The Role of Sirtuins in Type 2 Diabetes Mellitus

Mohammed Mohammed Hassaan[1], Emam Mohammed Esmayel[1], Samia Hussein[2], Ahmed Khaled Yehia Alkolaly[1*], Mayada Mohammed Mousa[1],

[1] Internal Medicine Department, Faculty of Medicine, Zagazig University

[2] Medical Biochemistry and Molecular Biology Department, Faculty of Medicine, Zagazig University

***Corresponding author:** Ahmed Khaled Yehia Alko

Email: ahalkolaly@gmail.com

Abstract:

The rising incidence of type 2 diabetes mellitus (T2DM) is a major public health concern, and novel therapeutic strategies to prevent T2DM are urgently needed worldwide. Aging is recognized as one of the risk factors for metabolic impairments, including insulin resistance and T2DM. Inflammation, oxidative stress, and mitochondrial dysfunction are closely related to both aging and metabolic disease. Calorie restriction (CR) can retard the aging process in organisms ranging from yeast to rodents and delay the onset of numerous age-related disorders, such as insulin resistance and diabetes. Therefore, metabolic CR mimetics may represent new therapeutic targets for insulin resistance and T2DM. Sirtuin 1 (SIRT1), the mammalian homolog of Sir2, was originally identified as a nicotinamide adenine dinucleotide (NAD^+)-dependent histone deacetylase. The activation of SIRT1 is closely associated with longevity under CR, and it is recognized as a CR mimetic. Currently, seven sirtuins have been identified in mammals. Among these sirtuins, SIRT1 and SIRT2 are located in the nucleus and cytoplasm, SIRT3 exists predominantly in mitochondria, and SIRT6 is located in the nucleus. These sirtuins regulate metabolism through their regulation of inflammation, oxidative stress and mitochondrial function via multiple mechanisms, resulting in the improvement of insulin resistance and T2DM.

Keywords: Sirtuins in Type 2 Diabetes Mellitus, inflammation.

Regul Sci. ™ 2023; 9(1): 8750 - 8756

DOI: doi.org/10.18001 /TRS.9.1. 620

Introduction:

In the early stages of Type 2 DM, insulin resistance is the prominent feature and as a result hyperinsulinemia occurs. Impaired glucose uptake and utilization follow this stage and hyperglycemia and hyperinsulinemia contribute the pancreatic β islet cell destruction with the progression of diabetes (**Janssen, 2021).**

By deacetylating FOXO1 and PGC1α, SIRT 1 induces gluconeogenesis and inhibits glycolysis in liver during fasting. What about the changes of both gluconeogenesis and glycolysis in diabetes

mellitus? **Wu (2021)** showed that hepatic PGC1α is up regulated and gluconeogenesis is also increased which can further aggravate hyperglycemia in diabetic mice. In type 1 diabetes mellitus model of mice, **Yechoor et al (2004**) demonstrated that SIRT3 mRNA is down-regulated. In another study done by **Abduraman et al (2021)** explored that SIRT3 induces the ketogenesis by activating acetyl-coA synthetase in the mammalian cells. Hence, one might expect that SIRT3 might play an important role for the increased ketogenesis observed during diabetes.

Hepatosteatosis is commonly seen in diabetic patients. As mention above, SIRT1,-3 and -4 play an important role in the pathogenesis of this entity. When taken together, inhibition of SIRT1 and 3 and/or activation of SIRT4 might be attributed to this heightened risk of hepatosteatosis in the progression of diabetes (**Nasrin et al., 2010).**

SIRT1 AS A THERAPEUTIC PERSPECTIVE IN T2DM

SIRT1 may participate in the control of glucose homeostasis through the following mechanisms: regulating insulin secretion and protecting pancreatic β-cells; improving insulin resistance via the modulation of postinsulin receptor signaling; decreasing inflammation, lipid mobilization, and adiponectin excretion; controlling fatty acid oxidation and mitochondrial biogenesis; and regulating hepatic glucose production and circadian rhythms, skeletal muscle, adipose tissue, monocytes/macrophages, and the liver (Table 1). Therefore, SIRT1 is a promising pharmacological therapeutic target for the treatment of insulin-resistance and subsequent T2DM (**Kitada and Koya, 2013).**

Table 1. Role of sirtuin 1 on glucose/lipid metabolism in relation to type 2 diabetes mellitus (Kitada and Koya, 2013).

Pancreas	Insulin secretion ↑ β-Cell protection ↑
Insulin signaling	Insulin sensitivity ↑
Inflammation	Insulin sensitivity ↑
Adipose tissue	Lipid mobilization↑ Adiponectin↑
Skeletal muscle	Mitochondria biogenesis ↑ Glucose uptake ↑
Mitochondria	Biogenesis ↑ ROS ↓ Fatty acid oxidation ↑
Liver	Glucose/Lipid metabolism Glucose production Fatty acid oxidation ↑
Circadian rhythm	Glucose/Lipid metabolism

The proposed roles for sirtuin 1 (SIRT1) include regulating insulin secretion and β-cell protection, repression of the inflammation, and regulation of insulin signaling, mitochondrial biogenesis and subsequent reactive oxygen species (ROS) generation, adipogenesis, adiponectin secretion, hepatic glucose/lipid metabolism, and circadian rhythms. SIRT1 can improve insulin resistance and diabetic status (**Kitada and Koya, 2013).**

Several studies have suggested that SIRT1 participates in the regulation of insulin secretion from pancreatic β-cells. The SIRT1 overexpression in β-cells enhances adenosine triphosphate (ATP) production by repressing uncoupling protein (UCP) 2. This process mediates the uncoupling of ATP synthesis from glucose, and elevated ATP levels lead to cell membrane depolarization and Ca^{2+}-dependent insulin exocytosis. β-Cells in SIRT1-deficient mice, however, produce less ATP in response to glucose than do normal mice. By deacetylating FOXO1, SIRT1 also promotes the activation and transcription of NeuroD and MafA, preserving insulin production and promoting β-cell survival *in vivo* (**Luo *et al., 2020,* Jalgaonkar et al., 2022).**

Additionally, **Lee et al. (2009)** demonstrated that SIRT1 protects β-cells against various toxic stresses, such as oxidative stress and cytokines, by suppressing NF-κB signaling. In β-cell-specific SIRT1 overexpression (BESTO) mice, increased SIRT1 levels in pancreatic β-cells improve glucose tolerance and enhance insulin secretion in response to glucose. Moreover, SIRT1 activity decreases with age due to decreased systemic NAD^+ biosynthesis, resulting in the failure of glucose-sensitive insulin secretion in β-cells. However, the administration of nicotinamide mononucleotide, a metabolite that is important for the maintenance of normal NAD^+ biosynthesis, restores glucose-sensitive insulin secretion and improves glucose tolerance in aged BESTO mice (***Kitada et al., 2013***). These findings indicate that SIRT1 modulates glucose-sensing ATP production and insulin secretion from β-cells through UCP2, FOXO1, and NAD^+ metabolism, resulting in protective effects against various toxic stresses through NF-κB pathway activation.

SIRT1 can directly interact with the insulin signaling pathway through several mechanisms. SIRT1 represses the expression of tyrosine phosphatase1 B, which negatively regulates insulin signaling in skeletal muscle, primarily through dephosphorylation of tyrosine residues on the insulin receptor (IR) and insulin receptor substrate (IRS)-1 (**Yang *et al., 2024*).**

Jalgaonkar et al. (2022) reported that SIRT1 regulates the insulin-induced tyrosine phosphorylation of IRS-2 through its deacetylation, which affects a crucial step in the insulin signaling pathway. In brief, the insulin-induced tyrosine phosphorylation of the IR and the activation of SIRT1 deacetylase were suggested to be separate events in the insulin signaling pathway. Although IRS-2 is acetylated at the basal state, insulin treatment leads to the tyrosine phosphorylation of the IR, which further recruits IRSs, including IRS-1 and IRS-2, to its kinase domain. The acetylated lysine residues in IRS-2 prevent IR kinase from further phosphorylating the tyrosine residues in IRS-2. Continued phosphorylation of the tyrosine residues in IRS-2 requires the removal of its acetylated lysine residues by insulin-activated SIRT1, and phosphorylated IRS-2 can then serve as an adaptor protein to further transmit insulin signaling to downstream targets, such as Akt.

Moreover, **Frojdo et al. (2011**) demonstrated that SIRT1 protein expression was decreased in muscle biopsies and primary myotubes that were derived from subjects with T2DM and that this effect was likely due to posttranscriptional modifications, as no differences in SIRT1 mRNA levels were observed between the controls and type 2 diabetic patients. Moreover, SIRT1 interacts in an insulin-independent manner with the phosphoinositide 3-kinase (PI3K) adapter subunit p85 and modulates insulin signaling at physiological insulin concentrations in skeletal muscle cells. PI3K interacts with IRS following insulin-stimulated tyrosine phosphorylation of IR; insulin signaling

can then continue to activate downstream molecules, such as Akt. Therefore, SIRT1 may positively regulate insulin signaling by interacting with PI3K. In addition, the SIRT1 activator resveratrol protects muscle cells, including human primary myotubes, from TNF-α or prolonged hyperinsulinemia-induced insulin resistance. SIRT1 protein can be detected in both nuclear and cytosolic fractions by cell fractionation, and interestingly, nuclear-associated SIRT1 interacts with cytoplasmic proteins, such as IRS-2.

Chronic low grade tissue inflammation is an important etiologic component of insulin resistance and T2DM. Elevated levels of proinflammatory cytokines, such as TNF-α, IL-6, and CRP, in the blood have been detected in individuals with insulin resistance and T2DM. The activation of monocytes in the circulation and adipose tissue has been demonstrated to lead to the release of various inflammatory mediators. Additionally, it has been demonstrated that macrophages residing in adipose tissue may also be a source of inflammatory factors and that these cells may modulate the secretory activity of adipocytes. Tissue macrophages, which are derived from blood monocytes play a central role in both orchestrating and initiating obesity-related tissue inflammatory responses. Moreover, monocytes/macrophages and adipose tissue have reported to exhibit significantly increased binding to NF-κB, the key proinflammatory transcription factor, and an increased levels of intranuclear expression of p65 (Rel A), the major protein component of NF-κB. Thus, the suppression of inflammatory cytokines overproduction in monocytes/macrophages and adipocytes may improve insulin resistance and T2DM. Decreased SIRT1 expression levels in circulating monocytes are correlated with metabolic syndrome, insulin resistance, and glucose intolerance in humans (***de Kreutzenberg et al., 2010***).

Moreover, **Gillum et al. (2011)** reported that SIRT1 expression was reduced in adipose tissues of obese males. In addition, mRNA expression of CD14, a macrophage marker, in adipose tissue is negatively correlated with SIRT1 expression. These data indicate that SIRT1 may contribute to the regulation of inflammation in monocytes/macrophages and adipose tissue in humans.

Schug et al. (2010) also demonstrated that myeloid cell-specific SIRT1 knockout mice that were challenged with a high fat diet displayed high levels of activated macrophages in the liver and adipose tissues, thereby predisposing these animals to the development of systemic insulin resistance and metabolic derangement. SIRT1 physically interacts with the p65 subunit of NF-κB and inhibits transcription by deacetylating p65 at lysine 310, leading to the suppression of inflammatory processes.

Yoshizaki et al. (2009) provided direct evidence that SIRT1 activation reduced the TNF-α-induced inflammatory response, potentially via the deacetylation of NF-κB (p65) in insulin-resistant adipocytes. Moreover, these authors reported that SIRT1 knockdown in 3T3-L1 adipocytes increased NF-κB (p65) acetylation and enhanced NF-κB binding to target inflammation-related genes promoters. In addition, **Yoshizaki et al. (2010**) reported that SIRT1 represses the activity of the IκB kinase (IKK)-NF-κB signaling pathway, inflammation-related gene expression, and the release of TNF-α following lipopolysaccharide stimulation in macrophages. These authors reported that the pharmacological SIRT1 activator SRT1720 or resveratrol induced various anti-inflammatory activities. Furthermore, the treatment of obese and insulin-resistant

Zucker fatty rats with another SIRT1 activator, SRT2379, led to improved glucose tolerance, enhanced systemic insulin sensitivity, and the normalization of tissue markers of inflammation.

Additionally, a report provided another mechanism with which to explain how SIRT1 inactivation induces inflammation in THP-1 cells. Specifically, SIRT1 inhibition may activate the NF-κB signaling pathway through the phosphorylation of NF-κB (p65) via the dysregulation of autophagy, resulting in the cellular accumulation of p62/Sqstm1. Moreover, the nutrient-sensing pathway regulates autophagy and involves SIRT1, mammalian target of rapamycin (mTOR) and 5' adenosine monophosphate (AMP)-activated kinase (AMPK). Notably, SIRT1 inactivation resulted in increased mTOR pathway activation and reduced AMPK activation, leading to impaired autophagy. Thus, SIRT1 may attenuate the inflammatory reaction in adipose tissues and monocytes/macrophages and thereby improve insulin resistance and T2DM (***Takeda-Watanabe et al., 2012*).**

Adipocytes play critical roles in the development of insulin resistance and T2DM given that they can store excess saturated lipids and produce adipokines. PPAR-γ is an essential molecule for the modulation of fatty acid storage and glucose metabolism, and this factor is involved in adipose tissue differentiation. In mature white fat cells, PPAR-γ regulates the induction of genes that are involved in free fatty acid (FFA) uptake and triglyceride synthesis, thereby increasing the lipid storage capacity of the cell (**Supriya *et al., 2024***). SIRT1 binds to PPAR-γ by docking to the nuclear receptor corepressor and silencing the mediator of retinoid and thyroid hormone receptors, effects that represses the transcription-activating effects of PPAR-γ. Furthermore, SIRT1 overexpression was observed to lead to decreased fat storage and increased lipolysis, resulting in fat mobilization in response to food limitation, whereas SIRT1-null mice exhibited a significant reduction in body weight (**Kitada *et al., 2013*)**.

Additionally, in the adipose tissue of those SIRT1-null mice, the average size of the adipocytes was smaller, the content of the extracellular matrix was lower, adiponectin and leptin were expressed at 60% of the normal level, and adipocyte differentiation was reduced. Moreover, a recent report demonstrated that SIRT1 promotes browning of white fat. SIRT1 deacetylates ligand-bound PPAR-γ on Lys268 and Lys293; therefore, SIRT1 and PPAR-γ coordinately induce the browning of white adipose tissue. These data indicate that SIRT1-dependent PPAR-γ deacetylation regulates energy homeostasis, promoting energy expenditure over energy storage. Therefore, the combination of thiazolidinediones with SIRT1 activator has potential as a therapy for obesity. Adiponectin exerts an antidiabetic effect, and plasma adiponectin levels are decreased in the contexts of obesity, insulin resistance, and T2DM. The administration of adiponectin has been demonstrated to induce glucose-lowering effects and to improve insulin resistance in mice (***Xu et al., 2012*).**

Moreover, adiponectin-deficient mice exhibit insulin resistance and diabetes. The mechanisms by which adiponectin exerts its insulin-sensitizing effects may be mediated by an increase in fatty acid oxidation via the activation of AMPK and PPAR-α. Additionally, SIRT1 regulates adiponectin expression in adipocytes and FOXO1 forms a transcriptional complex at the mouse adiponectin promoter with CCAAT/enhancer-binding protein α (C/EBPα) (**Engin, 2024).**

Thus, SIRT1 deacetylates FOXO1 and enhances its interaction with C/EBPα, resulting in the enhanced transcription of the gene that encodes adiponectin in adipocytes. Moreover, a study of muscle adiponectin receptor (adipoR) 1KO mice demonstrated that this protein has a crucial role in the physiological and pathophysiological significance of adiponectin in muscle cells and is involved in the regulation of Ca^{2+} signaling as well as PGC-1α expression and activation. Adiponectin activates AMPK by biding to adipoR1, thereby activating SIRT1 and deacetylating PGC-1α to improve mitochondrial function, oxidative stress, glucose and lipid metabolism, and exercise endurance (***Iwabu et al., 2010***).

SIRT1 can affect glucose-lipid metabolism and insulin resistance through the modulation of mitochondrial function. The maintenance of energy and nutrient homeostasis during nutrient deprivation is accomplished through an increase in mitochondrial fatty acid oxidation in skeletal muscle. Previous studies have demonstrated a reduced rate of mitochondrial oxidative phosphorylation (OXPHOS) activity and increased intramyocellular lipid accumulation in the skeletal muscle of insulin-resistant patients with type 2 diabetes and elderly individuals (**Kitada *et al., 2013***).

Specifically, these data indicate that defects in mitochondrial function may play an important role in T2DM pathogenesis. An important component that drives this cellular oxidative process in mitochondria is the transcriptional coactivator PGC-1α. PGC-1α activation in skeletal muscle leads to efficient β-oxidation of fatty acids, which is coupled to mitochondrial OXPHOS. In addition, PGC-1α maintains higher numbers of active mitochondria and OXPHOS protein, the levels of which are decreased in T2DM. Through PGC-1α regulation, SIRT1 modulates mitochondrial function and metabolic homoeostasis, increases the consumption of oxygen in muscle fibers and induces the expression of OXPHOS genes and mitochondrial biogenesis. Remarkably, the PGC-1α-induced upregulation of genes that regulate mitochondrial fatty acid utilization was largely prevented by SIRT1 knockdown (**Qian *et al., 2024***).

Furthermore, SIRT1 can regulate PPAR-α activation through PGC-1α deacetylation, leading to the increased fatty acid oxidation. Thus, SIRT1 activation may improve insulin resistance via accelerated fatty acid oxidation and mitochondrial biogenesis in skeletal muscle. In addition to the effect of increased lipid utilization via PGC-1α-mediated mitochondrial biogenesis, PGC-1α markedly upregulates glucose transporter 4 (GLUT4) expression and glucose transport activity in murine C2C12 myotubes. The effects of PGC-1α on the activation of GLUT4 gene expression are reflected in the increased ability of myocytes to transport glucose, suggesting that the SIRT1-regulated activation of PGC-1α influences insulin sensitization (**Zeng and Chen, 2022*)*.

The liver plays a central role in glucose and lipid metabolism in response to nutritional and hormonal signals. In a fasted state, the induction of hepatic glucose output and fatty acid oxidation is essential to sustain energetic balance. The production of glucose by the liver is controlled through a complex network of transcriptional regulators. During the early stage of fasting, glucagon induces cyclic AMP (cAMP) response element-binding (CREB) and CREB-regulated transcription coactivator 2 (CRTC2) to drive the expression of gluconeogenesis-related genes that supply the body with the necessary glucose. At the late stage of fasting, SIRT1 is activated and deacetylates CRTC2 to reduce the effects of glucagon (**Dimitriadis *et al., 2021***).

Moreover, at that time, SIRT1 can activate PGC-1α and FOXO1 through a deacetylation reaction, resulting in the induction of gluconeogenesis-related genes. Thus, SIRT1 participates in the regulation of the metabolic switch that controls the shift from the early to the late phase of gluconeogenesis during fasting to maintain glucose homeostasis. Conversely, various reports using animal models have indicated that SIRT1 may have an antidiabetic function. Transgenic mice with moderate SIRT1 overexpression exhibited improved glucose tolerance due to reduced glucose output from the liver (**Guo *et al., 2023*).**

References: