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Influence of Peroxisome Proliferator-Activated Receptor Gamma Coactivator 1 Alpha (PGC-1α) in Type 2 Diabetes: Review Article

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ABSTRACT

Background: According to the International Diabetes Federation, Egypt has one of the world's top ten highest concentrations of diabetics. This figure is anticipated to climb to 13.1million by 2032 from the current 7.5 million diabetics and 2.2 million pre-diabetic population in Egypt. Several transcription factors are coactivated by Peroxisome Proliferator-activated Receptor Gamma Coactivator 1 Alpha (PGC-1α), a transcriptional coactivator. Oxidative metabolism is one of its numerous biological impacts, and it affects ROS production and mitochondrial biogenesis. Mitochondrial dysfunction is seen in T2DM patients, who have fewer mitochondria in their skeletal muscles.

Objective: To determine if PGC-1α gene polymorphism is correlated with T2DM.

Methods: PubMed, Google Scholar, and Science Direct were searched using the following keywords: Type 2 Diabetes Mellitus, Peroxisome Proliferator-activated Receptor Gamma Coactivator 1 Alpha, and PGC-1α. The authors also screened references from the relevant literature, including all the identified studies and reviews, only the most recent or complete study was included, and in peer-reviewed articles between March 2001 and February 2021. Documents in a language apart from English have been excluded as sources for interpretation were not found. Papers apart from main scientific studies had been excluded: documents unavailable as total written text, conversation, conference abstract papers, and dissertations.

Conclusion: PGC-1α has been implicated in the regulation of genetic pathways leading to homeostatic liver and muscle glucose use, mitochondrial biogenesis as well as insulin production.

Keywords: Type 2 Diabetes Mellitus, Peroxisome Proliferator-activated Receptor Gamma Coactivator 1 Alpha.

INTRODUCTION

It is a group of metabolic diseases that are characterized by high blood sugar, insulin resistance, and anomalies in the metabolism of glucose (glucose), lipids (fat) and proteins. To blame is either an abnormality in the secretion or the effect of insulin (or both) **(1).**

The prevalence of diabetes is a huge public health issue. Global diabetes prevalence is anticipated to climb from the current 451 million people to 693 million by 2045 **(2).** More than one billion people worldwide have diabetes mellitus, a disease that has quadrupled in prevalence in only three decades. Diabetes mellitus affects approximately one in every eleven persons worldwide, with 90 percent of those cases being type 2 diabetes mellitus (T2DM) **(3).**

The Peroxisome proliferator-activated receptor gamma coactivator:

There are three members of the (PGC-1) family: PGC-1α, PGC-1β, and PRC (PGC1-related coactivator), all of which share structural traits and action mechanisms in common. PGC-1, the first member of the PGC-1 family, was discovered in brown adipose tissue in the late 1990s and found to interact with the PPAR- transcription factor, which is abundant in brown adipose tissue because of its abundance of mitochondria and specialization in thermogenesis **(4).**

For the most part, PGC-1 is found in high-energy tissues like the heart and kidneys, but it can also be found in skeletal muscle and other tissues as small as the testicles **(5).**

To carry out their biological roles, they interact with other coactivator complexes and transcription factors rather than serving as DNA-binding transcription regulators **(4).**

To regulate gene expression, they help to construct pre-initiation complexes. PGC-1 coactivators have surprisingly similar protein domain structures, which explains the partial overlap in their physiological roles **(6).**

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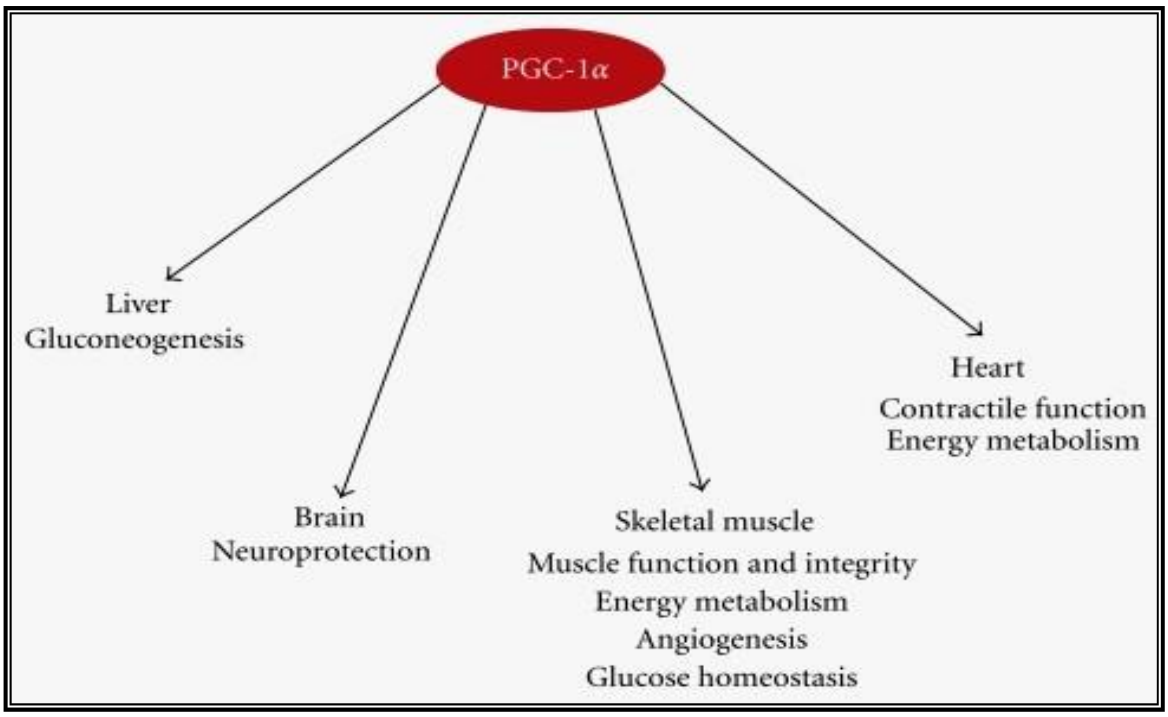

Figure (1): The heart, liver, brain, skeletal muscle, and heart all use PGC-1 in various ways[6].

Role of PGC-1α in type 2 diabetes:

Fasting, high-fat diets, or physical activity may alter the posttranslational changes of PGC-1 α that affect mitochondrial function, energy metabolism, and insulin sensitivity. PGC-1 α is recognized as a possible cause of T2DM and a potential treatment target because of its critical function in regulating energy metabolism and insulin sensitivity [7].

Glucose metabolism is also regulated by PGC-1 α. The MEF2 transcription factor is activated when PGC-1 α is induced in skeletal muscle, enhancing the production of GLUT4 and thus the cells' capacity to absorb glucose [8]. Increased intracellular glucose concentration is associated with decreased glycolysis and increased glycogen storage [9].

ERRα promotes PDK4 expression by inducing PGC-1 α. Glycogen production is promoted by inhibiting glucose oxidation through PDH inhibition, which is the mechanism by which this enzyme works [10].

There is a direct correlation between an increase in mitochondrial oxidation and the formation of ROS. Cell death and genotoxic stress can both be brought on by elevated ROS levels. Thus, cells have created defense mechanisms against these potentially harmful species as a result of this development. By stimulating the production of various enzymes that detoxify ROS, such as superoxide dismutase (SOD), catalase, and glutathione peroxidase, PGC-1 α is involved in regulating ROS levels (GPx) [11].

If PGC-1 α can activate these antioxidant enzymes, ROS-induced cell damage and death can be avoided. Coenzyme A (MCAD) and CPT1 mRNA levels are both increased by PGC-1, two key enzymes in the metabolism of fatty acids [12].

Insulin-induced blood glucose absorption primarily targets skeletal muscle, although its functional deterioration contributes significantly to the progression of insulin resistance in type 2 diabetes. Diabetic patients' and animals' skeletal muscle PGC-1 α expression is drastically reduced [13].

Insulin resistance in muscles is caused by a high quantity of free fatty acids in plasma. Reducing the expression of PGC-1 α in skeletal muscle reduces the expression of β- oxidation genes, which in turn reduces FAO in humans. Muscle cells become insulin resistant due to the buildup of fatty acids [12].

Oxidative damage and mitochondrial dysfunction can be prevented by PGC-1 α, which regulates the expression of mitochondrial antioxidant genes including manganese superoxide dismutase, catalase, peroxiredoxin 3 and 5, and uncoupling protein 2, among others [14].

When PGC-1 levels are out of whack, cells are unable to maintain their redox balance and become more susceptible to an inflammatory response. Low levels of PGC-1 α reduce the expression of mitochondrial antioxidant genes, causing oxidative stress and activating nuclear factor kappa B during inflammation [14].

PGC-1 dysregulation alters mitochondrial function and promotes ROS accumulation in the metabolic syndrome, which is characterized by a continuous low-grade inflammation. Several metabolic illnesses may be improved by targeting PGC-1 α, which

serves as a key link between metabolic regulation, the management of redox, and inflammation [14].

Insulin resistance and mitochondrial dysfunction have been linked to a considerable drop in PGC-1 α mRNA levels, according to recent studies [15]. T2DM is related to mitochondrial dysfunction, which may lead to oxidative stress. Since T2DM is associated with PGC-1 α and oxidative stress [16].

The hepatic oxidative stress sensor Vanin-1 (VNN1) is elevated in the blood and urine of diabetics. VNN1 may contribute to uncontrolled hyperglycemia by excessively activating PGC-1α/HNF-4α complex-controlled gluconeogenesis [17]. Protecting dorsal root ganglion cells from damage induced by excessive glucose may be accomplished by increasing the expression of PGC-1α [18].

Because of mitochondrial dysfunction and a decrease in antioxidant capacity caused by PGC-1α deficiency, high glucose stimulation promotes the expression of miR-34a in human retinal microvascular endothelial cells, a finding that has just been made in human research and is consistent with previous findings [19].

Inflammation and metabolic disease can be triggered by alterations in PGC-1 expression, which is essential for mitochondrial function, oxidative metabolism, and ROS removal. The ability of PGC-1α to modify metabolic pathways makes it an interesting option in the treatment of metabolic disorders [14]. PGC-1α activity can now be altered using a wide variety of medications [20].

PGC-1α and the liver:

The liver is a vital organ responsible for glucose homeostasis. Normally, blood glucose concentration is stably maintained within a narrow range in both well-fed and fasting states. This is mainly determined by three factors: (i) glucose absorption by the intestine, (ii) gluconeogenesis by the liver, and (iii) glucose utilization by skeletal muscle. In this process, the liver acts as a glucose reservoir that balances the glucose storage and release. In the well-fed state, the liver uptakes glucose from the blood and stores it in the form of glycogen (glycogenesis).

In the fasting state, the liver synthesizes glucose through glycogenolysis and gluconeogenesis and releases it into the bloodstream. Impaired hepatic glucose uptake and excessive hepatic glucose production are partially responsible for hyperglycemia in T2DM. Especially, previous studies indicated that PGC-1α plays a central role in the regulatory network of glucose metabolism in the liver [21].

PGC-1α is a downstream sensor of metabolic, hormonal and inflammatory signals that is responsible for the balance of hepatic gluconeogenesis, fatty acid β-oxidation, and mitochondrial biogenesis. The process has been reviewed elsewhere [22]. Briefly, in the fasting state, the pancreatic alpha cells synthesize and release glucagon to maintain a normal blood glucose level. Glucagon binds to its receptor present on hepatocytes and subsequently triggers the conformational change of G protein, which results in the dissociation of α-subunit from the G-protein complex.

Free α-subunits subsequently bind to adenylate cyclase, thereby catalyzing the conversion of adenosine triphosphate (ATP) into adenosine 3′,5′-monophosphate (cAMP). Two cAMP molecules bind to each regulatory subunit of protein kinase (PKA), releasing its catalytic subunit, which translocates into the nucleus and phosphorylates the cAMP response element (CRE)-binding protein (CREB) at Ser133. The phosphorylated CREB recruits CREB-binding protein (CBP) to the PGC-1α promoter and regulates its expression.

PGC-1α can coactivate several transcriptional factors, including hepatocyte nuclear factor-4α (HNF-4α) and forkhead box O (FOXO) 1, and therefore control the transcription of the rate-limiting gluconeogenic enzymes, such as phosphoenolpyruvate carboxykinase (PEPCK), pyruvate dehydrogenase kinase isoenzyme 4 (PDHK4) and glucose-6-phosphatase (G6Pase). However, after a meal, pancreatic beta cells synthesize and release insulin which binds to its receptor and triggers the phosphorylation of Akt, which in turn phosphorylates PGC-1α and inhibits its activity. This results in the stimulation of glycogen synthesis and inhibition of gluconeogenesis in the liver [21].

Moreover, accumulating evidence suggests an important role for PGC-1α in the regulation of lipid and bile acid metabolism that could contribute to gluconeogenesis [23, 24]. Recent studies have demonstrated that several signaling pathways, transcription factors, and coactivators contribute to these processes through the regulation of PGC-1α expression and activity. Abnormal activation of these glucose metabolic processes is closely implicated in the pathogenesis of hepatic IR and T2DM [21, 23, 24].

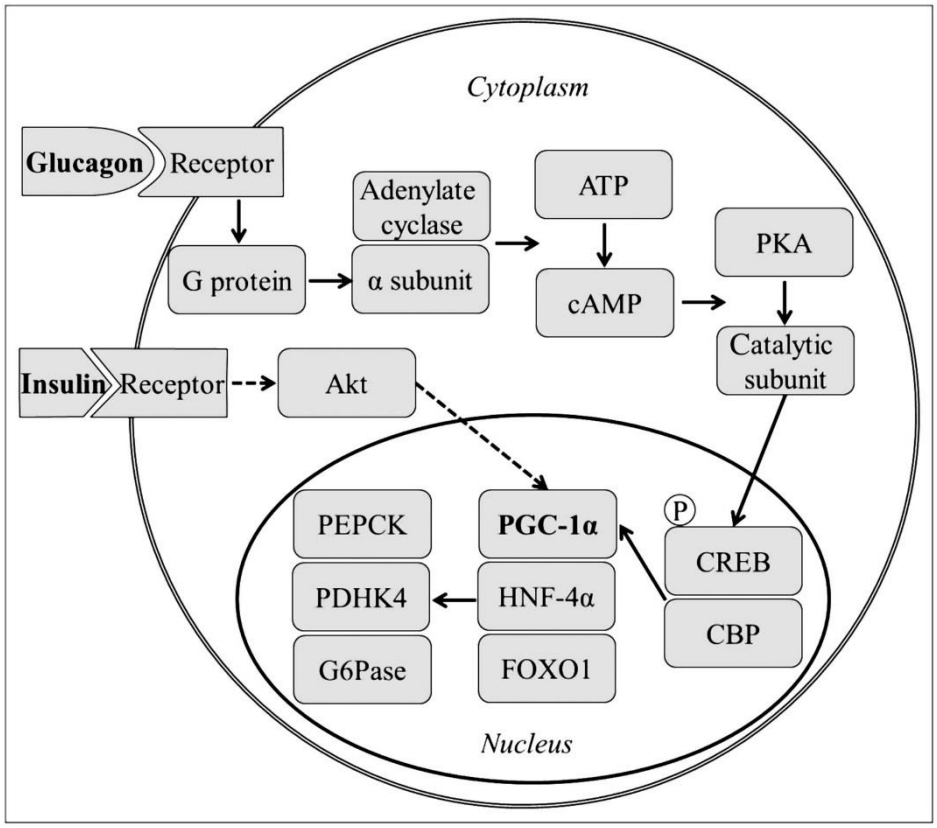

Figure (2): Signaling pathways of PGC-1α-regulated glucose metabolism in the liver [(21)].

Pancreatic β-cell apoptosis:

PGC-1α is an important regulator of pancreatic β-cell apoptosis. On one hand, PGC-1α is involved in the glucotoxicity-induced pancreatic β cells apoptosis. Glucokinase, a key regulatory enzyme that catalyzes glucose to glucose-6-phosphate, plays an important role in the regulation of glucose-stimulated insulin secretion by acting as a 'glucose sensor' in pancreatic islets. It has been reported that YH-GKA, a novel benzamide activator of glucokinase, dramatically reduces the mRNA level of PGC-1α and prevents glucotoxicity-induced INS-1 pancreatic β-cell apoptosis [(25)]. Interestingly, PGC-1α overexpression in isolated rat islets induces the expression of G6Pase and suppresses glucokinase and glycerol-3-phosphate dehydrogenase, and therefore blunts membrane depolarization and insulin exocytosis in response to glucose [(26)]. On the other hand, PGC-1α mediates the FFA-induced pancreatic β-cell apoptosis in the development of T2DM, a process known as 'lipotoxicity' [(21)].

Pancreatic β-cell regeneration:

The development of T2DM partly depends on the balance between β-cell proliferation and death (apoptosis). Therefore, the regeneration of pancreatic β cells is considered to be a potentially curative treatment for T2DM. A recent study has demonstrated that the increased expression of PGC-1α is closely related to glucocorticoid-suppressed expansion and transdifferentiation of porcine neonatal pancreatic cell clusters into β cells [(27)]. Subsequently in 2014, the same research team reported that the silencing of PGC-1α by siPGC-1α significantly improved the glucocorticoid-suppressed expansion and transdifferentiation of porcine neonatal pancreatic cell clusters via the FOXO1–PDX1 pathway [(28)]. These data indicate that PGC-1α is a critical regulator of pancreatic β-cell regeneration.

Insulin secretion:

Impaired insulin secretion by pancreatic β cells is a characteristic feature of T2DM. Uncoupling protein 2 (UCP2), a mitochondrial transporter protein, has been reported to participate in the regulation of glucose-stimulated insulin secretion from pancreatic β cells**.** In cold-exposed rats, inhibition of islet PGC-1α expression by antisense oligonucleotide corrects UCP2 expression level and partially normalizes insulin secretion in pancreatic islets [(29)]**.** Oberkofler and coworkers subsequently characterize the underlying mechanism that PGC-1α can enhance the expression of sterol regulatory element-binding protein isoforms (SREBP)-1c via coactivation of the liver X receptor and upregulate the expression of SREBP2 via coactivation of the GR, resulting in an increase in UCP2 expression in INS-1E β cells [(30)]**.**

CONCLUSION

PGC-1α has been implicated in the regulation of genetic pathways leading to homeostatic liver and muscle glucose use, insulin production, and mitochondrial biogenesis.

The expression and activity of PGC-1α are regulated by various cytokines, transcription factors, and other external stimuli via multiple intracellular signaling pathways. This complex pathway should be considered a novel therapeutic strategy and potential pharmacological agent for T2DM treatment.

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