following exercise training at an adequate duration and intensity in Iranian diabetics.https://www.nature.com/articles/ijo2016230 - ref-CR15 However, caution is needed when comparing the results of our study with others because some studies included aerobic exercise (24, 56) or resistance exercise (57), and combined aerobic-resistance exercise (58). Nevertheless, high heterogeneity was also found in previous racial/ethnic meta-analyses (23). In this regards, racial/ethnic differences may be a reason for the significant differences between our study and other systematic reviews and meta-analysis studies. The present systematic review and meta-analysis of Iranian RCTs provides new empirical evidence on racial/ethnic heterogeneity in diabetes-related risk factors for adults with diabetes. The present systematic review and meta-analysis of RCTs had both strengths and limitations that should be considered. First, publication bias could not be avoided and excluded. Moreover, some Iranian RCTs included in the present study reported concealed allocation. Furthermore, some Iranian RCTs had small sizes (fewer than 20 subjects for each group), which tend to lead to extreme effects. One of the major strengths of the present systematic review was the evaluation of the effects of exercise training on Iranians with diabetes. This was achieved using a comprehensive search strategy, which included Iranian RTCs and a more homogenous racial population.

CONCLUSION

It has been well-established that exercise training is a feasible and beneficial method for management of diabetes risk factors, including hypoadiponectinemia. However, in terms of minimizing the risk of hypoadiponectinemia, the optimal quality of exercise training and the mechanisms involved in hypoadiponectinemia, diabetes, and ethnicity/race are relatively unclear. Furthermore, this benefit may be moresubstantial when accompanied by racial considerations. It is recommended to conduct large RCTs focusing on the effects of different exercise modalities on diabetes-related risk factors. In addition, we suggest considering ethnic diversities when recommending exercise training regimens for decreasing diabetes-related risk factors. However, RCT articles with larger sample sizes and different racial subgroups of diabetic patients are needed to confirm the effect of exercise.

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DECLARATIONS

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Ethics approvals and consent to participate

Not applicable.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest regarding publication of this article.

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