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# The correlation between S-nitrosylation and type 2 diabetes mellitus: a review

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**Abstract**

Type 2 diabetes mellitus (T2DM) represents a chronic metabolic disorder, constituting over 90% of all diabetes cases. Its primary characteristics include insulin deficiency and insulin resistance. The aetiology of T2DM is complex, which is attributed to a convergence of genetic and environmental factors. Moreover, it can engender various complications such as diabetes retinopathy, diabetes nephropathy, and diabetes neuropathy. T2DM cannot be cured fundamentally, it can only delay the development of the disease by controlling the blood sugar level. If the blood sugar is at a high level for a long time, it will aggravate the disease progress, and even lead to death in serious cases. Therefore, understanding the pathogenesis of diabetes, early detection, and intervention are the main means of treatment. S-nitrosylation (SNO), a post-translational modification of proteins based on redox, possesses the capacity to regulate a variety of physiological and pathological processes, and it is also involved in the occurrence and development of T2DM. However, the relationship between the dysregulation of SNO homeostasis and the occurrence of diabetes is not fully understood. This article reviews the correlation between SNO and T2DM, elucidating the mechanism by which SNO contributes to T2DM, encompassing diminishing insulin secretion, inducing insulin resistance, and affecting glucokinase activity. Understanding the correlation between SNO and T2DM provides a new research direction for the pathogenesis and treatment targets of diabetes. **(Endokrynol Pol 2024; 75 (5): 473–478)**

**Key words:** *S-nitrosylation; type 2 diabetes mellitus; insulin resistance; glucokinase*

## Introduction

Diabetes stands as a complex chronic metabolic ailment, distinguished by hyperglycaemia and various complications [1]. It primarily manifests in 2 classifications: type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM), with T2DM constituting approximately 90% of all diabetes cases [2]. The aetiology of T1DM lies in the destruction of cellular immunity, whereas T2DM ensues from decreased insulin sensitivity and insulin resistance (IR) [3]. Diabetes poses a substantial global health challenge, with the incidence rate and prevalence rate witnessing a notable surge in recent years, owing to the change of lifestyle and dietary habits. It is estimated that by 2045, approximately 693 million people worldwide will be afflicted with diabetes [4]. Diabetes not only compromises the quality of life for patients, but also imposes a substantial economic burden on medical systems. Depending on the different affected tissues, the complications of diabetes can be categorised into diabetes nephropathy (DN), diabetes peripheral neuropathy (DPN), and diabetes cardiovascular disease (DCD), among others [5–7]. The management of diabetes poses considerable difficulty due to the multitude of factors influencing its onset, the complexity of its pathological progression, and the gradual decline in $\beta$-cells function with the prolongation of the disease course. Presently, for certain special patients, monotherapy with a single hypoglycaemic drug is inadequate for maintaining ideal blood glucose levels, necessitating the combination of multiple drugs to achieve diverse therapeutic effects to stabilise blood glucose. Consequently, delving deeper into the pathogenesis and contributing factors of diabetes, alongside the development of targeted therapeutic drugs, emerges as a novel direction for diabetes treatment.

S-nitrosylation (SNO) denotes the covalent connection between a portion of nitrite (NO) and the thiol residue (S) of a protein, forming S-nitroso. The thiol residue belongs to a subset of specific cysteine residues in proteins, yielding the resultant SNO, denoted as SNO protein [9]. The half-life of SNO protein is notably short, with various reductases present in the cytoplasm capable of denitrosylating proteins, including glutathione (GSH) and thioredoxin [10]. Hence, SNOs are commonly stored in the folds of the plasma membrane, vesicles, stroma, and lipophilic proteins to forestall denitrification by reductases. The process of SNO is reversible, with denitrification being an enzyme-catalysed process that reverses the SNO process [11]. Nonetheless, SNO

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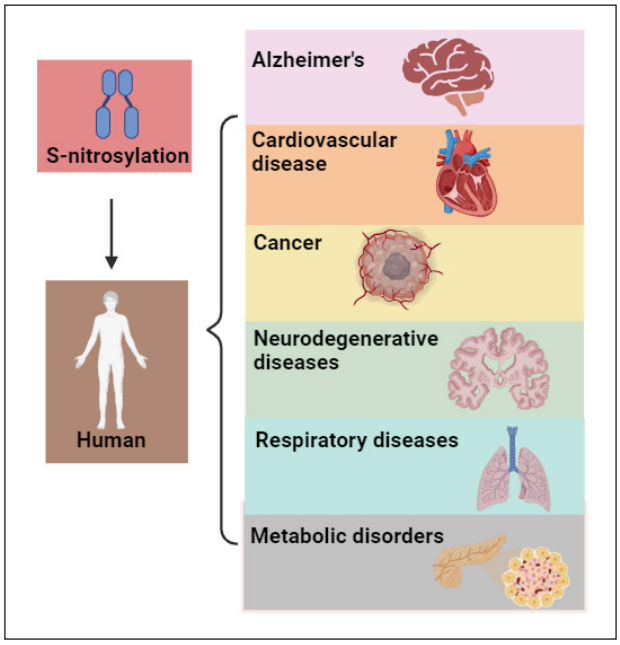


**Figure 1.** *S-nitrosylation (SNO) is implicated in various human diseases such as Alzheimer's disease, cardiovascular disease, cancer, neurodegenerative diseases, respiratory diseases, and metabolic disorders*



is not a stochastic event and specifically targets certain cysteine residues [12]. Abnormal SNO may result in protein misfolding, synaptic damage, and cell apoptosis, and it is implicated in various human diseases such as Alzheimer's disease, cardiovascular disease, cancer, neurodegenerative diseases, respiratory diseases, and metabolic disorders [13–18] (Fig. 1).

Similarly, elevated levels of SNO have been observed in patients with T2DM, with several studies affirming that modulating SNO can contribute to the management of diabetes and its complications. Chen et al. demonstrated that basic fibroblast growth factor (bFGF) can mitigate endothelial damage in diabetes by suppressing inflammatory reactions through the regulation of the SNO pathway [19]. Additionally, Chao *et al.* also found an increased SNO level of guanine nucleotide-binding protein 2 (GNAI2) at cysteine 66 in coronary artery samples from diabetes mice and patients with diabetes. Following melatonin treatment, the SNO-GNAI2 level decreased, concomitant with a reduction in atherosclerosis in diabetes mice and restoration of endothelial cell function [20]. Therefore, SNO exerts a significant influence on the onset and progression of diabetes. This article reviews the pathogenesis of SNO affecting T2DM and offers a novel therapeutic target for T2DM treatment (Fig. 2).

## Primary mechanisms underlying T2DM induced by SNO

### *The protein related to insulin secretion undergoes SNO, inhibits insulin secretion, and then induces the development of T2DM*

The production and secretion of insulin operate as largely independent processes. Mature insulin is stored

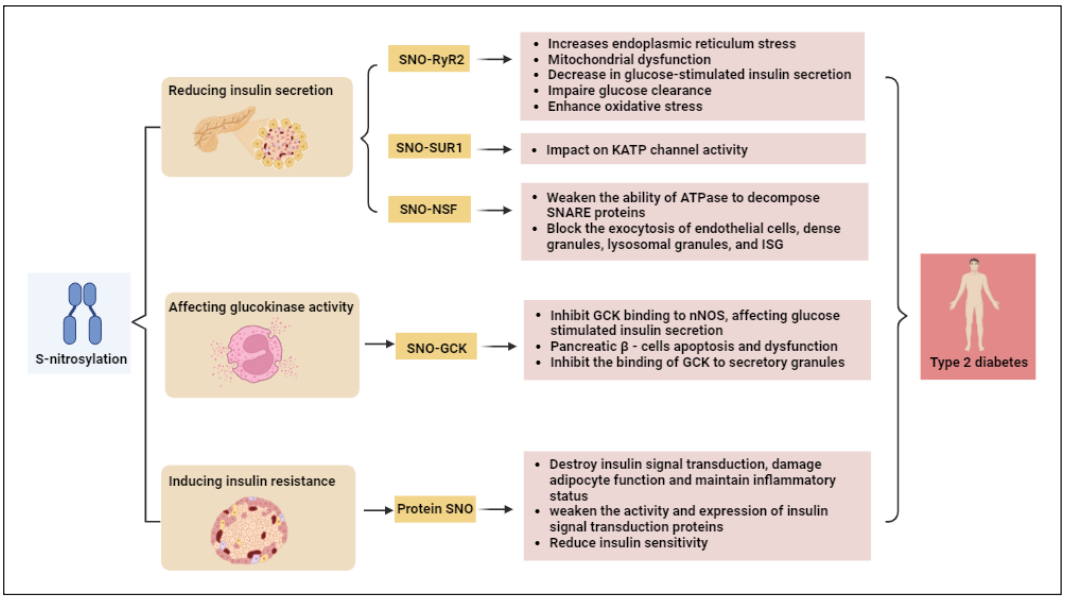


**Figure 2.** *Primary mechanisms underlying type 2 diabetes mellitus (T2DM) induced by S-nitrosylation (SNO). Encompassing diminishing insulin secretion, inducing insulin resistance, and affecting glucokinase activity. RyR2 — type 2 ryanodine receptor; SUR1 — sulfonylurea receptors 1; NSF — N-ethylmaleimide sensitive factor; GCK — glucokinase; KATP — adenosine triphosphate-sensitive potassium; ATP — adenosine triphosphate; SNARE — soluble N-ethylmaleimide sensitive factor attachment protein receptor; ISG — insulin secretory granules; nNOS — nitric oxide synthases*

in insulin secretory granules (ISG) within β-cells. Upon elevation of blood glucose levels, intracellular calcium concentrations rise, prompting ISGs to undergo fusion to secrete insulin [21]. Indeed, it is known that type 2 ryanodine receptor (RyR2) serves as the primary factor for $Ca^{2+}$ release on the endoplasmic reticulum (ER) membrane. Alterations in RyR2 can lead to diminished glucose-stimulated insulin secretion (GSIS) and compromised glucose clearance, involving various pathological processes, including endoplasmic reticulum stress (ERS) and mitochondrial dysfunction [22]. It has been verified that nitrosylation of RyR2 in β-cells precipitates heightened ERS increases, further impairing GSIS. Concurrently, impediments to glucose clearance result in elevated blood glucose levels and diabetes [23]. A study investigating the association between RyR2 nitrosylation and T2DM in diabetes mice revealed that RyR2-SNO augments oxidative stress in β-cells and triggers ERS in both patients with diabetes and mouse β-cells [24].

The adenosine triphosphate-sensitive potassium (KATP) channel plays a critical role in insulin secretion, furnishing energy to β-cells and sustaining an electrically excited state, which can be inhibited by ATP and activated by adenosine diphosphate (ADP) [25]. Sulfonylurea receptor 1 (SUR1) constitutes one of the principal subunits regulating ATP channels, facilitating KATP channel opening through binding to ADP [26]. Thus, SUR1 serves to enhance insulin secretion and is employed as a therapeutic target in clinical diabetes management [27]. Abnormal SUR1 will influence the KATP channel, contributing to metabolic diseases such as congenital hyperinsulinaemia and neonatal diabetes [28]. Nitric oxide (NO) activates the KATP channel in mammalian sensory neurons by binding to SNO-SUR1 at cysteine 717 (Cys717). Mutation of Cys717 on alanine restricts NO-induced KATP channel activation, underscoring the pivotal role of SNO-SUR1 in KATP channel regulation [29].

The secretion of ISG is also subject to regulation by exosomes and is associated with soluble N-ethylmaleimide sensitive factor attachment protein receptor (SNARE) complexes and Munc18 protein [30]. SNARE proteins, positioned on organelles and vesicles, act as transmembrane proteins capable of instigating vesicular fusion and participating in ISG secretion [31]. N-ethylmaleimide sensitive factor (NSF) functions as an ATPase that hydrolyses ATP to disassemble SNARE complexes, facilitating their recycling and fusion with membranes for further utilisation [32]. Nevertheless, when NSF undergoes SNO, it loses its capacity to hydrolyse ATPase, diminishes its ability to decompose SNARE protein, and impedes the exocytosis of endothelial cells, dense granules, lysosomal granules, and ISG topics, thereby impacting insulin secretion [33]. NSF is modified at 3 cysteine residues (Cys 11, 91, and 264). The SNO of Cys-11 hinders the interaction between NSF and SNARE complexes, whereas the SNO of Cys-91 and Cys-264 enables the interaction between NSF and SNARE complexes but prevents the decomposition of NSF in SNARE complexes [34].

### *Glucokinase undergoes SNO, reduces its activity, and then develops into T2DM*

Glucokinase (GCK) stands as the principal regulator of β-cell metabolism and insulin secretion, assuming a pivotal role in glucose-stimulated insulin secretion in pancreatic β-cells [35]. The inactivation of GCK precipitates a decline in glucose stimulated insulin secretion and mild fasting hyperglycaemia [36]. The localisation and survival of GCK in β-cells mainly depend on its binding ability to neuronal nitric oxide synthases (nNOS). Investigations have revealed that when GCK undergoes SNO, it hampers its binding to nNOS, thereby impacting glucose-stimulated insulin secretion [37]. Jin et al. found that in ethanol-fed mice, the capacity of pancreatic β-cells to produce insulin was diminished, accompanied by decreased expression of GCK and insulin. Upon further exploration of the mechanism, it emerged that the inactivation and downregulation of GCK are principally mediated by peroxynitrite generated through ethanol metabolism. Chronic ethanol can trigger tyrosine nitrosylation of GCK, leading to downregulation and inactivation of GCK, culminating in apoptosis and dysfunction of pancreatic β-cells [38]. It is well-known that the binding of GCK to insulin secretory granules is regulated by NOS. When GCK undergoes SNO, it inhibits its binding to NOS, thereby influencing insulin secretion. An investigation into the function of GCK revealed the existence of 2 pathways by which GCK experiences SNO alterations. One pathway involves the blockade of the V367M mutation, while the other pathway entails the blockade of the GCK mutation (C371S). Both mechanisms have the capability to impede the binding of GCK to secretory granules and diminish insulin secretion [39].

### *The SNO of insulin signalling pathway protein leads to IR and then induces T2DM*

IR constitutes a pathological condition. Initially, during the early stage of IR, β-cells augment insulin secretion to compensate for the elevated blood glucose levels. However, in the advanced stage of IR, β-cells fail to produce adequate insulin to compensate for the heightened blood glucose, thereby fostering the onset of T2DM [40]. Several studies have corroborated the pivotal role of SNO in the pathogenesis

of IR. By assessing the SNO levels in islets of patients with T2DM, it has affirmed the inducement of T2DM by SNO [41–43].

It is acknowledged that inducible nitric oxide synthase (iNOS) is an inflammatory mediator, exerting a significant influence on IR, whereby an overabundance of NO production can provoke nitroso reactions, subsequently exacerbating damage to pancreatic islets $\beta$-cells. To be precise, the excessive production and aberrant expression of iNOS induce protein SNO, disrupt insulin signal transduction, impair adipocyte function, and perpetuate inflammatory status, thereby fostering IR and the development of T2DM [44]. Research findings have validated the correlation between iNOS and IR. In this investigation, 2 distinct obesity models (diet-induced obesity and non-diet-induced obesity) were employed as research subjects. The results unveiled that iNOS-induced IR is mediated through the SNO of proteins involved in insulin signal transduction. SNO attenuates the functionality and expression of insulin signal transduction proteins, resulting in diminished insulin secretion, reduced glucose tolerance, and the onset of T2DM [45].

It has been substantiated that there are various kinds of protein SNO in the insulin signalling pathway of diabetic mice, predominantly including the insulin receptor beta (INSR-$\beta$), insulin receptor substrate 1 (IRS1), and protein kinase B (AKT). Among these, SNO of INSR-$\beta$ and AKT diminishes their activity, while the SNO of IRS-1 reduces its expression [46–48]. Xu et al. discerned that inducing IR in Wistar rats can significantly elevates the SNO levels of INSR-$\beta$, IRS1, and AKT. Conversely, inhibition of iNOS expression in Wistar rats augments insulin sensitivity, accompanied by a reduction in SNO of INSR-$\beta$, IRS-1, and AKT. The aforementioned research indicates that the SNO of INSR-$\beta$, IRS-1, and AKT serves as the primary molecular mediator of iNOS-induced IR [49]. Furthermore, another study corroborates this perspective, revealing that iNOS-mediated SNO of INSR-$\beta$, IRS-1, and AKT is implicated in aging-induced IR. To validate this standpoint, diminishing the expression of iNOS or inhibiting iNOS activity can reduce the SNO levels of INSR-$\beta$, IRS-1, and AKT in skeletal muscles of elderly mice, consequently ameliorating insulin signalling and insulin sensitivity [50]. Hence, certain studies propose that reducing the SNO of INSR-$\beta$, IRS-1, and AKT holds potential in preventing diabetes. For instance, substantial intake of aspirin to inhibit iNOS expression and SNO of INSR-$\beta$, IRS-1, and AKT can significantly ameliorate fasting and postprandial blood glucose levels in T2DM patients [51]. Similarly, reducing iNOS-mediated AKT SNO in the liver of obese rats through exercise has shown efficacy in improving IR, reversing diet-induced obesity in Wistar rats with SNO of INSR-$\beta$, IRS-1, and AKT, augmenting insulin sensitivity, and diminishing iNOS expression [52, 53].

## Discussion

SNO constitutes a protein modification mediated by NO, wielding diverse biological and biochemical functions and participating in an array of pathological and physiological processes. Virtually all proteins with biological functions undergo SNO, and the regulation of SNO assumes paramount importance in preserving normal cellular signal transduction (Tab. 1). The imbalance of SNO regulation may precipitate the onset of various diseases, encompassing cancer, cardiovascular disease, Alzheimer's disease, Parkinson's disease, and others. Simultaneously, SNO assumes a critical role in the occurrence and development of T2DM. SNO participates in insulin production, processing, transportation, signal transduction, secretion release, and other processes, modulating insulin secretion, IR, and insulin sensitivity, and affecting glucose kinase activity.

This article has summarised the main causes of SNO resulting in T2DM, encompassing the SNO of insulin secretion-related proteins such as RyR2 and SUR1, which cause a reduction in insulin secretion. The SNO of glucokinase leads to a decrease in its activity, and the SNO of insulin signalling pathway proteins like INSR and AKT results in IR. Various causes jointly operate to ultimately induce the occurrence of T2DM. Hence, by reversing the SNO of insulin secretory proteins and pathway proteins through targeted therapy, insulin secretion can be enhanced and IR can be inhibited. Additionally, inhibiting the SNO of glucokinase can increase its activity. To sum up, by regulating SNO-related enzymes, proteins, and pathways, reducing the risk factors of T2DM from its pathogenesis provides a new research direction and concept for the treatment of diabetes.

In addition to the points raised in this article, SNO-induced T2DM also involves a variety of proteins and mechanisms. In-depth understanding of the correlation between SNO and T2DM, and targeted treatment measures are expected to make the drug treatment of diabetes possible.

### *Author contributions*

F.H. contributed to all aspects of this study and article. L.L. contributed to the study conception, interpretation, and the critical revision of the article. All authors read and approved the final version of the manuscript.

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**Table 1.** *S-nitrosylation (SNO) — proteins and their effects on insulin and type 2 diabetes (T2D)*

| SNO — Protein | The process that affects insulin action | The impact on insulin release | Whether to induce diabetes | Reference |
|---|---|---|---|---|
| SUR1 | Insulin secretion | Inhibition | Yes | [26] |
| NSF | Insulin secretion | Inhibition | Yes | [32] |
| INSR-$\beta$ | Insulin resistance | Inhibition | Yes | [54] |
| IRS1 | Insulin resistance | Inhibition | Yes | [55] |
| AKT | Insulin resistance | Inhibition | Yes | [56] |
| PPARr | Insulin resistance | Inhibition | Unknown | [57] |
| PDE3B | Insulin resistance | Inhibition | Yes | [58] |
| CTSB | Insulin resistance | Inhibition | Yes | [59] |
| HexB | Insulin resistance | Inhibition | Yes | [60] |
| UBE2D1 | Insulin resistance | Inhibition | Unknown | [61] |
| PDI | Insulin resistance | Inhibition | Unknown | [62] |
| IRE1 | Insulin resistance | Inhibition | Yes | [63] |
| SIRT1 | Insulin resistance | Inhibition | Yes | [64] |

SUR1 — sulfonylurea receptors1; NSF — N-ethylmaleimide sensitive factor; INSR-$\beta$ — insulin receptor $\beta$; IRS1 — insulin receptor substrate 1; AKT — protein kinase B; PPARr — peroxisome proliferators receptor $\alpha$; PDE3B — phosphodiesterase 3B; CTSB — cathepsin B; HexB — hexosaminidase B; UBE2D1 — ubiquitin-conjugating enzyme E2D1; PDI — protein disulfide isomerase; IRE1 — inositol-requiring enzyme 1alpha; SIRT1 — sirtuin 1



## *Conflict of interest*

The authors declare that they have no potential conflicts of interest related to this work.

## *Availability of data and materials*

All data used and/or analysed during the present study are available from the corresponding author on reasonable request.

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