



# The Pattern of Peroxisome Proliferator-activated Receptor Gamma Coactivator 1-alpha Gene Expression in Type-2 Diabetes Mellitus Rat Model Liver: Focus on Exercise

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## Abstract

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**BACKGROUND:** Peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1 $\alpha$ ) has an important role in mitochondria biogenesis which generated cellular metabolism. Carbohydrate metabolism in the liver is crucial to maintain plasma blood glucose.

**AIM:** This research aimed to determine the expression of PGC-1 $\alpha$  gene in the liver type-2 diabetes mellitus (T2DM) rat model, after treatment with a focus on exercise.

**METHODS:** We used 25 healthy male Wistar rats as subjects. Rats were modified to T2DM models by feeding a high-fat diet and low-dose streptozotocin injection. We divided the rats into five groups, that is, sedentary group as a control and four others as treatment groups. The exercise was assigned for treatment groups by a run on the treadmill as moderate intensity continuous (MIC), highintensity continuous (HIC), slow interval (SI), and fast interval (FI). The treatment groups were exercise throughout 8 weeks with a frequency of 3 times a week.

**RESULTS:** The results showed that expression of PGC-1 $\alpha$  gene was lower in all treatment groups compared to controls ( $p < 0.05$ ). Expression in HIC was higher than MIC ( $p < 0.05$ ), so was the expression in FI more than SI ( $p < 0.05$ ).

**CONCLUSIONS:** Exercise affected PGC-1 $\alpha$  gene expression in the liver of the T2DM rat model. The expression of PGC-1 $\alpha$  was linear with exercise intensity.

## Introduction

The prevalence of Type-2 diabetes mellitus (T2DM) has been growing in Indonesia. The World Health Organization estimated that the prevalence will still rise until 2030. Indonesian Health Ministry has reported that the prevalence of T2DM rose from 6.9% in 2013 to 8.5% in 2018. This phenomenon correlated with lifestyle change on diet and physical activity in Indonesian people, where the data show that people with physical inactivity in Indonesia increased by 33.5% in 2018 [1], [2]. Lack of physical activity, nutrient excess, and obesity influenced DNA methylation including peroxisome proliferator-activated receptor (PPAR)-1 alpha coactivator (PGC-1 $\alpha$ ) activity as a key regulator of cellular energy metabolism. This condition was an important risk factor for insulin resistance (IR) [3], [4].

PPAR PGC-1 $\alpha$  is a protein complex that increases the probability of a gene being transcribed

by interacting with transcription factors such as Forkhead box O1, glucocorticoid receptor, and hepatic nuclear factor-4 $\alpha$ . By regulating the activities of these transcription factors, PGC-1 $\alpha$  acts as a molecular switch for multiple cellular processes, including mitochondrial biogenesis and respiration, gluconeogenesis. In gluconeogenesis, PGC-1 $\alpha$  binds to the promoter region from genes that encode enzymes gluconeogenesis such as phosphoenolpyruvate carboxykinase and glucose-6-phosphatase (G-6-Pase) in the liver [5], [6], [7].

The liver is a crucial organ to maintain glucose homeostasis. Blood glucose concentration is mainly determined by glucose absorption at intestine, gluconeogenesis by the liver, and glucose utilization by skeletal muscle. In this process, the liver acts as a glucose reservoir that balances the glucose storage and release. Impaired hepatic glucose uptake and excessive hepatic glucose production are partially responsible for hyperglycemia in T2DM [8]. PGC-1 $\alpha$  is a downstream sensor of metabolic, hormonal, and

inflammatory signals that are responsible for the balance of hepatic gluconeogenesis, fatty acid  $\beta$ -oxidation, and mitochondrial biogenesis [9].

The previous studies have found that mitochondrial dysfunction is one of the causes of decreasing fatty acid oxidation, which plays a role in the pathogenesis of IR and T2DM [8], [10], [11]. Mitochondrial dysfunction is known to produce excessive reactive oxidative stress (ROS) that eventually leads to oxidative stress and pancreatic  $\beta$ -cell dysfunction. ROS as a result of oxidative stress mitochondrial decreased PGC-1 $\alpha$  expression and reduced glucose-stimulated insulin secretion [12]. Expression of PGC-1 $\alpha$  gene also found decreased in skeletal muscle so that muscle glucose uptake was disrupted, meanwhile, gene expression in the liver increased as compensation for the lack of cellular energy in T2DM [13], [14]. PGC-1 $\alpha$  expression modification might be a candidate for the management of mitochondrial dysfunction, leading to the treatment for diabetes mellitus [13], [15].

Few studies have been conducted to find out the effect of exercise on PGC-1 $\alpha$ , especially at skeletal muscle [13], [16]. Studies proved that exercise could decrease plasma blood glucose and IR by improving mitochondrial function in T2DM patients [17], [18]. However, there was still limited information about the effect of exercise with different intensity to the expression of PGC-1 $\alpha$  liver gene. As we know that liver is also a homeostatic organ for blood glucose regulation and PGC-1  $\alpha$  promote mitochondrial biogenesis in gluconeogenesis. The aim of this research was to determine the expression of PGC-1  $\alpha$  liver gene in T2DM rats model with a focus on exercise that was carried out as continuously and interval with different intensity.

## Methods

### Animal model

This research was carried out using T2DM model rat (*Rattus norvegicus* sp.) as the subjects. Eight weeks of age Wistar were made T2DM by combining the administration of a high-fat diet and low-dose streptozotocin injections twice (30 mg/kg BW and 45 mg/kg BW in 0.1 citrate buffer pH 4.5 given intraperitoneal). T2DM was determined if fasting blood glucose <200 mg/dl and homeostatic model assessment-IR (HOMA-IR) >6.5. Cage placement, feeding and drinking of the subjects was done in accordance with the ethics approval of research in experimental animals.

### Animal intervention

We intervened subjects with exercise ran on the treadmill as moderate-intensity continuous (MIC),

high-intensity continuous (HIC), slow interval (SI), and fast interval (FI) while the control group was made sedentary. Exercise intensity determination based on protocol of Huang *et al.* (Table 1). Exercise was carried out every 2 days with 30 min each session, for 8 weeks. Plasma blood glucose and HOMA-IR were assessed before and after exercise procedure. All rats were terminated under sedation (ketamine 30 mg intramuscular) subsequent the intervention. Duration and intensity for each treatment groups are shown in Table 1.

**Table 1: Duration and intensity of exercise for each treatment group**

Groups	Exercise procedure
MIC	25 m/min, 30 min
HIC	30 m/min, 30 min
SI	25 m/min, 10 $\times$ 2 min, 1 min interval
FI	30 min, 15 $\times$ 30 s, 1 min interval

MIC: Moderate-intensity continuous, HIC: High-intensity continuous, SI: Slow interval, FI: Fast interval.

### mRNA PGC-1 $\alpha$ examination

About 20–30 mg liver tissue was mixed with  $\beta$ -mercaptoethanol 10  $\mu$ l +1 ml buffer RLT as much as 600  $\mu$ l and homogenized with a mortar. RNA isolation procedure followed RNeasy Mini Kit (Qiagen, Germany). Two microliters template RNA, two-step Sybr Green reagent, primer PGC-1 $\alpha$  forward and reverse, and beta-actin primer forward and reverse were mixed in 0.2 ml PCR tube. Rotor gene was setting; hold 95 $^{\circ}$ C (2 min), denaturation 95 $^{\circ}$ C (5 s), and annealing 60 $^{\circ}$ C (30 s) for 40 cycles. Cycling threshold from each group both target and reference gene was taken. Delta-delta  $C_T$  was calculated by livask method to determine whether the expression higher or lower than control.

### Blood glucose and IR examinations

Blood from rat vein tail was taken for about 2–3 ml then centrifuged at 6.000 rpm for 3 min for serum isolation. Blood glucose level was assessed by spectrophotometer and insulin assessed with ELISA method followed Qia-Byee procedure. IR was determined by calculate fasting insulin (U/ml)  $\times$  fasting plasma glucose (mmol/l)/22.5 and named as HOMA-IR.

### Statistical analysis

Data normality was confirmed using Shapiro–Wilk test. Plasma blood glucose and HOMA-IR before and after intervention in treatment groups were analyzed with dependent t-test. To find out whether the PGC-1 $\alpha$  gene mRNA expression in each group was significantly different, the cycling threshold of each group was analyzed with one-way ANOVA test and followed by *post hoc* least significant difference (LSD) to analyze the different between groups. Data were significant if  $p < 0.05$  was considered.

## Results

### mRNA PGC-1 $\alpha$ gene expression

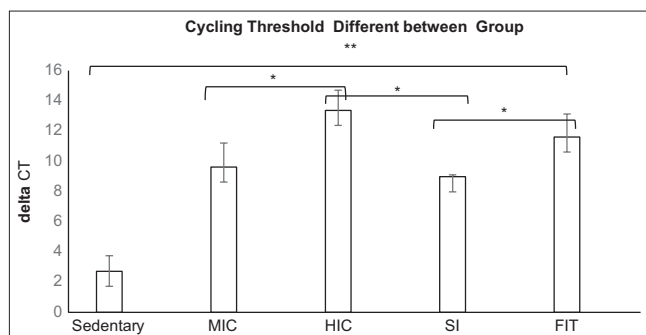
The average of cycling threshold of each group and gene expression compared to control is shown in Table 2. The cycling threshold value is opposite with gene expression. The extended cycling threshold time showed decreased of gene expression otherwise shorter cycling threshold mean gene expression increase.

**Table 2: The average cycling threshold of each group**

Group	Sedentary Mean ± SD (n = 5)	MIC Mean ± SD (n = 5)	HIC Mean ± SD (n = 5)	SI Mean ± SD (n = 5)	FI Mean ± SD (n = 5)	p
$\Delta C_t$	2.72 ± 1.03	9.62 ± 1.59	13.37 ± 1.33	8.98 ± 0.12	11.61 ± 1.52	0.000**

$\Delta C_t$ : Target gene-reference gene, MIC: Moderate-intensity continuous, HIC: High-intensity continuous, SI: Slow interval, FI: Fast interval.

From Table 2, we found that time of cycling threshold value mRNA PGC-1 $\alpha$  gene at treatment groups was significantly different than control after 8 weeks of exercise ( $p < 0.05$ ). *Post hoc* LSD analysis showed that differences in the length of the cycling threshold between groups were seen in the MIC group with HIC ( $p = 0.004$ ), HIC with SI ( $p = 0.01$ ), and SI with FI ( $p = 0.016$ ), as shown at Figure 1. Calculation with livask method shown that 8 weeks of exercise were able to decrease the expression of mRNA PGC-1 $\alpha$  gene in liver T2DM rat model, MIC = 0.0084, HIC = 0.0006; SI = 0.0130; FI = 0.0023.



**Figure 1: Cycling threshold showed significantly different between moderate intensity and high intensity. Moderate-intensity continuous (MIC)-high-intensity continuous (HIC) ( $p = 0.004$ ); MIC-slow interval (SI) ( $p = 0.311$ ); MIC-fast interval (FI) ( $p = 0.098$ ); HIC-SI ( $p = 0.01$ )**

### Blood glucose and IR

Fasting blood glucose and IR in treatment groups before and after exercise assignment are shown in Table 3. Fasting blood glucose each treatment group after exercise assignment was significantly declined, as well as HOMA-IR except HOMA-IR in MIC group.

The magnitude of decreasing in fasting plasma glucose and IR after exercise protocol is shown in Figure 2.

**Table 3: Plasma blood glucose and insulin resistance in treatment groups before and after exercise assignment**

Groups	Pre-test	Post-test	p-value
Blood glucose			
MIC	339 ± 103.7	191.6 ± 5.4	0.014*
HIC	396.8 ± 25.7	198.2 ± 75	0.009*
SI	452.6 ± 31.3	227.2 ± 87.8	0.001*
FI	451.2 ± 83.2	259 ± 25	0.006*
HOMA-IR			
MIC	90.5 ± 40.5	43.3 ± 8.6	0.066
HIC	81.3 ± 6.1	18.5 ± 6.4	0.000*
SI	94.0 ± 21.1	16.6 ± 4.0	0.001*
FI	91.1 ± 19.7	19.7 ± 7.8	0.004*

\* $p < 0.05$ , MIC: Moderate-intensity continuous, HIC: High-intensity continuous, SI: Slow interval, FI: Fast interval, HOMA-IR: Homeostatic model assessment-insulin resistance.

## Discussion

The purpose of this research was to determine the expression of PGC-1 $\alpha$  gene in liver of T2DM rat model after treatment with a focus on exercise that was carried out as continuously and interval with different intensity. Our research found that expression of PGC-1 $\alpha$  gene in the liver was lower in exercise groups compared sedentary group. It was shown that exercise has an effect on PGC-1 $\alpha$  gene expression in the liver. This research is in line with Safdar *et al.* that endurance exercise alters biogenesis of mitochondria by enhancing PGC-1 $\alpha$  function in mitochondria [17]. Meanwhile, Buler *et al.* found that PGC-1 $\alpha$  has beneficial effect of physical exercise and caloric restriction and becomes a regulatory interlink between energy homeostasis and the hepatic immune system [18] and improved mitochondrial dysfunction [19].

The expression of PGC-1 $\alpha$  gene in the liver after exercise was contrast with the expression in skeletal muscle. A previous research has proven that PGC-1 $\alpha$  expression has been reported to be increased in the liver of both Type 1 and Type 2 diabetic mouse models, in contrast to the reported observations that PGC-1 $\alpha$  expression was decreased in the muscle of human Type 2 diabetic subjects [13]. The influence of exercise on both expressions is reverse. Exercise increased PGC-1 $\alpha$  gene in skeletal muscle while decreased in liver [17], [20].

Increased hepatic PGC-1 $\alpha$  expression could be expected to stimulate hepatic glucose output in T2DM concerned with the default of plasma glucose to enter the cell [21]. Impaired insulin signaling in the liver disrupts the mechanism of glycogenesis and stimulates gluconeogenesis and glycolysis [22]. Induction of PGC-1 $\alpha$  and PGC-1 $\beta$  expression in liver is a critical regulatory event leading to the activation of energy metabolic pathways that serve to increase ATP production by fatty acid oxidation and exert homeostatic control, especially in fasted state as it is observed in diabetes mellitus. Moreover, PGC-1 $\alpha$  may promote IR directly by inducing TRB-3, an inhibitor of Akt signaling, a critical downstream component of the insulin signaling pathway,

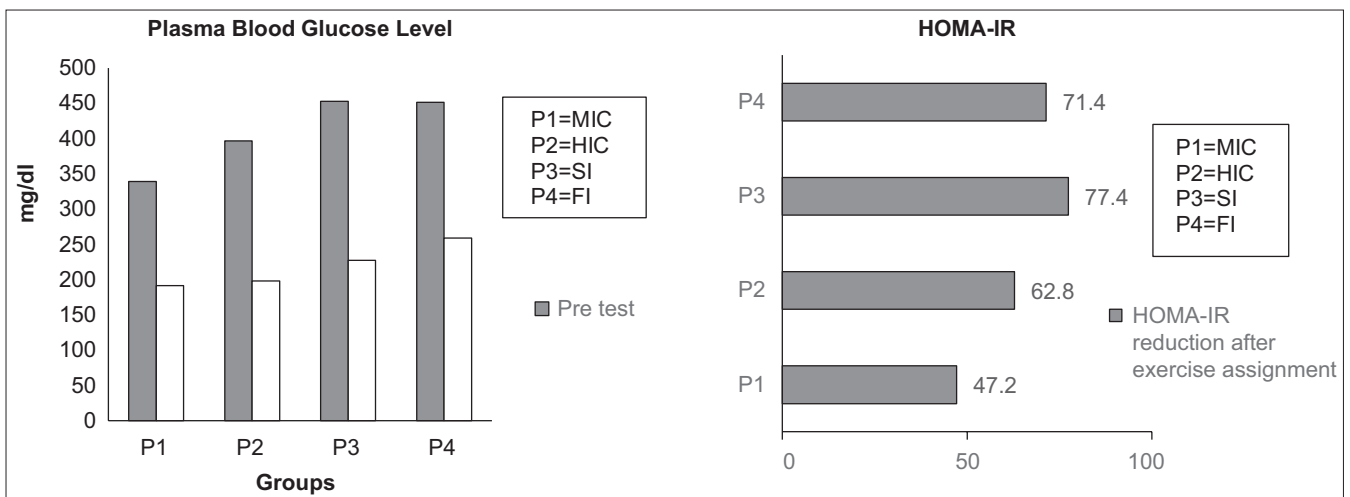


Figure 2: Plasma blood glucose and insulin resistance before and after 8 weeks of exercise. Reduction plasma blood glucose in moderate-intensity continuous (MIC) group decreased as much as 147.2 mg/dl, high-intensity continuous (HIC) = 198.6 mg/dl, slow interval (SI) = 225.4 mg/dl, fast interval (FI) = 192.2 mg/dl (A). Meanwhile, homeostatic model assessment-insulin resistance in MIC group decreases as much 47.2 HIC = 62.8, SI = 77.4, FI = 71.4

potentially increasing hepatic glucose production that contributes to circulating hyperglycemia. Exercise has been shown improved IR in the liver by reducing the inflammatory process, including the inhibition of TRB3, and suppressing gluconeogenesis [23].

Exercise enhanced mitochondrial biogenesis to produce energy for muscle needs. Increased activity of mitochondrial enzymes and nitric oxide of the muscle stimulates PGC-1 $\alpha$  being more active [24]. This mechanism impacts insulin sensitivity in skeletal muscle and liver so that IR and plasma blood glucose were decreased [25]. Improvement in IR degrades liver gluconeogenesis, IR, and activated Akt signaling so that the PGC-1 $\alpha$  gene in liver was decreased [26].

In this research, PGC-1 $\alpha$  liver gene expression in HIC training was lower than in MIC so that the expression of PGC-1 $\alpha$  in FI was lower than SI. In vigorous intensity, cell metabolism produces more energy that promotes insulin sensitivity improvement at skeletal muscle [27]. Decreasing IR at skeletal muscle followed by decreasing on liver gluconeogenesis [28]. This finding suggests a connection between PGC-1 $\alpha$  liver gene expression and exercise intensity.

## Conclusions

We conclude that exercise affected PGC-1 $\alpha$  gene expression in the T2DM rat model liver. The expression was associated with exercise intensity, especially in continuous exercise. We suggested advanced research to obtain more insight into the mechanism.

## Declarations

### Authors' contributions

YM and DL designed the research. YM and YSP collect data, YM and NSH analyzed the data. YM wrote the original draft of the manuscript, and all authors contributed to the concept and also all revised drafts of the manuscript. All authors read and approved the final version of manuscript.

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### Ethical approval

This research has obtained ethical approval from medical faculty and RSUP H. Adam Malik Medan ethic committee. Because of we used animal model in this research, a statement about consent to participate is not applicable.

### Availability of data and materials

I wish to share my data. All data and materials are available from the corresponding author on request.

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