



Bisphenol A instigates diminished sirtuin-1 mediated vascular complications in type 2 diabetes mellitus

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ABSTRACT

Endocrine society has evidence that plastics can disrupt the endocrine system to cause severe diseases in humans and animals. However, plastics are still used in a variety of models for their applications. The overproduction of plastics simultaneously increases health hazards in human and animal living society. The pancreas is an endocrine system to produces insulin to maintain the glucose level in the blood when that insulin level resists or does not synthesize causing diabetes mellitus. It is one of the highest prevalence diseases occurred in worldwide. Sirtuin-1 is a protein involved in glucose homeostasis and it regulates insulin action. In the human body, hampered the level of insulin, sirtuin-1, and glucose cause diabetes and its vascular complications. Furthermore, many researchers evidenced that the endocrine disruptor of bisphenol A (BPA) causes diabetes mellitus and its vascular complications. Nevertheless, the biological pathway is unclear. This review discusses the linkage between the endocrine disruptor of BPA and diabetes and explores Sirtuin-1 mediated BPA-induced diabetic vascular complications.

Implication for health policy/practice/research/medical education:

The endocrine disruptor BPA has a possible mechanism to decrease the sirtuin protein to develop diabetes-associated vascular complications. We explored the possible mechanism of sirtuin-induced diabetes and related vascular complications with the impact of BPA.

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Introduction

Diabetes mellitus (DM) has been the most common disease and International Diabetes Federation (IDF)-2021 reports that there are 541 million people with impaired glucose tolerance worldwide. When insulin level is hampered or resists insulin action leads to type 2 diabetes mellitus (T2DM). In T2DM, uncontrolled blood glucose disrupts the renal function system, cardiovascular system, cerebrovascular system, and peripheral nerve system causing vascular complications such as cardiovascular disease, peripheral arterial disease, stroke, diabetic nephropathy, retinopathy, and neuropathy (1).

The sirtuin-1 (SIRT1) protein has received a lot of attention as an epigenetic regulator for a variety of physiology and is a member of the silent information

regulator 2 (Sir2) protein family. It has seven types of proteins are SIRT1 to 7. All these sirtuin proteins are located in different localities and have unique functions and characteristics are described in Table 1. Sirtuin proteins are involved in cellular functions and regulate glucose and fatty acid metabolism. Hampered Sirtuin protein is associated with a wide range of diseases such as diabetes, obesity, cancer, and neurodegeneration (2,3). Researchers found the association of SIRT1 with insulin resistance and metabolic syndrome in peripheral blood mononuclear cells. In that study, both in vivo and in vitro found that SIRT1 significantly correlated with insulin secretion through activation of peroxisome proliferator-activated receptor- γ coactivator-1-alpha (PGC-1 α) and forkhead box protein O1 (FoxO1). Researchers found

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Table 1. Sirtuins protein localization and functions

Sirtuins	Localization	Enzyme activity	Functions
SIRT1	Nucleus	Deacetylase	Mitochondrial biogenesis (+) Insulin secretion (-) Adipogenesis (-) Lipogenesis (-)
SIRT2	Cytoplasm	Deacetylase, ADP-ribosyltransferase, Demyrystoylase	Adipogenesis (-) Lipogenesis (+), Fatty acid oxidation (+), Insulin sensitivity (-) in skeletal muscle, Mitochondrial dysfunctions (-)
SIRT3	Mitochondrial	Deacetylase, Decrotonylase	Fatty acid oxidation (+), Insulin resistance (-) in skeletal muscle
SIRT4	Mitochondrial	ADP-ribosyltransferase, Deacetylase, Lipoamidase	Fatty acid oxidation (-) Lipogenesis (+) Insulin secretion (-) Mitochondrial biogenesis (-)
SIRT5	Mitochondrial	Deacetylase	Ammonia detoxification (+), Regulate glucose oxidation and cellular antioxidant defense (+)
SIRT6	Nucleus	Deacetylase	Insulin resistance (-) Gluconeogenesis (-)
SIRT7	Nucleus	Deacetylase	Adipogenesis (+), Fatty acid uptake (+), Hepatic Lipid accumulation (+)

(+) Increased, (-) Decreased.

evidence for the relationship between SIRT1 and glucose homeostasis in diabetes and prediabetes groups. That study showed the down-regulation of SIRT1 occurred in pre-diabetics compared to those with normal glucose regulation (4).

Endocrine-disrupting chemicals (EDCs), which are man-made synthetic compounds such as dioxin, bisphenol A (BPA) and phthalates are abundant in the environment. EDCs enter the human cells by bounding with nuclear receptors such as estrogen receptors, androgen receptors, glucocorticoid receptors, and progesterone receptors to cause health problems. Recently, EDCs like BPA have received special attention for their mechanistic role in metabolic disruption and this man-made synthetic compound is used to make less expensive plastic containers, water bottles, and thermal paper, which cause human health issues including diabetes, hypertension, kidney disease, and cancer (5).

According to a study of the literature, BPA interferes with the body's metabolic processes, which can result in diabetes mellitus and diabetic vascular complications. Moreover, a review of the literature revealed a dearth of research detailing the molecular mechanisms underlying BPA's role in the development of diabetic vascular complications. This review explores the role of BPA in diabetic vascular complications and discusses BPA/SIRT1 axis to develop the diabetic vascular complications in T2DM.

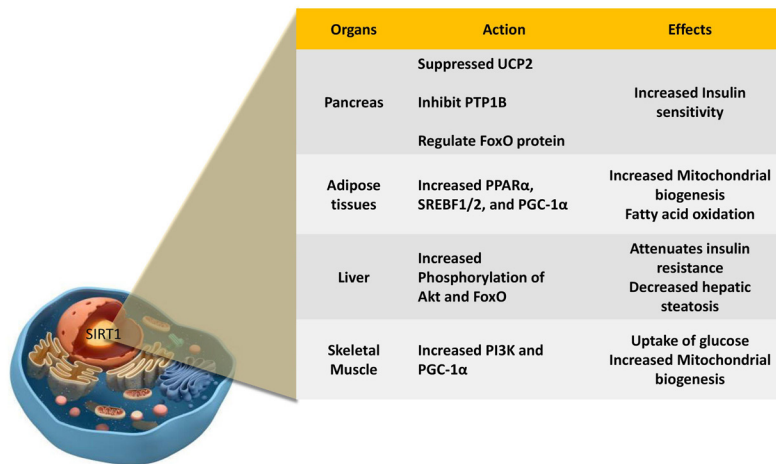
Relationship between SIRT1 and T2DM

SIRT1 is located in the cell nucleus of skeletal muscle, liver, pancreas, and adipose tissues. Pancreatic beta cell dysfunction is a key risk factor to develop T2DM. In

these pancreatic beta cells, increased levels of SIRT1 directly bind with the promoter region of the uncoupling protein 2 (UCP2) to increase ATP production leading to enhance insulin secretion. When the SIRT1 level is reduced the active UCP2 inhibits insulin production (6). Likewise, another insulin secretion inhibitor protein tyrosine phosphatase 1b (PTP1B) is negatively correlated with insulin secretion. SIRT1 protein enhances insulin action by inhibiting the activity of PTP1B, which is the inhibitor of the insulin receptor (7). FoxO1 plays a crucial role in the pancreas, which protects the beta cells and secretes more insulin to the maintained glucose level in the blood. In pancreatic beta cells, when the FoxO1 level was decreased to induce oxidative stress by hyperglycemia leads to decreased transcription factors such as NeuroD and Mafa. These transcription factors are the regulator for insulin secretion in pancreatic beta cells (8).

High levels of mTORC1 activity were found in SIRT1 deficient mice leading to resisting insulin signaling and causing T2DM. However, supplementation of SIRT1 attenuates insulin resistance, maintains glucose homeostasis, and decreased steatosis in hepatic. Moreover, the researcher demonstrated the linkage between the SIRT1 and FoxO protein. In that study, SIRT1 deletion mice expressed a low level of phosphorylated Akt and FoxO in the liver leading to insulin resistance. Reduced SIRT1/ mTORC /Akt/FoxO pathway to enhance the expression of glucose 6-phosphatase (G6Pase) and phosphoenolpyruvate carboxykinase (PEPCK) and increased glucose production and diminished synthesis of glycogen in the liver (9).

An animal study found the association of depleted SIRT1 with adipose dysfunction and lipid metabolism,



Organs	Action	Effects
Pancreas	Suppressed UCP2	Increased Insulin sensitivity
	Inhibit PTP1B	
	Regulate FoxO protein	
Adipose tissues	Increased PPAR α , SREBF1/2, and PGC-1 α	Increased Mitochondrial biogenesis Fatty acid oxidation
Liver	Increased Phosphorylation of Akt and FoxO	Attenuates insulin resistance Decreased hepatic steatosis
Skeletal Muscle	Increased PI3K and PGC-1 α	Uptake of glucose Increased Mitochondrial biogenesis

Figure 1. Sirtuin-1 functions in different organs with metabolic actions.

evidenced by white adipose tissue markers of PANK3 and AGT increased and decreased level of brown adipose tissue (BAT) markers PRDM16 found in adipose tissues. In that study, adipose dysfunction biomarkers were elevated with found decreased levels of fatty acid oxidation transcription factors in adipose cells including PPAR α , SREBF1/2, and PGC-1 α , which led to decreased fatty acid oxidation and impaired mitochondrial functions causing metabolic alteration that leads to T2DM. SIRT1-dependence of SREBF1c and PPAR activation was effectively confirmed by the negative correlation of transcription factors with SIRT1. Supplementation of the SIRT1 activator leads to promoting both mitochondrial biogenesis and fatty acid metabolism (10).

Relationship between SIRT1 and diabetic macrovascular complications

SIRT1 deacetylase is protect the endothelial cells through maintain their structural integrity and preventing cellular senescence. Diminished SIRT1 levels disrupt endothelial dysfunction to affect the cardiovascular system through aging (11). Researchers demonstrated that decreased SIRT1 induced atherosclerosis developed in ApoE $^{-/-}$ mice as well as disturbing autophagy through irregular lipid-droplet formation in THP-1 cells (12). SIRT1 protects the body from a neurodegenerative disorder through decreased ROCK1 protein to regulate the amyloid beta secretion. Loss of SIRT1 protein in the central nervous system to induce aging leads to cerebrovascular diseases (13). mTOR mammalian target of rapamycin (mTOR) drives Cerebrovascular dysfunction and cognitive disease like Alzheimer's (14). In both animal and cell lines studies, researchers found that SIRT1 knockout animals and SIRT1 null cells expressed more mTOR and this level was dropped by the treatment of the SIRT1 activator (15).

Relationship between SIRT1 and diabetic microvascular complications

Sirt1 protects the kidney when its level is decreased to

induce kidney-related diseases and diabetic nephropathy. In the proximal renal tubule, diminished SIRT1 leads to increased claudin-1 to causes podocytes in diabetic kidneys, which results in albuminuria (16). SIRT1 protects the kidney through deacetylating transcription factors like nuclear factor kappa B (NF- κ B), Smad3, FOXO, and p53 in diabetic kidney disease (17). In the animal study, researchers found the association of sirt1 with diabetic retinopathy. In that study, SIRT1 deletion gradually resists the vascular endothelial cell migration through inhibition of vascular endothelial growth factor (VEGF)-A, Vascular endothelial growth factor receptor-2 (VEGFR-2), metalloproteinase-14 (MMP-14), and hypoxia-inducible factor-1 α (HIF-1 α) expression leading to diabetic retinopathy (DR) (18). Uncontrolled glucose accumulates in nerves leading to neuropathy in T2DM and reduced SIRT1 levels were unable to control the neuronal degeneration pathway leading to diabetic neuropathy and distal axonopathy. SIRT1 to control mitochondrial activity in the peripheral nerve through PGC-1 α (19).

The strong association of bisphenol A with diabetes mellitus

Endocrine-disrupting chemicals, which are man-made synthetic compounds such as dioxin, BPA, phthalates, etc, are abundant in the environment and these EDCs are causing health problems in both human beings and animals. BPA is used to make less expensive plastic containers, water bottles, and thermal paper, which cause human health issues including diabetes, hypertension, kidney disease, and cancer (20). In the US, the National Health and Nutrition Examination Survey 2003-2004 study found a positive association of BPA with diabetes and obesity. That study found a higher urinary level of BPA concentration in obesity-associated diabetes subjects than the normal subjects (21). In China, a study conducted with 40 years of old adults found a higher body mass index (BMI) and insulin resistance in obese subjects, who also had a higher level of BPA (22). An Indian study confirms

that the serum BPA level was detected higher in diabetic subjects than the normal subjects (23).

Development of macrovascular disease by BPA/SIRT1/NLRP3/CASPASE-1/IL-1 β axis in diabetes

Nucleotide-binding, leucine-rich repeat containing proteins (NLR) family pyrin domain containing 3 (NLRP3) is a component of the inflammasome and is predominantly expressed in macrophages to regulate interleukin (IL)-1 β production. Innate immunity system components of NLRP3 to activate caspase-1 lead to initiate's inflammatory response through activation of IL-1 β (24). In an animal study, chronic BPA exposure significantly decreases SIRT1 levels and raises inflammatory cytokines, which activate macrophages in the atherosclerotic plaque locations. Additionally, the researcher found the increased levels of caspase-1, which induced myocardial apoptosis, which was the main progression of heart failure. However, resveratrol treatment greatly reduced NLRP3 and caspase 1 activation as well as interleukin-1 production that was exacerbated by BPA (25). The peripheral immune cells and inflammatory molecules play a vital role in central nervous disorders. Both systemic and local inflammation is the main driver of the peripheral and central immune response against the infection. SIRT1 decreased the level of NLRP3 followed by suppressing the maturation of caspase-1 and IL-1 β (26).

Development of micro-vascular disease by BPA/SIRT1/NMN/CLAUDIN-1 axis in diabetes

SIRT1 is involved in maintaining the cytoskeletal integrity and protecting the kidney from podocytes. SIRT1 administration showed a restoration of SIRT1 levels and protects the kidney from albuminuria, glomerular hypertrophy, and kidney fibrosis (27). Nicotinamide

mononucleotide (NMN) is the precursor of nicotinamide adenine dinucleotide (NAD⁺) and it regulates various cell functions, including DNA repair, metabolism, cell growth, and survival. In an animal study, NMN has administered to diabetic rats and showed enhanced insulin sensitivity by restoring normal NAD⁺ levels. Administration of NMN enhances insulin sensitivity in overweight or obese postmenopausal women with prediabetes (28). Claudin-1 are tight junction membrane protein present in the glomerular nephron of the kidney. An enhanced level of claudin-1 occurred in podocytes in diabetes (29). SIRT1 is the key regulator for both claudin1 and NMN, when increased SIRT1 enhances the NMN level and down streamed the claudin-1 level to protect the kidney from podocytes. SIRT1/NMN /claudin1 axis regulates the normal process of the glomerulus, when the SIRT1 level decreased it causes albuminuria (30).

Conclusion

Based on the review of literature, SIRT1 is conducted as the best therapeutic compound to treat diabetes and diabetes-associated vascular complications. However therapeutic purpose administrated SIRT1 levels may be hampered by endocrine disruptor chemical of BPA and less level of SIRT1 only involved in treatment mechanisms lead to the effective treatment given to patients. Few research articles described the association and metabolic pathway between BPA and SIRT1 protein. This review is explained SIRT1 mediated BPA enhanced diabetic vascular complications via BPA/SIRT1/NLRP3/CASPASE-1/IL-1 β axis and BPA/SIRT1/NMN/CLAUDIN-1 axis respectively macro and microvascular complications. Further study will be needed to understand the xenobiotic activity of BPA and it will help to treat or recover patients from disease or illness of health.

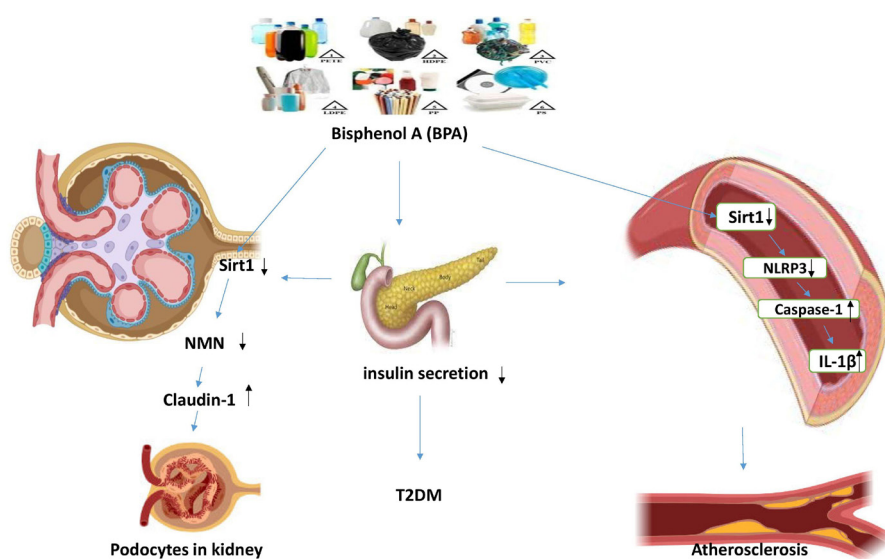


Figure 2. SIRT1 mediated BPA induced macro and micro vascular complications.

Authors' contribution

Conceptualization: Mohanraj Nehru.
Data curation: Prasanth Subramanian.
Formal analysis: Venkataraman Prabhu.
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Conflicts of interest

No conflict of interest was declared by the authors.

Ethical issues

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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