High-intensity interval training induced PGC-1α and AdipoR1 gene expressions and improved insulin sensitivity in obese individuals

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ABSTRACT

Introduction: High-intensity interval training (HIIT) has been found to improve cardiometabolic health outcome as compared to moderate-intensity continuous exercise. However, there is still limited data on the benefits of HIIT on the expression of regulatory proteins that are linked to skeletal muscle metabolism and insulin sensitivity in obese adults. This study investigated the effects of HIIT intervention on expressions of peroxisome proliferator-activated receptor-γ coactivator 1-α (PGC-1α) and adiponectin receptor-1 (AdipoR1), insulin sensitivity (HOMA-IR index), and body composition in overweight/obese individuals.

Methods: Fifty overweight/obese individuals aged 22-29 years were assigned to either no-exercise control (n=25) or HIIT (n=25) group. The HIIT group underwent a 12-week intervention, three days/week, with intensity of 65-80% of age-based maximum heart rate. Anthropometric measurements, homeostatic model of insulin resistance (HOMA-IR) and gene expression analysis were conducted at baseline and post intervention.

Results: Significant time-by-group interactions (p<0.001) were found for body weight, BMI, waist circumference and body fat percentage. The HIIT group had lower body weight (2.3%, p<0.001), BMI (2.7%, p<0.001), waist circumference (2.4%, p<0.001) and body fat percentage (4.3%, p<0.001) post intervention. Compared to baseline, expressions of PGC-1α and AdipoR1 were increased by approximately three-fold (p=0.019) and two-fold (p=0.003) respectively, along with improved insulin sensitivity (33%, p=0.019) in the HIIT group.

Conclusion: Findings suggest that HIIT possibly improved insulin sensitivity through modulation of PGC-1α and AdipoR1. This study also showed that improved metabolic responses can occur despite modest reduction in body weight in overweight/obese individuals undergoing HIIT intervention.

KEY WORDS:
exercise, obesity, PGC-1α, insulin resistance, adiponectin

INTRODUCTION

Adults should obtain a minimum of 150 minutes per week of moderate-intensity physical activity for health, and possibly higher levels to promote weight loss or maintenance. Despite the well-established benefits of regular physical activity for improving cardiometabolic health, it remains difficult for health professionals to get individuals to adhere to current physical activity guideline by American College of Sports Medicine (ACSM) of at least 30 min per day of moderate intensity exercise five days a week, or vigorous exercise for 20 min per day, three days a week.[1] Over the past decade there has been considerable interest surrounding high-intensity interval training (HIIT), a type of training that is characterised by brief, intermittent bursts of vigorous activity, often using bodyweight as resistance, interspersed by periods of rest or low-intensity exercise.[2] Due to the nature of the exercise, HIIT thereby challenges both the aerobic and anaerobic systems in comparison to steady-state aerobic exercises.[2] As the safety of HIIT becomes clearer, focus has shifted away from using HIIT in healthy individuals towards clinical populations in improving health-related outcomes. The rationale of using HIIT in both healthy and clinical populations is that the vigorous activity component of HIIT promote greater adaptations via increased cellular stress, yet their short duration, and the ensuing recovery intervals, allow even untrained individuals to work harder than would otherwise be possible in traditional, steady-state exercises.[3]

A growing body of evidence has demonstrated comparable or superior improvements in cardiometabolic health outcomes using HIIT as compared to traditional, moderate-intensity continuous training (MICT). HIIT have been shown to yield benefits of similar, if not greater magnitude to MICT on glycaemic control,[4] blood pressure[5] and aerobic endurance[6] despite relatively shorter time commitment. The impact of

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HIIT on metabolic health is in part influenced by physiological adaptations of the skeletal muscles, possibly involving activation of biochemical signalling cascades in muscle, resulting in expression of transcriptional factors and gene products that constitutes to the metabolic flexibility of skeletal muscles in mediating fat and glucose metabolism.[7] Recently, studies have reported that HIIT activates molecular signalling pathways linked to peroxisome proliferator-activated receptor gamma coactivator-1α (PGC-1α).[8] PGC-1α, a well-known master regulator of mitochondrial gene expression, has been shown to facilitate skeletal muscle mitochondrial adaptations and oxidative capacity resulting in improved fatty acid oxidation and insulin sensitivity in response to exercise.[9] The skeletal muscle is also an important target tissue for adiponectin where it regulates glucose and fatty acid metabolism directly and via insulin sensitising effects.[10] Adiponectin exerts its action via binding to adiponectin receptors, with adiponectin receptor-1 (AdipoR1) being abundantly expressed in skeletal muscles.[11] In addition, peripheral blood mononuclear cells and macrophages express AdipoR1, allowing adiponectin to exert anti-inflammatory and anti-atherogenic effects by modulating macrophage functions from the pro-inflammatory M1 to the anti-inflammatory M2 phenotype.[12] AdipoR1 levels have been shown to be significantly decreased in the muscle and adipose tissue of insulin-resistant ob/ob mice,[13] indicating its role in glucose homeostasis and insulin sensitivity. On the contrary, exercise training increases adiponectin receptors, which may mediate the improvement of insulin resistance often seen with regular exercise, which then contributes to the overall anti-diabetic outcome of adiponectin action.[14]

Although it appears that exercise may induce favourable changes within the skeletal muscle that in turn promotes oxidative capacity and metabolic homeostasis, only little is known about changes in PGC-1α and AdipoR1 gene expressions in relation to insulin sensitivity following HIIT intervention. These changes, along with other adaptations, not only may improve insulin sensitivity but also increase the efficiency for muscle to oxidise fat as a substrate for energy, therefore facilitating greater weight loss, which will benefit individuals with obesity.

The primary aim of the present study was to investigate the effects of a 12-week HIIT intervention on the expression of genes linked to insulin sensitivity, i.e., PGC-1α and AdipoR1 in overweight/obese adults. In addition, we also aim to assess the changes in insulin sensitivity and body composition in response to the HITT intervention. We hypothesized that 12 weeks of HIIT intervention would increase the expression of PGC-1α and AdipoR1 genes as well as improved insulin sensitivity and body composition in overweight/obese adults.

METHODOLOGY

Participants

Seventy (70) overweight/obese individuals, aged 22-39 years, were recruited into this study and were assigned into two groups. A final total of 50 (n=50) participants were included in the statistical analysis (Figure 1). A quasi-experimental design with purposive sampling was used for this study. We neither employed randomisation nor blinding in this study. Participants were allowed to be in their preferred group. Inclusion criteria were overweight/obese (BMI>25kg/m^2), not meeting the current physical activity guidelines in the preceding year, non-smokers and willing to participate in an exercise intervention. Exclusion criteria included diagnosis of chronic diseases (type 2 diabetes, cardiovascular, renal, etc.), musculoskeletal problems, and taking medications or dietary supplements known to affect the primary outcomes of the study. The study was conducted in Universiti Teknologi MARA, Shah Alam. Following a verbal and written explanation of the nature and risks involved in the study, written, informed consent was obtained from all volunteers. The study was performed in accordance with the Declaration of Helsinki and is based on principles of Good Clinical Practice. The study protocol was approved by the Ethics Committee of Universiti Kebangsaan Malaysia Medical Center (NN-083-2015).

Pre-Intervention Measurements

All subjects were assessed at baseline, prior to start of the intervention. Subjects attended the research laboratory after a minimum of a 10-hour overnight fast for anthropometric measurements and blood sample collection. Upon completion of baseline measurements, subjects were assigned into either the intervention (HIIT; n=25) or control (CON; n=25) groups.

Anthropometric Measures

All subjects were weighed barefoot and with minimal clothing. Body height was measured by the digital stadiometer and body weight was determined by a digital scale (SECA®, Vogel & Halke GmbH, Germany). Body mass index (BMI) was calculated as the weight (kg) divided by the square of the height (m^2). Waist circumference was measured with a flexible, non-elastic band (SECA®, Vogel & Halke GmbH, Germany) according to standard protocol. Waist circumference was defined as the smallest abdominal girth between the lowest rib and the upper anterior iliac spine. Percentage of body fat was determined using bioelectrical impedance analysis (BIA) (TANITA, Japan).

Blood Sampling

Fasted blood samples (10ml) were collected in the morning using the standard phlebotomy technique into vacutainers containing either EDTA, sodium fluoride or serum separator for RNA extraction, glucose measurement and insulin measurement respectively. Blood samples containing EDTA were processed immediately for PGC-1α and AdipoR1 gene analysis. Blood samples for glucose and insulin analysis were centrifuged at 1000g and 4°C for 10 minutes. Aliquots of plasma and serum were frozen and stored at -80°C until analysis. Insulin levels were measured in duplicate using an enzyme-linked immunosorbent assay kit (Demeditec Diagnostics GmbH, Germany). The homeostasis assessment model of insulin resistance (HOMA-IR) was used as a surrogate measure of insulin sensitivity (HOMA-IR = fasting insulin (μU/ml) × fasting glucose (mM)/22.5)[15]. Plasma glucose levels were measured using the Cobas system (Roche Diagnostics GmbH, Germany).

HIIT Intervention

All participants in the HIIT group received an intervention of high-intensity interval training, consisting of 60-min sessions, three times weekly for a total of 12 weeks. Meanwhile, subjects in the CON group were required to maintain their regular daily activities and diet throughout the same period. Briefly, the core of the HIIT intervention consisted of 10 exercise stations targeting different muscle groups. The selected exercises are jumping jack (total body), squat (lower body), push up (upper body), abdominal crunch (core), burpee (total body), mountain climber (lower body), side to side push up (upper body), plank (core), high knees (total body) and lunges (lower body). Subjects were required to perform as many repetitions as possible for 30 seconds of each exercise followed by a 30-sec rest. Each exercise was to be performed in three sets with a 2-min interval between sets. Subjects were guided to keep their exercise intensity at 65-80% of maximal heart rate using heart rate monitors (S610, POLAR, Finland). Active warm-up and cool-down periods were included in all sessions. All exercise sessions were actively conducted and supervised by an investigator. The HIIT was solely an exercise intervention and did not include education for dietary modification or behavioural modification to minimise the influence of additional factors. A record of attendance was maintained throughout the 12 weeks.

Post-Intervention Measurements

Post-training measurements were assessed >48 hours (and no longer than five days) following the last training session. Subjects reported to the research laboratory after an overnight fast (minimum 10 hours) and underwent identical assessments to those outlined in 'pre-intervention measurements.'

Gene Analysis Procedures

RNA Extraction

Total RNA was extracted from whole blood using Nucleospin RNA blood kit (Macherey Nagel, Germany) according to manufacturer's protocol and optimisation technique. RNA yield and purity were determined using ND-1000 spectrophotometer (NanoDrop Technologies, Wilmington, USA). cDNA conversion was performed on 20ng of each RNA sample using Quantinova Reverse Transcription Kit (Qiagen, Hilden, Germany) according to manufacturer's protocol and stored at -20°C prior to analysis.

Quantitative Real-Time PCR

The PCR recipe was comprised of 1.0µl of each cDNA served as a template in 5µl of SYBR® Green supermix (Bio-Rad, CA, USA), 1.0µl forward and reverse primers at 400nM concentration and 2.0µl dH2O. Primer pairs for PGC-1α and AdipoR1 were obtained from previous studies[16,17] and the sequences were confirmed through Bioinformatics (reverse compliment, BLAST & Oligo explorer) and PCR amplification. Forward and reverse primers for PGC-1α and AdipoR1 were as follows: PGC-1α-F: 5′GGTCTCTCCTTGCAGCACAA3′, PGC-1α-R: 5′CTGGGA TGACCGAAGTGCTT3′; AdipoR1-F: 5′CCTTCTACTGCTCCCCACAG3′, AdipoR1-R: 5′CTATCGCTGAGGGCTTTGTC3′. Amplification and gene expression analysis were carried out in CFX96TM Real-Time PCR Detection System (Bio-Rad, CA, USA). Gene expressions were normalised to the expression of the housekeeper Glyceraldehyde 3-phosphate dehydrogenase (GAPDH) gene, which has been found to be stable in response to exercise.[18] GAPDH primers were as follows: F: 5′GTGAAGGTCGGAGTCAACG3′, R: 5′GAGGTCAATGAAGGGGTC3′. All procedures were performed in triplicate. Data from the reaction was collected and analysed using computer software CFX Manager ver. 3.1 (Bio-Rad, CA, USA). Gene expression was considered significantly different when the ΔΔCT exceeds a two-fold change.[19]

Statistical Analysis

Sample size calculation was primarily based on the number of participants needed to detect a difference of at least 10% in insulin sensitivity.[29] *A priori* power calculation indicated that 25 subjects per arm would enable detection of said change with 80% power. Data was expressed as mean ± standard deviation (SD). Normality of distribution for dependent variables was assessed using the Shapiro-Wilk test. Gene expression data were relative and therefore were log10 transformed to ensure normality of errors. Data analysis was performed using per-protocol analysis. Independent t-test was used to compare the baseline data between groups for all parameters. A two-factor (time: pre and post; group: control and exercise) with mixed-design ANOVA was used to evaluate possible interactions followed by paired-sample t test to determine the effect of intervention in both groups. All statistical analyses were performed using Statistical Package for the Social Sciences (version 23.0; SPSS, Inc., Chicago, IL), with a type I error of α=0.05.

RESULTS

Subjects' Characteristics

Baseline characteristics of the subjects is summarised in Table I. All subjects in the HIIT group completed the intervention with at least 80% adherence. The numbers of male and female participants in the study were equal (25 vs. 25). Overall, the mean age and BMI for all participants were 29 (SD5) years and 29.4 (SD3.7)kg/m^2 respectively. About 35% (n=17) subjects were categorised as overweight while the rest were as obese (65%, n=33). Waist circumference measurements indicated that 45% of males and 25% of females were classified as high risk (male: >102cm; female: >88cm) At baseline, there were no significant differences between the HIIT and CON groups for body composition, as well as for fasting glucose and insulin concentrations.

Body Composition

The changes in body composition of subjects in response to 12-week HIIT intervention is summarised in Table II. Significant time-by-group interactions were found for weight, BMI, waist circumference and percentage of body fat ($p<0.001$ for all). Subjects in the HIIT group had significant reductions in body weight (2.3%, $p<0.001$), BMI (2.7%, $p<0.001$), waist circumference (2.4%, $p<0.001$) and percentage of body fat (4.3%, $p<0.001$) following 12 weeks of intervention. While subjects in the HIIT group lost an average of 1.8 (SD1.3) kg of body weight, those in CON gained an average of 1.2 (SD 1.4) kg at the end of the intervention. Similarly, subjects in CON had increased waist circumference (0.9; SD0.7cm), while those in HIIT group lost 2.2 (SD1.6)cm.

Table I: Baseline characteristics of the participants in the high-intensity interval training (HIIT) and control (CON) groups

Characteristics	HIIT group (n=25) Mean (SD)	CON group (n=25) Mean (SD)
Sex		
Male (n)	11	14
Female (n)	14	11
Age (years)	29.6 (5.4)	29.8 (5.1)
Body weight (kg)	78.1 (11.2)	80.5 (17.3)
Body mass index (kg/m^2)	29.4 (3.4)	29.4 (4.0)
Waist circumference (cm)	91.7 (9.2)	90.8 (11.8)
Body fat percentage (%)	34.0 (6.4)	34.4 (7.3)
Fasting blood glucose (mmol/l)	5.2 (1.1)	5.03 (0.75)
Insulin (µU/ml)	11.5 (10.1)	12.3 (10.1)
HOMA-IR index	2.7 (2.5)	2.9 (2.9)
PGC-1α (relative fold change)	1.00 (0.00)	1.00 (0.00)
Adipo R1 (relative fold change)	1.00 (0.00)	1.00 (0.00)

SD – Standard deviation

Table II: Body composition and insulin sensitivity pre and post High Intensity Interval Training (HIIT) Intervention and control groups (CON)

Parameters	HIIT group (n=25)		CON group (n=25)	
	pre Mean (SD)	Post Mean (SD)	Pre Mean (SD)	Post Mean (SD)
Body weight (kg)	78.1 (11.2)	76.3 (10.9)[a, b]	80.5 (17.3)	81.7 (18.0)[a, b]
BMI (kg/m2)	29.4 (3.3)	28.6 (3.2)[a, b]	29.4 (4.0)	29.9 (4.0)[a, b]
Waist circumference (cm)	91.7 (9.2)	89.5 (9.0)[a, b]	90.8 (11.8)	91.7 (12.1)[a, b]
Body fat percentage (%)	34.0 (6.4)	32.5 (6.4)[a, b]	34.4 (7.3)	34.8 (6.9)
Blood glucose (mmol/l)	5.2 (1.1)	4.7 (0.8)[a, b]	5.0 (0.7)	5.2 (0.8)[a, b]
Insulin (µU/ml)	11.5 (10.1)	8.8 (8.7)[a, b]	12.3 (10.1)	14.8 (10.8)[a, b]
HOMA-IR index	2.7 (2.5)	1.8 (1.7)[a, b]	2.9 (2.9)	3.6 (3.3)[a, b]

SD – Standard Deviation
[a] significant (p<0.01) for comparison between group (HIIT vs. CON)
[b] significant (p<0.01) for comparison within group (pre vs. post)

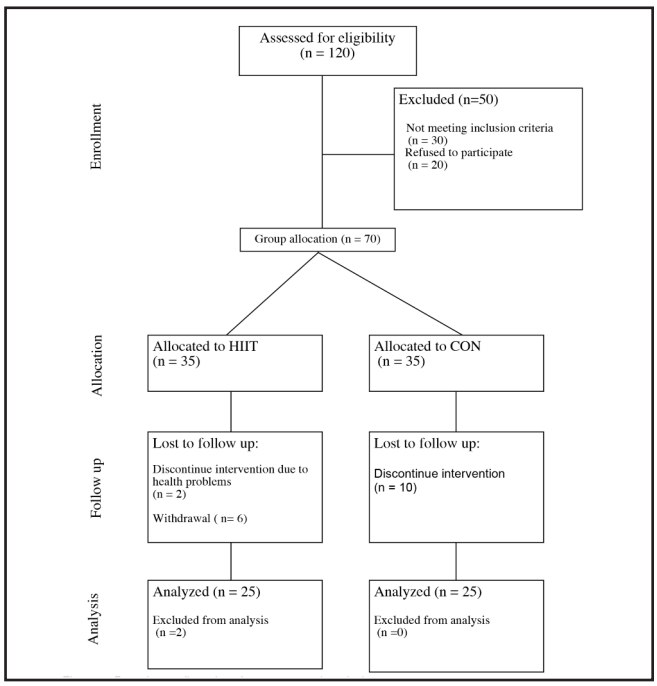

Fig. 1: Recruitment flow chart for per-protocol analysis.

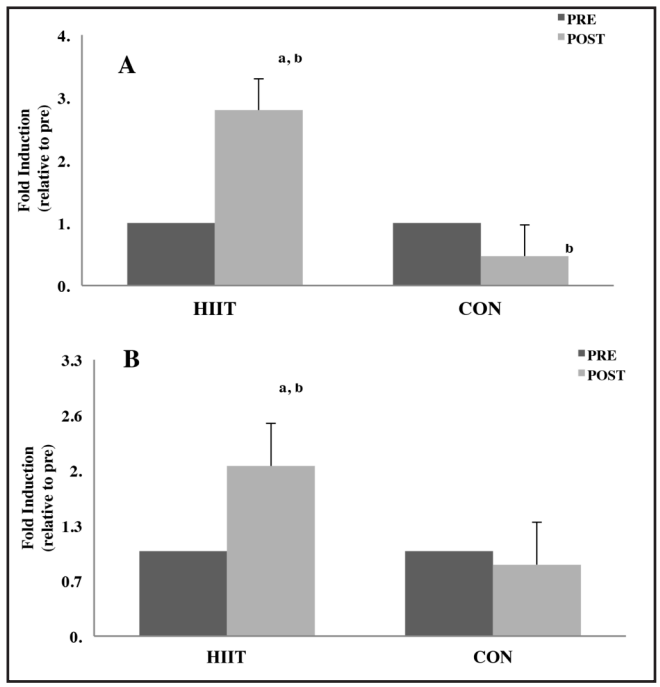

Fig. 2: Changes in PGC-1α (A) and AdipoR1 (B) expression in peripheral blood mRNA levels. Glyceraldehyde 3-phosphate dehydrogenase (GAPDH) was used as internal loading control. The expression of genes was calculated by the ΔΔCT method, and expressed as fold induction relative to pre intervention. Data are mean ± Standard Error.
[a] significant (p<0.01) for comparison between group (high-intensity interval training (HIIT) vs. control (CON))
[b] significant (p<0.01) for comparison within group (pre vs. post)

The observed changes in body weight and waist circumference in relation to baseline were significant in CON ($p<0.001$ for both).

Insulin Sensitivity

The changes in fasting glucose, insulin and insulin sensitivity (HOMA-IR) in response to 12-week HIIT intervention is summarised in Table 2II. Significant time-by-group interactions were found for fasting glucose ($F(1,48)=24.98$, $\eta^2=0.34$, $p<0.001$), fasting insulin ($F(1,48)=24.25$, $\eta^2=0.33$, $p<0.001$), and HOMA-IR ($F(1,48)=25.17$, $\eta^2=0.34$, $p<0.001$). Compared to baseline, subjects in the HIIT group had reduced fasting glucose (9.6%, $p<0.001$) and fasting insulin (23.5%, $p=0.002$) following 12 weeks of intervention. These reductions had resulted favourably in improved insulin sensitivity (represented by lower HOMA-IR values) by 33% ($p=0.003$) in the HIIT group. On the contrary, fasting glucose (4%, $p<0.001$), fasting insulin (19%, $p=0.002$) and HOMA-IR (24%, $p<0.001$) were significantly increased in CON group following the same intervention period when compared to baseline. At the end of the 12-week intervention, insulin sensitivity was twice as increased in the HIIT group (1.8; SD 1.7) compared to CON (3.6; SD3.3; $p=0.011$).

Gene Expression

Figure 1 represents the PGC-1α (A) and AdipoR1 (B) expressions in peripheral blood mRNA levels, expressed in fold-change relative to baseline levels in HIIT and CON groups. Significant time-by-group interactions were found for PGC-1α ($F(1,48)=10.69$, $\eta^2=0.18$, $p=0.0002$), and AdipoR1 ($F(1,48)=11.00$, $\eta^2=0.19$, $p=0.002$) gene expression levels. The HIIT intervention resulted in increased expressions of PGC-1α by 2.8-fold ($p=0.019$) and AdipoR1 by two-fold ($p=0.003$) following 12 weeks when compared to baseline. The increased expressions in PGC-1α ($p=0.004$) and AdipoR1 ($p=0.001$) were significantly greater in HIIT group when compared to CON. Interestingly, the expression of PGC-1α was significantly reduced in CON following 12 weeks compared to baseline ($p<0.001$). No change in AdipoR1 expression was detected in CON following the same period.

DISCUSSION

To our knowledge, very few studies have reported on the possible alterations in gene expressions primarily involved in energy homeostasis and glucose metabolism in response to high intensity interval training (HIIT), especially in the obese, human populations. The major finding of this study was that 12 weeks of HIIT intervention led to increased PGC-1α and AdipoR1 gene expression levels, and more importantly these increases were followed by improvements in insulin sensitivity and body composition in overweight/obese individuals.

There is a growing understanding that HIIT induces molecular mechanisms underlying skeletal muscle adaptations,[2] possibly due to high mechanical loads on the muscles in combination with increased activation of anaerobic metabolism.[20] The PGC-1 family of transcriptional coactivators, particularly PGC-1α have been shown to be important mediators of cellular adaptation to diverse stimuli in major organs in the body and most notably the skeletal muscle.[9] In addition to regulating important cellular processes, local activation of the various PGC-1s is communicated to other tissues in the body, thus eliciting an integrated systemic response.[21] Studies have reported that exercise training activates molecular signalling pathways linked to PGC-1α[9,22] in the skeletal muscle. The expression of PGC-1α is thought to be strongly influenced by muscle contractile activity in both humans and rodents.[22] Moreover, studies have shown that the expression of PGC-1α is significantly decreased in the skeletal muscle and adipose tissue of insulin-resistant and morbidly obese individuals,[9] implicating the role of PGC-1α in maintaining glucose homeostasis. Notably in the present study, we observed low baseline mRNA expression of PGC-1α and AdipoR1 in all our subjects (data no shown), which may be indicative of impaired insulin sensitivity and sedentary lifestyle.

Following 12 weeks of HITT intervention however, a near three-fold increase in PGC-1α expression levels were observed in the exercised group. This finding is consistent with similar studies in which high-intensity interval-type training led to increases in PGC-1α expression by several folds in skeletal muscles.[23] The increase in PGC-1α expression in the study was also accompanied by a two-fold increase in AdipoR1 expression. Over the last few years, comprehensive reviews have highlighted the pleiotropic actions of adiponectin in various tissues and cells in response to stresses. Importantly, many of these effects were mediated and dependent on AdipoR1, a muscle-specific adiponectin receptor. It has been reported that disruption of AdipoR1 receptor expression in skeletal muscle have been associated with mitochondrial dysfunctions and insulin resistance.[13,23] In parallel with our finding, several studies have shown increased mRNA expression of AdipoR1 in both skeletal muscle[24] and plasma[25] in response to aerobic-type training. In addition, Cho et al.,[26] recently demonstrated that eight weeks of HIIT prevented the reduction of AdipoR1 expression in both serum and adipose tissue in high-fat-diet-induced obese mice. Together, our findings further support the potency of HITT as a stimulus for upregulation of PGC-1α and AdipoR1 mRNA expressions in the overweight/obese.

In concurrent with increased expressions of PGC-1α and AdipoR1, the present study also observed improved insulin sensitivity in response to the HIIT intervention. Our findings are consistent with established evidence that HIIT is effective in improving insulin sensitivity, even more so compared to traditional continuous moderate intensity exercise.[27] Despite these beneficial metabolic effects, the molecular mechanisms underlying the glycaemic-lowering effects of HIIT have yet to be defined. One possible mechanism by which HIIT may improve insulin sensitivity involves the activation of AMP-activated protein kinase (AMPK) in the skeletal muscle, most likely due to accelerated ATP consumption by contracting muscles.[28] AMPK exerts its metabolic effects via several key downstream mediators including the PGC-1α.[29] The increased expression of PGC-1α observed in the study may have contributed to insulin sensitivity as it has been shown that PGC-1α activates the expression and translocation of glucose transporter 4 (GLUT4) and insulin-stimulated glucose transport in skeletal muscle.[30] In addition, the improved insulin sensitivity in the study may also be partly contributed by the increased expression of AdipoR1. Binding of adiponectin to its receptors mediates the activation of AMPK,

which is important for sensitising peripheral tissues to insulin, consequently leading to increased glucose uptake in muscle cells as well as fatty acid oxidation.[10] Moreover, suppression of AdipoR1 has been associated with decreased PGC-1α expression,[31] suggesting a possible linked pathway leading to insulin resistance.[24] Interestingly, we also noted a marked reduction in PGC-1α expression in the control group following 12 weeks, and this reduction was accompanied by a marked decrease in insulin sensitivity, as much as twice as low than the HIIT group. Decreased PGC-1α activity may contribute to insulin resistance by decreasing glucose transport and impairing mitochondrial oxidative metabolism,[30] causing the accumulation of incompletely oxidised fatty acid intermediates that are then thought to trigger insulin resistance in skeletal muscle.[32] Building on these observations, data from the current study suggest a potential link between insulin sensitivity and the regulation of PGC-1α and AdipoR1, though the directionality of the link remains unclear. In either case, the changes in gene expressions coupled with increased insulin sensitivity indicate that the study subjects had effectively lowered their metabolic risk in response to the HIIT intervention.

Anthropometric measures are highly valuable and reliable clinical measures, and they strongly correlate with an individual's metabolic profile. Improvements in insulin sensitivity have been associated with a reduction in body weight.[33] In agreement with previous findings,[3] our 12-week HIIT intervention led to an average reduction of 1.8kg and 2.2cm in body weight and waist circumference respectively, a modest but nevertheless significant reductions. Fisher et al.,[34] recently demonstrated that six weeks of HIIT led to a similar reduction in body weight compared to aerobic training in obese males, despite requiring only one hour of activity per week compared to five hours per week in the aerobic group. It is also worth to mention that some studies have established that HIIT can lower blood glucose and insulin resistance independently of alterations in adiposity or body mass in individuals with insulin resistance and type 2 diabetes.[35] This is further supported by Jelleyman et al.[27] in their meta-analysis stating that changes in body weight did not predict changes in insulin resistance or glucose regulation. In support of this, it has been highlighted that abdominal adiposity seems to play a greater role in the association of obesity with insulin resistance than the overall body or fat mass.[36] Thus, it is very likely that the reduction in waist circumference, a surrogate measure of abdominal adiposity, is partly responsible for the observed improvement in insulin sensitivity in our exercised subjects. Our findings further strengthen the evidence that HIIT can be used as modality for exercise-induced improvements in cardiometabolic profile regardless of significant weight loss in the overweight/obese.

One important aspect that is unclear from the published literature is the precise intensity and minimal volume of HIIT that is needed to potentiate beneficial effects, in this case, cardiometabolic health outcomes. Our protocol involved 35 minutes of high-intensity exercise (65-80% of maximum heart rate) over a 60-min training session, which was longer in duration than most published studies.[2] It is very likely that the favourable effects can still be achieved with shorter duration of exercise, provided the intensity is similar or higher. Such shorter time commitment is important from a public health perspective, given that 'lack of time' remains one of the most commonly cited barriers to regular exercise participation.[37] Whilst having a non-exercise control group is a clear strength of this study, we acknowledge certain limitations that may impact interpretation of the present findings. A primary limitation of this study is the expressions of both PGC-1α and AdipoR1 were not measured in skeletal muscle, but in the peripheral blood. Therefore, we cannot conclude that the changes observed were a direct result of skeletal muscle adaptation. However, it is noteworthy that PGC-1α and AdipoR1 gene expressions have been consistently investigated in peripheral blood samples of clinically-ill subjects. For example, elevations in PGC-1α expression in peripheral blood could serve as a prognostic marker for cardiac recovery following acute myocardial infarction,[38] whereas AdipoR1 expression in peripheral blood has been shown to be downregulated in patients with coronary artery disease compared to healthy controls.[39] Furthermore, a significance concordance (80-90%) of gene expression profiles between peripheral blood and different tissues has been demonstrated, suggesting that peripheral blood gene expression analysis could be a representative measure for tissue changes,[40] especially when invasive sample collection is not made possible. Secondly, the assessment of insulin sensitivity using HOMA-IR is limited by the fact that it was based on a single fasting blood sample. Lastly, it must be acknowledged that the present findings are based on a somewhat heterogeneous sample of inactive adult males and females. On the basis of our encouraging findings for the efficacy of HIIT in improving markers of metabolic health, future studies should include the quantification of PGC-1α and AdipoR1 at organ levels (e.g. skeletal muscles, liver, adipose tissue) if possible, upstream signalling pathways as well as gold standard measurement of whole body insulin sensitivity using hyperinsulinemic-euglycemic clamp to address the metabolic changes to HIIT in a more meaningful way.

CONCLUSION

The results of the present investigation demonstrate that 12 weeks of HIIT induces gene expressions of PGC-1α and AdipoR1 and improves insulin sensitivity among previously physically-inactive, overweight/obese adults despite modest weight loss. This suggests that manipulation of the expression of these genes could be a potential surrogate for exercise-mediated improvements of metabolic profile in overweight/obese individuals. Taken as a whole, our HIIT intervention shows significant and positive physiological adaptations associated with cardiometabolic health in overweight/obese individuals and may therefore reduce the development and progression of disease-related risk factors that are associated with overweight/obesity. The present findings add new information to the current knowledge regarding the efficacy of HIIT versus traditional aerobic training on metabolic health in obese population. HIIT therefore presents as an excellent alternative exercise modality given the range of variables that can be manipulated to make exercise more appealing and suitable for a wide range of populations.

CONFLICT OF INTEREST

The authors declared no conflict of interest regarding the publication of this manuscript.

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REFERENCES

1. Garber CE, Blissmer B, Deschenes MR, Franklin BA, Lamonte MJ, Lee IM, et al. American College of Sports Medicine position stand: Quantity and quality of exercise for developing and maintaining cardiorespiratory, musculoskeletal, and neuromotor fitness in apparently healthy adults: guidance for prescribing exercise. Med Sci Sports Exerc 2011; 43(7): 1334-59.
2. Gibala MJ, Little JP, MacDonald MJ, Hawley JA. Physiological adaptations to low-volume, high-intensity interval training in health and disease. J Physiol 2012; 590(Pt 5): 1077-84.
3. Kessler HS, Sisson SB, Short KR. The potential for high-intensity interval training to reduce cardiometabolic disease risk. Sports Med 2012; 42(6): 489-509.
4. Wormgoor SG, Dalleck LC, Zinn C, Harris NK. Effects of high-intensity interval training on people living with type 2 diabetes: a narrative review. Can J Diabetes2017; 41(6): 642-7.
5. Batacan RB Jr, Duncan MJ, Dalbo VJ, Tucker PS, Fenning AS. Effects of high-intensity interval training on cardiometabolic health: a systematic review and meta-analysis of intervention studies. Br J Sports Med 2017; 51(6): 494-503.
6. Macpherson RE, Hazell TJ, Olver TD, Paterson DH, Lemon PW. Run sprint interval training improves aerobic performance but not maximal cardiac output. Med Sci Sports Exerc 2011; 43(1): 115-22.
7. Hoffman NJ, Parker BL, Chaudhuri R, Fisher-Wellman KH, Kleinert M, Humphrey SJ, et al. Global phosphoproteomic analysis of human skeletal muscle reveals a network of exercise-regulated kinases and AMPK substrates. Cell Metab 2015; 22: 922-35.
8. Little JP, Safdar A, Wilkin GP, Tarnopolsky MA, Gibala MJ. A practical model of low-volume high-intensity interval training induces mitochondrial biogenesis in human skeletal muscle: potential mechanisms. J Physiol 2010; 588: 1011-22.
9. Lira VA, Benton CR, Yan Z, Bonen A. PGC-1α regulation by exercise training and its influences on muscle function and insulin sensitivity. Am J Physiol Endocrinol Metab 2010; 299(2): E145-61.
10. Liu Y, Sweeney G. Adiponectin action in skeletal muscle. Best Pract Res Clin Endocrinol Metab 2014; 28(1): 33-41.
11. Yamauchi T, Kadowaki T. Adiponectin receptor as a key player in healthy longevity and obesity-related diseases. Cell Metab 2013; 17: 185-96.
12. Lovren F, Pan Y, Quan A, Szmitko PE, Singh KK, Shukla PC, et al. Adiponectin primes human monocytes into alternative anti-inflammatory M2 macrophages. Am J Physiol Heart Circ Physiol 2010; 299(3): H656-63.
13. Tsuchida A, Yamauchi T, Ito Y, Hada Y, Maki T, Takekawa S, et al. Insulin/foxo1 pathway regulates expression levels of adiponectin receptors and adiponectin sensitivity. J Biol Chem 2004; 279: 30817-22.
14. Passos MC, Gonçalves MC. Regulation of insulin sensitivity by adiponectin and its receptors in response to physical exercise. Horm Metab Res 2014; 46(9): 603-8.
15. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 1985; 28: 412-9.
16. Tunstall RJ, Kate AM, Glenn DW, Gregory RC, Arend B, Mark H, et al. Exercise training increases lipid metabolism gene expression in human skeletal muscle. Am J Physiol Endocrinol Metab 2002; 283: E66-72.
17. Zhang P, Wang Y, Fan Y, Tang Z, Wang N. Overexpression of adiponectin receptors potentiates the anti-inflammatory action of sub-effective dose of globular adiponectin in vascular endothelial cells. Arterioscler Thromb Vasc Biol 2009; 29(1): 67-74.
18. Jemiolo B, Trappe S. Single muscle fiber gene expression in human skeletal muscle: validation of internal control with exercise. Biochem Biophys Res Commun 2004; 320: 1043-50.
19. Livak KJ, Schmittgen TD. Analysis of relative gene expression data using real-time quantitative PCR and the 2(-Delta Delta C(T)) Method. Methods 2001; 25: 402-8.
20. Buchheit M, Laursen PB. High-intensity interval training, solutions to the programming puzzle. Part II: anaerobic energy, neuromuscular load and practical applications. Sports Med 2013; 43(10): 927-54.
21. Correia JC, Ferreira DM, Ruas JL. Intercellular: local and systemic actions of skeletal muscle PGC-1s. Trends Endocrinol Metab. 2015; 26(6): 305-14.
22. Schnyder S, Kupr B, Handschin C. Coregulator-mediated control of skeletal muscle plasticity - A mini-review. Biochimie 2017; 136: 49-54.
23. Hood MS, Little JP, Tarnopolsky MA, Myslik F, Gibala MJ. 2011. Low-volume interval training improves muscle oxidative capacity in sedentary adults. Med Sci Sports Exerc 2011; 43(10): 1849-56.
24. Bluher M, Williams CJ, Kloting N, Hsi A, Ruschke K, Oberbach A, et al. Gene expression of adiponectin receptors in human visceral and subcutaneous adipose tissue is related to insulin resistance and metabolic parameters and is altered in response to physical training. Diabetes Care 2007; 30: 3110-15.
25. Lee S, Hong H, Han T, Kang H. Aerobic training increases the expression of adiponectin receptor genes in the peripheral blood mononuclear cells of young men. Biol Sport 2015; 32(3): 181-6.
26. Cho JK, Kim S, Hong HR, Yoon JH, Kang H. Exercise training improves whole body insulin resistance via adiponectin receptor. Int J Sports Med 2015; 37(1): e5.
27. Jelleyman C, Yates T, O'Donovan G, Gray LJ, King JA, Khunti K, et al. The effects of high-intensity interval training on glucose regulation and insulin resistance: a meta-analysis. Obes Rev 2015; 16(11): 942-61.
28. Gibala MJ, McGee SL, Garnham AP, Howlett KF, Snow RJ, Hargreaves M. Brief intense interval exercise activates AMPK and p38 MAPK signaling and increases the expression of PGC-1alpha in human skeletal muscle. J Appl Physiol 2009; 106(3): 929-34.
29. Jäger S, Handschin C, St-Pierre J, Spiegelman BM. AMP-activated protein kinase (AMPK) action in skeletal muscle via direct phosphorylation of PGC-1alpha. Proc Natl Acad Sci USA 2007; 104: 12017-22.
30. Michael LF, Wu Z, Cheatham RB, Puigserver P, Adelmant G, Lehman JJ, et al. Restoration of insulin-sensitive glucose transporter (GLUT4) gene expression in muscle cells by the transcriptional coactivator PGC-1. Proc Natl Acad Sci USA 2001; 98(7): 3820-25.
31. Iwabu M, Yamauchi T, Okada-Iwabu M, Sato K, Nakagawa T, Funata M, et al. Adiponectin and AdipoR1 regulate PGC-1alpha and mitochondria by Ca(2+) and AMPK/SIRT1. Nature 2010; 464(7293): 1313-9.
32. Brøns C, Vaag A. Skeletal muscle lipotoxicity in insulin resistance and type 2 diabetes. J Physiol 2009; 587(Pt 16): 3977-78.
33. Ana H, Gabriela R. Changes in fasting plasma glucose, HBA1c and triglycerides are related to changes in body composition in patients with type 2 diabetes. Maedica (Buchar) 2016; 11(1): 32-7.
34. Fisher G, Brown AW, Bohan Brown MM, Alcorn A, Noles C, Winwood L, et al. High intensity interval vs moderate intensity training for improving cardiometabolic health in overweight or obese males: a randomized controlled trial. PLoS ONE 2015; 10(10): e0138853.
35. Marcinko K, Sikkema SR, Samaan MC, Kemp BE, Fullerton MD, Steinberg GR. High intensity interval training improves liver and adipose tissue insulin sensitivity. Mol Metab 2015; 4(12): 903-15.
36. Hocking S, Samocha-Bonet D, Milner KL, Greenfield JR, Chisholm DJ. Adiposity and insulin resistance in humans: the role of the different tissue and cellular lipid depots. Endocr Rev 2013; 34(4): 463-500.
37. Godin G, Desharnais R, Valois P, Lepage L, Jobin J, Bradet R. Differences in perceived barriers to exercise between high and low intenders: observations among different populations. Am J Health Promot 1994; 8: 279-85.
38. Fabregat-Andres O, Paredes F, Monsalve M, Milara J, Ridocci-Soriano F, Gonzalez-Hervas S et al. mRNA PGC-1α levels in blood samples reliably correlates with its myocardial expression: study in patients undergoing cardiac surgery. Anatol J Cardiol 2016; 16(8): 622-9.
39. Sopić M, Joksić J, Spasojević-Kalimanovska V, Kalimanovska-Oštrić D, Anđelković K, Jelić-Ivanović Z. Are decreased AdipoR1 mRNA levels associated with adiponectin resistance in coronary artery disease patients? Clin Exp Pharmacol Physiol 2015; 42(4):331-6.
40. Liew CC, Ma J, Tang HC, Zheng R, Dempsey AA. The peripheral blood transcriptome dynamically reflects system wide biology: a potential diagnostic tool. J Lab Clin Med 2006; 147: 126-32.