

Exploring the mechanisms connecting the sympathetic nervous system and type 2 diabetes: Focus on renal denervation

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The interplay between sympathetic nervous system activation and metabolic disorders, particularly type 2 diabetes mellitus (T2DM) and hypertension, has been increasingly recognized as a critical factor in cardiovascular morbidity and mortality. This review explores the potential mechanisms linking sympathetic overactivity to insulin resistance (IR) and T2DM, highlighting the role of renal denervation (RDN) as a promising therapeutic intervention. Sympathetic activation contributes to metabolic dysregulation by increasing plasma fatty acids, enhancing hepatic gluconeogenesis, and impairing pancreatic insulin release, while also inducing vasoconstriction and reducing glucose uptake in skeletal muscle. RDN, a catheter-based procedure targeting renal sympathetic nerves, has shown efficacy in managing resistant hypertension and improving glucose metabolism by reducing sympathetic drive, normalizing hepatic gluconeogenesis gene expression, and enhancing insulin sensitivity. Experimental and clinical studies suggest that RDN may mitigate IR, improve glycemic control, and reduce renal complications in diabetic models, independent of obesity or glucose tolerance status. However, the long-term effects on glycemic control and broader clinical applicability require further investigation.

Key words: Diabetes mellitus, insulin resistance, renal denervation, sympathetic system

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INTRODUCTION

The World Health Organization announced that, by 2030, diabetes is going to be the seventh major cause of mortality.^[1]

Type 2 diabetes (T2D) is characterized by insulin resistance (IR). Following the decline of insulin production and pancreatic beta (β)-cell failure, there is a decrease in glucose transport into the muscle and fat cells, as well as the liver.^[2]

The declining impact of therapeutic drugs on blood glucose is followed by multiple risks, such as medication tolerance, side effects, and even toxicity.^[3]

Various treatments, including the use of supplements such as GABA and magnesium, have also been considered for the treatment of diabetes.^[4-6]

The kidneys are abundantly innervated by both renal afferent sensory and efferent sympathetic nerves and communicate with the central nervous system (CNS) via the sensory afferent nerves. Increased renal afferent activity directly influences sympathetic outflow to the kidneys via efferent nerves. The efferent sympathetic nerves are crucial for the production of norepinephrine (NE), a key effector of the sympathetic nervous system (SNS). Epinephrine and NE act by binding to adrenergic receptors (ARs), classified as α_1 -, α_2 -, or β -AR.^[7]

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Recently, it has been suggested that increased renal sympathetic nerve activity (rSNA) plays an important role in the pathogenesis of diabetic nephropathy in humans and in the streptozotocin (STZ)-induced animal model. The increase in rSNA promotes renal vasoconstriction, increases sodium reabsorption, and activates the peripheral renin-angiotensin system (RAS). Sodium-glucose cotransporter 2 (SGLT2) is responsible for approximately 90% of glucose reabsorption in the kidneys. SGLT2 is translocated to the cell surface of the proximal tubule by the activation of beta-ARs, resulting in increased plasma glucose concentration.^[8]

Catheter-based renal denervation (RDN) has garnered great interest and debate as a potentially effective percutaneous intervention to treat hypertension and related major cardiac and metabolic disorders.^[9,10] Destruction of these nerves interrupts both efferent renal nerves (ERNs) and afferent renal nerves (ARNs). ERNs are postganglionic sympathetic fibers that release NE and contribute to hypertension by causing renal vasoconstriction, renin release, and renal sodium and water retention. ARNs are sensory fibers that arise in the renal pelvis and cortex. These signal the CNS about changes in the chemical composition of the urine and intrarenal pressure^[11] when activated by uremic metabolites such as urea, ischemic metabolites such as adenosine, or increased intrarenal pressure from excessive perinephric fat mass in animal models of obesity.^[12] Renal afferents can trigger sustained reflex increases in sympathetic nerve activity (SNA) targeted to multiple extrarenal tissues and vascular beds.^[13]

In the early-phase trials, RDN was accompanied by reduced fasting glucose, C-peptide, and plasma insulin levels, suggesting improved insulin sensitivity (SI) in patients with resistant hypertension^[10] and in patients with hypertension and polycystic ovary syndrome (PCOS)^[14] or obstructive sleep apnea.^[15]

This review primarily focuses on the mechanisms linking SNS overactivity to type 2 diabetes mellitus (T2DM), with catheter-based RDN as a potential therapeutic intervention. Hypertension is examined as a key comorbidity that often coexists with T2DM and exacerbates SNS activation, while PCOS and diabetic nephropathy are discussed secondarily to provide a mechanistic context on IR and renal complications. Primary outcomes focus on fasting glucose and Homeostatic model assessment of insulin resistance (HOMA-IR) as markers of glucose metabolism; secondary outcomes include glycosylated hemoglobin (HbA1c) and insulin. Overall, the review underscores the therapeutic potential of RDN in addressing the vicious cycle of sympathetic overactivity and metabolic dysfunction, paving the way for future research into its role in preventing and managing T2DM and its related comorbidities.

LITERATURE SEARCH STRATEGY

A comprehensive literature search was conducted across four major electronic databases: Scopus, Web of Science, PubMed, Google Scholar, and Embase. The search encompassed all publications from 1977 to 2024 to ensure a thorough exploration of the mechanisms connecting the SNS and T2D, with a specific focus on RDN.

The search strategy was constructed using a combination of relevant keywords, Medical Subject Headings (MeSH), and Emtree terms where applicable. The included keywords: ("Kidney Denervation," "Renal sympathetic denervation," "Renal nerve ablation," "Hypertension," hypertense "Blood Pressure," "high blood pressure," ("Diabetes Mellitus," Type 1", "Diabetes Mellitus, Type 2", "type 1 diabetes," "type 2 diabetes" diabetic.

The core search concepts were combined using Boolean operators (AND, OR) to optimize the retrieval of relevant literature.

Study selection

Following the database search, articles were screened for eligibility based on predefined inclusion and exclusion criteria. The screening process was conducted in two phases: initial screening of titles and abstracts, followed by full-text review of potentially eligible articles.

Inclusion criteria

Articles were included if they met the following criteria:

- Studies investigating the mechanisms connecting SNS activity and T2D
- Research specifically addressing RDN as an intervention or mechanism.

Original research articles (randomized controlled trials, cohort studies, case-control studies and experimental studies).

Systematic reviews and meta-analyses

In vivo, *ex vivo*, or *in vitro* studies examining relevant pathophysiological mechanisms

- Studies published in English between 1977 and 2024
- Studies in both human subjects and animal models.

Exclusion criteria

Articles were excluded based on the following criteria:

- Publications focusing only on clinical outcomes without addressing mechanisms
- Conference abstracts, letters to editors, commentaries, and opinion pieces
- Studies focused on the denervation of organs other than the kidney without connection to RDN

- Studies only mentioning SNS or RDN tangentially, without substantive investigation
- Duplicate publications or secondary analyses without new mechanistic insights.

All search results were imported into a reference management software for deduplication. Two independent reviewers screened the articles according to the eligibility criteria, with disagreements resolved through discussion or consultation with a third reviewer when necessary.

The initial use of renal denervation

It is customary to acknowledge that the earliest insight into the influence of the renal nerves on renal function is that of Bernard in 1859.^[16] He observed that cutting the greater splanchnic nerve (i.e., RDN) produced an ipsilateral diuresis, whereas electrical stimulation of its peripheral cut end (i.e., renal sympathetic nerve stimulation) produced an ipsilateral antidiuresis. With early methods for the measurement of renal blood flow (RBF), it was seen that RDN was associated with an increase in RBF and that renal sympathetic nerve stimulation was associated with a decrease in RBF.^[17]

Several studies conducted on the relationship between RDN and glucose metabolism are presented in Table 1.

Positive: Clear beneficial effect on primary glycemic outcomes (e.g., ↓ fasting glucose, insulin, and HOMA-IR).

Neutral/modest/inconsistent: No significant or only modest/inconsistent changes, especially in recent human meta-analyses and sham-controlled trials (e.g., no significant difference in fasting glucose/HbA1c/HOMA-IR across 19 studies/2245 patients).

Animal studies consistently show stronger positive effects; human studies show early promise, but recent evidence (2023–2025 meta-analyses) indicates modest/neutral glycemic impact beyond blood pressure (BP) reduction.

MECHANISMS OF RENAL DENERVATION IN HUMAN

RDN is an evolving therapeutic approach for managing resistant hypertension, targeting the renal sympathetic nerves through minimally invasive techniques. In the United States, three primary percutaneous methods accessing the renal artery are under development: radiofrequency ablation (RFA), ultrasound, and neurotoxin injection. RFA employs a catheter to deliver medium-frequency alternating current via electrodes, typically four, arranged in a spiral configuration with approximately 6 mm spacing. This generates heat that is

generally well-tolerated by the renal arterial wall but is cytotoxic to surrounding nerves within a 7-mm energy field from the arterial lumen. The ultrasound approach utilizes a catheter equipped with an inflatable balloon system and multiple ultrasound-emitting sources, typically four, to deliver energy. The balloon facilitates irrigation with a cooling solution, maintaining a lower temperature in the arterial lumen compared to the perivascular space, thus protecting the arterial wall while targeting nerves. The third method involves a smaller catheter with three concentrically arranged microneedles. Upon precise positioning, these microneedles extend through the renal artery wall into the perivascular space, simultaneously injecting a small volume of neurotoxin, typically 0.6 mL of absolute ethanol, to ablate the nerves. The therapeutic efficacy of RDN is attributed to the disruption of renal sympathetic nerve activity, which modulates several physiological processes. Progressive stimulation of these nerves leads to increased renin release at lower stimulation levels, reduced sodium excretion at intermediate levels, and heightened renal vascular resistance at the highest levels. By interrupting these neural pathways, RDN mitigates the sympathetic overactivity associated with hypertension, offering a promising intervention for patients unresponsive to conventional pharmacological treatments. These approaches, while distinct in their mechanisms, collectively aim to achieve precise and effective denervation, with ongoing research refining their safety and efficacy profiles for broader clinical application.^[17,18]

RDN ablates the afferent and efferent sympathetic nerves in the adventitia of the renal arteries. The device catheter is inserted percutaneously into the femoral artery and advanced into the main renal arteries under fluoroscopic guidance. After excluding renovascular abnormalities by angiography, a generator is then activated to deliver radiofrequency energy to the renal artery wall. The strategy of the procedure is to maximize nerve disruption by applying four to six ablation treatments to each renal artery, with ablations spaced both longitudinally and circumferentially along the vessel wall. Each ablation lasts ≤ 2 min, and the entire procedure takes about 40 min to complete. RDN reduces sympathetic activity both locally in the kidney and systemically,^[19,20] which in turn reduces renin activity and increases RBF [Figure 1].

Bilateral renal denervation in rat

In rats, this procedure is conducted as follows:

The rats are anesthetized intraperitoneally (i.p.) with a mixture of ketamine (80 mg/kg) and xylazine (10 mg/kg) for the bilateral renal denervation (BRD) surgical procedure.

Table 1: Studies regarding the effect of renal denervation in parameters of glycemic control

Authors/Year	Study type & sample	Intervention	Primary outcomes	Results summary	Potential mechanism & Notes	REF
Szalay <i>et al.</i> (1977)	Animal (Dogs)	Unilateral surgical denervation	Glucose tubular reabsorption	Significantly decreased in denervated dogs.	Alteration in renal glucose reabsorption. (Positive effect)	[1]
Schaan <i>et al.</i> (2003)	Animal (Rats)	Bilateral denervation	Cortical GLUT1 protein levels, albuminuria	GLUT1 decreased toward normal; no albuminuria regression.	Modulation of GLUT1 expression. Diabetic nephropathy model.	[2]
Schaan <i>et al.</i> (2005)	Animal (Rats)	Denervation	GLUT2 levels	Reduced by 21% (non-DM) and 15% (DM).	Direct modulation of GLUT2.	[3]
Iyer <i>et al.</i> (2021)	Animal (Canines)	RDN in obese model	Hepatic insulin sensitivity	Decreased post-RDN.	Downregulation of gluconeogenesis via natriuretic pathway.	[4]
Chen <i>et al.</i> (2016)	Animal (Rats)	Unilateral/ bilateral RDN	Gluconeogenesis and glycogenolysis	Bilateral: 31.9% ↓ gluconeogenesis and 42.8% ↓ glycogenolysis.	Enhanced suppression of hepatic glucose production. Dose-dependent.	[5]
Pan <i>et al.</i> (2018)	Animal (33 dogs)	Multi-electrode catheter-based RDN	Fasting glucose, insulin, HOMA-IR, gluconeogenic genes	Fasting glucose: 9.64 → 5.12 mmol/L; insulin ↓; HOMA-IR ↓.	Reduced gluconeogenesis/ glycogenolysis; IR-AKT activation in liver.	[6]left renal denervation (LRDN)
de Oliveira <i>et al.</i> (2021)	Animal (Rats)	Bilateral RDN	Glycemia, glycosuria, SGLT2, albuminuria, rSNA	↓ glycemia, glycosuria, albuminuria; normalized SGLT2 & rSNA.	Reduced SGLT2, afferent signaling, intrarenal RAS. STZ-DM rats.	[4]
Luippold <i>et al.</i> (2020)	Animal (Rats)	Chronic RDN	GFR, glomerular volume	Prevented hyperfiltration (GFR to normal) and enlargement.	Prevention of sympathetic-mediated hyperfiltration.	[7]
Mahfoud <i>et al.</i> (2011)	Human (37 patients)	Catheter-based RDN	Fasting glucose, insulin, C-peptide, HOMA-IR	Fasting glucose 6.55 → 5.99 mmol/L; insulin ↓; C-peptide ↓.	Improved insulin sensitivity. (Early pilot; resistant HTN)	[8]
Witkowski <i>et al.</i> (2011)	Human (Small cohort)	Catheter-based RDN	Glycemic control in resistant HTN + sleep apnea	Modest improvement in some patients.	Reduced sympathetic drive. (OSA comorbidity)	[9]
Rosa <i>et al.</i> (2015–2020)	Human (106 patients)	RDN vs. intensified pharmacotherapy	Fasting glucose	No statistically significant reduction versus pharmacotherapy.	Limited metabolic impact beyond BP. (Sham/ comparator trial)	[10]
Various meta-analyses (2023–2025)	Human meta-analysis (19 studies, n>2245)	Catheter-based RDN	Fasting glucose, insulin, HbA1c, HOMA-IR, C-peptide	No significant difference (inconsistent/neutral).	Limited or no overall metabolic benefit.	[11]

The renal pedicle is carefully separated from the connective tissue, and then, the renal artery was separated from the vascular nervous bundle using a loop.

All nerves visualized using a loop along the renal artery are carefully sectioned, topical application of 10% phenol around the renal artery is performed for chemical denervation of any remaining renal nerve innervation.

This procedure is performed bilaterally for the denervation of the right and left renal nerves.^[21] Animals recovered from anesthesia 10–20 min after the end of surgery, and 2.5 mg/kg/day of meloxicam was intramuscularly administered for three consecutive days for analgesia. The experiments were performed 2 weeks after RDN since earlier studies showed that after 3 weeks of surgery, there is some reinnervation^[22] [Figure 2].

Similar methods have been performed in dogs, cats, sheep, Guinea pigs, mice, and rabbits.

THE POTENTIAL MECHANISMS LINKING SYMPATHETIC ACTIVATION TO TYPE 2 DIABETES MELLITUS

Since 1664, Thomas Willis first described the SNS in detail;^[23] researches had been carried on the role of it. Besides in cardiovascular regulation, the activation of SNS also may have profound metabolic effects, leading to increased levels of fatty acids in plasma, increased hepatic gluconeogenesis, and alterations in pancreatic insulin release.^[21,24]

It has been demonstrated that in response to a cold pressor test, which predominantly activates alpha adrenergic responses, noradrenaline independently predicted IR at 18-year follow-up.^[25]

These findings were supported by observations that acute activation of endogenous noradrenaline release antagonized insulin-mediated glucose uptake in forearm skeletal muscle.^[26]

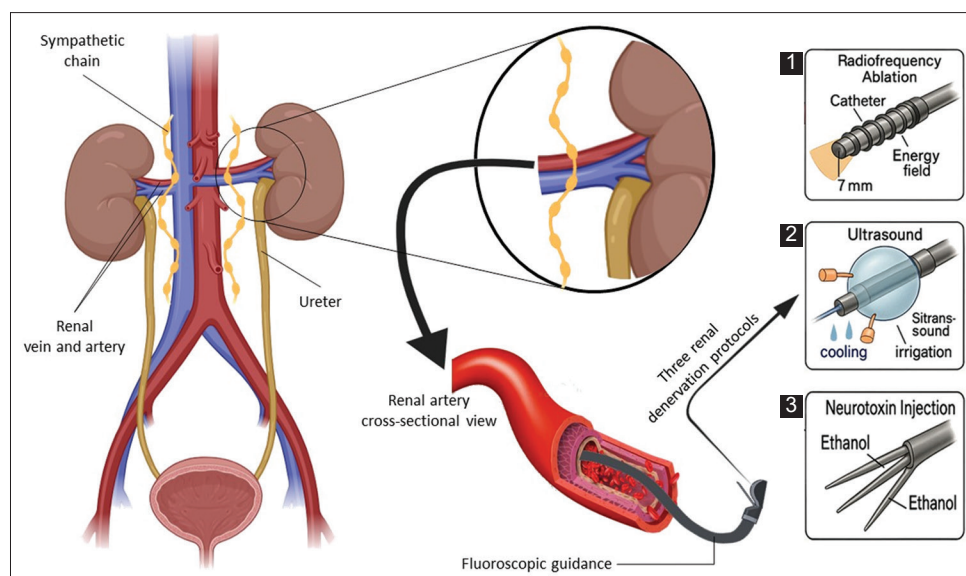


Figure 1: Illustration of percutaneous renal denervation via femoral-artery catheter under fluoroscopic guidance, showing: (1) spiral-electrode radiofrequency ablation creating a 7-mm cytotoxic field in the adventitia, (2) balloon-cooled ultrasound energy delivery to selectively heat perivascular nerves, and (3) microneedle injection of ethanol neurotoxin into the adventitial space

According to Jamerson *et al.*,^[27] a decrease in blood flow after the raise of noradrenaline concentration could impair the ability of cells to transport glucose through their membranes, which is probably the result of alpha adrenoceptor-mediated vasoconstriction caused by sympathetic overactivity.

This physiological activity could reduce the number of open capillaries and increase the distance that insulin has to travel from the intravascular compartment to reach the cell membrane.^[28]

Collectively, these studies suggest that pathological activation of the SNS plays a significant role in the process of IR, making patients more prone to the development of impaired glucose tolerance and T2DM.^[28,29]

Almost 20 years ago, Landsberg proposed a link between IR and activation of the SNS. Thereafter, IR could lead to an increase in SNS activation, which has been confirmed.^[30]

Subsequent studies in healthy volunteers supported that infusions of insulin increased muscle sympathetic nerve activity, which appeared to be independent of the vasodilatory effects of insulin.^[31]

Then, it comes to a “chicken and egg” scenario; in other words, which abnormality comes first and originates the vicious circle that maintains both sympathetic overactivity and IR.^[28]

Ferrannini *et al.* found that in the development of hypertension, Japanese individuals showed an increase in both plasma

noradrenaline and insulin levels, while 10 years earlier, they only showed an increase in plasma noradrenaline.

Accumulating evidence from both experimental and human studies exists to suggest that IR and hyperinsulinemia are common features of systemic hypertension that occur independently of obesity, impaired glucose tolerance, and diabetes status.^[32,33]

Hyperinsulinemia raises BP directly through activation of the renal tubules, resulting in sodium retention,^[34,35] such that its antinatriuretic effect contributes importantly to chronic BP elevation.

Sympathetic activation results in peripheral vasoconstriction through the release of NE, which acts upon vascular smooth muscle adrenoreceptors. Consequently, sympathetic activation may reduce insulin sensitivity through the direct effect on the regulation of glucose transport in the skeletal muscle. Insulin-stimulated glucose uptake by skeletal muscle can be modulated by a reduction in skeletal muscle blood flow mediated via neural vasoconstriction,^[26] resulting in reduced glucose utilization.^[27,36]

Given the relevance of skeletal muscle for whole body glucose utilization, it might be anticipated that the detrimental impact of IR on muscle skeletal microvascular circulation adversely influences whole body glucose utilization preceding the development of T2DM.

Accordingly, a beneficial effect on insulin metabolism in hypertension has been observed following treatment with $\alpha 1$ receptor blockers^[37] [Figure 3].

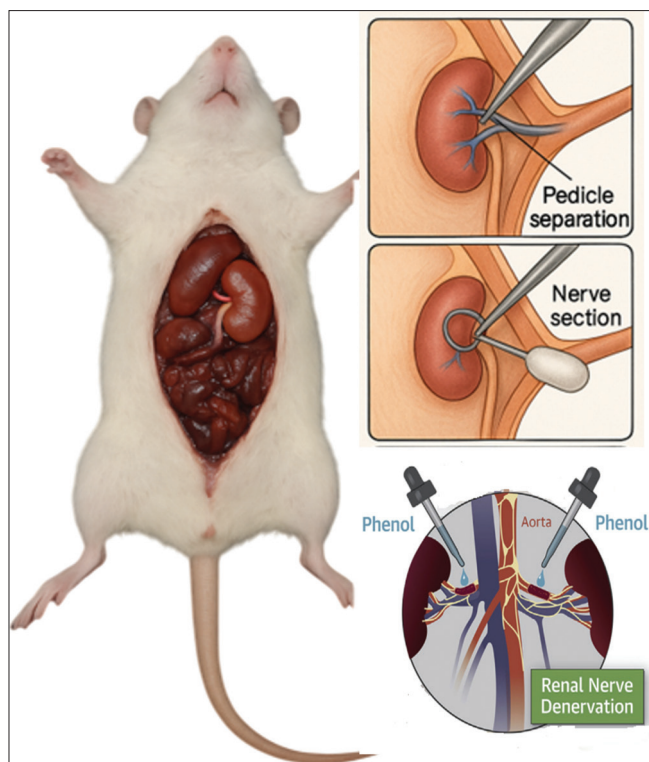


Figure 2: Illustration of bilateral renal denervation in a rat: intraperitoneal ketamine/xylazine anesthesia, flank exposure and pedicle separation, loop isolation and transection of renal nerves, topical 10% phenol application for chemical denervation, and postoperative analgesia

EFFECT OF RENAL DENERVATION ON GLUCOSE METABOLISM

RDN normalizes hepatic S_I by reducing the hepatic-specific expression of multiple GNG genes, including G6Pase, PEPCK, and transcription factors – FOXO1, PGC-1 α , and PPAR- α . IR previously has been characterized by increased hepatic expression of these genes.^[38,39]

RDN surgery was accompanied by increased expression of Liver X Receptor Alpha (LXR- α), a transcription factor regulator involved in the control of GNG genes through downregulation of PGC-1 α , G6Pase, and PEPCK.^[40]

LXR- α also may interact with natriuretic peptides and ADRs.^[41,42] RDN surgery reduced the expression of NPR-C, suggesting increased natriuretic peptide content in the liver.^[43] Further studies are necessary to elucidate whether natriuretic peptides have a direct effect on hepatic glucose output and/or mediate the observed effects of renal nerves on hepatic gluconeogenesis.

Several observations implicate hepatic ADR mediation because RDN was accompanied by (1) increased hepatic NE content, suggesting increased hepatic SNA; (2) lower expression of the hepatic α -1A ADR, which is involved in

upregulation of hepatic GNG genes through a $G_q/11$ GPCR pathway;^[17,44-46] and (3) increased expression of both hepatic α -2A ADR (G_i , adenylyl cyclase inhibitor) and hepatic β -1 ADR (G_s , adenylyl cyclase stimulator). Diaz-Cruz *et al.*^[47] demonstrated that activation of α -1 ADR inhibits β -ADR-stimulated pathways through NOX2 activation. Together, the current results suggest suppression of hepatic gluconeogenesis with RDN surgery through α -1 ADR, natriuretic peptides, and the LXR- α pathway. Further investigation is necessary to develop a complete picture of the mechanistic underpinnings [Figure 4].

ADVERSE EFFECTS AND SAFETY CONSIDERATIONS

RDN is generally considered safe, with most adverse events being mild and procedure-related. The most frequently reported complications include access-site hematoma or pseudoaneurysm ($\approx 1\%$ – 3%), transient back pain or abdominal discomfort postablation (usually self-limiting), and rare cases of renal artery dissection or stenosis (0.5% – 2% in long-term follow-up). In contemporary sham-controlled trials using optimized radiofrequency or ultrasound systems, the incidence of new-onset renal artery stenosis has dropped significantly ($<1\%$) compared with early-generation devices. No consistent evidence links RDN to worsening of renal function (estimated glomerular filtration rate decline) or new-onset diabetes in hypertensive or diabetic populations. However, long-term data (>5 years) in patients with T2D remain limited, and potential risks such as incomplete denervation, late reinnervation, or microvascular damage are still under investigation. Preclinical models have not shown significant parenchymal injury when energy delivery is properly controlled.^[10,18,48]

DISCUSSION

In the study by de Oliveira *et al.* (In preclinical animal models), the effects of BRD on metabolic, cardiovascular, and renal function in diabetic (diabetic mellitus) rats were investigated. The main new findings were: (1) BRD improved metabolic parameters, renal function, glycemia, and morphology and reduced urinary glucose and albumin excretion and (2) it normalized renal SGLT2 gene expression and renal sympathetic nerve activity (sSNA). In addition, the relative contribution of BRD to improving reflex control of the cardiovascular system was examined.^[8]

Hyperactivity of renal nerves is typically due to diabetic nephropathy. In this condition, the kidneys, through sensory afferent fibers, report their status to the CNS, and the CNS processes this information, increasing sympathetic vasomotor drive.^[49,50] Consequently, as diabetic nephropathy is sustained and exacerbated by sympathetic hyperactivity, a vicious cycle is perpetuated, increasing afferent nerve

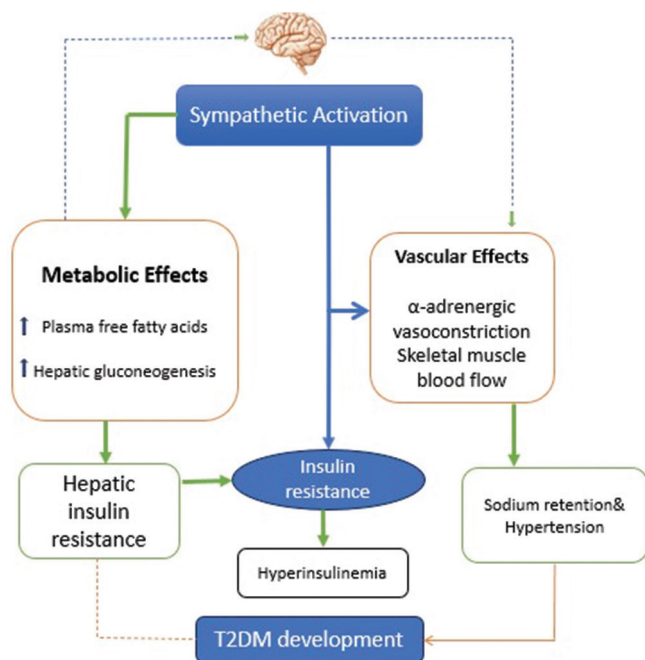


Figure 3: The potential mechanisms linking sympathetic activation to type 2 diabetes mellitus

activity and triggering an excessive sympathetic response. These observations align with the results of this study, which found a positive correlation between baseline glucose levels and renal sympathetic nerve activity (rSNA).

Similarly, renal nerves play a significant role in renal function in the diabetic model. Diabetic rats exhibit renal dysfunction through increased urinary albumin levels. Interestingly, BRD significantly attenuated these increases. Renal sympathetic nerve hyperactivity causes glomerular changes through the loss of epithelial cells (podocytes) and the elimination of structural proteins.^[51] Furthermore, previous studies have shown that treating diabetic rats with nebivolol, a selective beta-1 adrenergic antagonist and vasodilator, significantly increased the percentage of podocins.^[52] This suggests that RDN may reduce glomerular structural damage by decreasing intercellular gaps, thereby reducing macromolecule loss in diabetic animals.

A key finding of this study (In preclinical animal models) was the reduction in glycemia and an increase in body weight following BRD in diabetic rats. The mechanisms by which BRD affects glycemic balance are unknown. de Oliveira *et al.* found that BRD may act through: (1) reducing signaling in the sensory afferent pathway, which subsequently triggers efferent sympathetic nerve activity changes; (2) reducing the intrarenal renin–angiotensin–aldosterone system (RAAS); and (3) decreasing renal SGLT2 expression. The mechanism by which RDN improves glucose homeostasis may involve increased insulin receptor

sensitivity and/or enhanced glucose uptake by muscles.^[53–55] In addition, increased splanchnic sympathetic nerve activity in denervated diabetic rats may have facilitated insulin release through a mechanism dependent on the activation of beta-pancreatic receptors.^[56] However, further studies are needed to test these hypotheses.

Moreover, de Oliveira *et al.* showed that BRD reduced renal SGLT2 expression in diabetic rats (In preclinical animal models), thereby lowering blood glucose levels. Previous studies have indicated that inhibiting renal SGLT2 likely reduces blood glucose levels by increasing glycosuria and provides cardioprotective effects by reducing albuminuria, inflammation, and atherosclerosis in diabetic individuals.^[57–59] A study observed reduced glycemia in diabetic rats' post-BRD, with an unexpected decrease in glycosuria 2 weeks later, suggesting improved glucose uptake due to enhanced peripheral insulin sensitivity, leading to better glycemic control. In a 2024 case study by Su *et al.* (Clinical studies in humans), a young patient with treatment-resistant hypertension and T2D underwent three-dimensional guided intravascular and renal sympathetic nerve ablation, yielding positive results. Follow-up assessments at 1 week, 1-, 3-, and 6-month postsurgery monitored body weight, waist circumference, 24-h BP, heart rate, HbA1c, fasting and postprandial glucose, renal and liver function, lipid profile, and angiotensin levels. One month postsurgery, antihypertensive medications decreased from four to three, then to two by 3 months. At 6 months, 24-h BP dropped by 20/75 mmHg, HbA1c reduced by 3.6%, fasting glucose reached 6.8 mmol/L, and postprandial glucose levels were 7.1 and 14.0 mmol/L. No abnormalities were found in renal artery imaging, and no surgical complications occurred, indicating the procedure's safety and efficacy in managing diabetes and hypertension.^[60]

In a 2018 study (In preclinical animal models), Tao Pan *et al.* showed that multi-lectrode catheter-based RDN improved insulin sensitivity and glucose metabolism in a canine model of T2DM. After 3 months, the BRDN group showed significant reductions in fasting plasma glucose (9.64 ± 1.57 – 5.12 ± 1.08 mmol/L), insulin (16.19 ± 1.43 – 5.07 ± 1.13 mIU/mL), and HOMA-IR (6.95 ± 1.33 – 1.15 ± 0.33). Western blot analyses revealed suppression of gluconeogenesis-related genes and activation of insulin receptor-AKT signaling in the liver. Importantly, computed tomography angiography and histopathology showed no vascular damage, indicating that the procedure was both effective and safe.^[61]

Luippold *et al.* (In preclinical animal models) demonstrated that chronic RDN prevents glomerular hyperfiltration in diabetic rats. In nondiabetic rats with intact nerves (CON-INN), the glomerular filtration

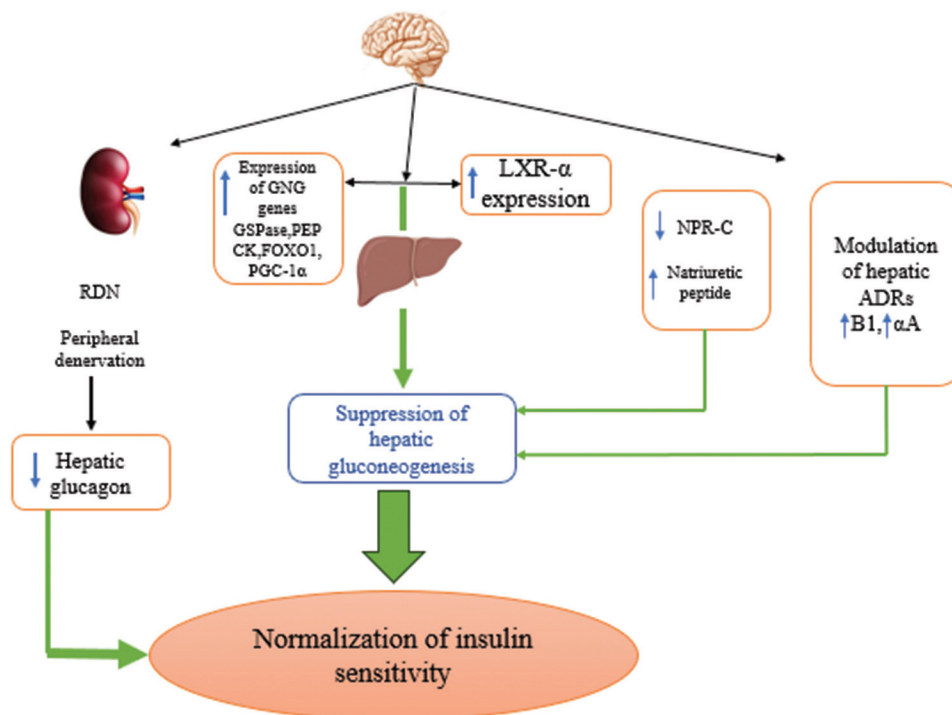


Figure 4: Effect of renal denervation on glucose metabolism

rate (GFR) was $0.82 \pm 0.03 \text{ ml} \cdot \text{min}^{-1} \cdot 100 \text{ g}^{-1}$ body weight. Diabetic rats with innervated kidneys showed significant hyperfiltration ($1.13 \pm 0.03 \text{ ml} \cdot \text{min}^{-1} \cdot 100 \text{ g}^{-1}$), but RDN reduced GFR to near CON-INN levels ($0.88 \pm 0.03 \text{ ml} \cdot \text{min}^{-1} \cdot 100 \text{ g}^{-1}$). Glomerular volume in the CON-INN group was $0.69 \pm 0.03 \cdot 10^6 \mu\text{m}^3$, significantly lower than in diabetic rats with intact nerves ($0.86 \pm 0.04 \cdot 10^6 \mu\text{m}^3$). RDN prevented glomerular enlargement in diabetic rats, indicating that renal nerves mediate hyperfiltration in experimental diabetes, and denervation mitigates early diabetic nephropathy structural changes.^[62]

In a study (Clinical studies in humans) of 37 patients with resistant hypertension, Mahfoud *et al.* showed that RDN, in addition to the effect of bilateral catheter-based RDN, resulted in a mean BP reduction of 28 and 10 mmHg for systolic and diastolic, respectively, that is accompanied by a significant improvement in glucose metabolism. Specifically, fasting plasma glucose decreased from $6.55 \pm 0.19 \text{ mmol/L}$ to $5.99 \pm 0.21 \text{ mmol/L}$ ($P = 0.039$), with parallel reductions in insulin (20.8 ± 3.0 vs. $9.3 \pm 2.5 \text{ mIU/L}$; $P = 0.006$) and C peptide (5.3 ± 0.6 vs. $3.0 \pm 0.9 \text{ ng/ml}$; $P = 0.002$) levels 3 months after RDN.^[10]

While early pilot studies suggested that RDN improves glycemic parameters in patients with resistant hypertension (e.g., reduced fasting glucose from 6.55 to 5.99 mmol/L, insulin from 20.8 to 9.3 mIU/L, and HOMA-IR),^[10] subsequent larger sham-controlled trials and meta-analyses have shown inconsistent or modest effects on glucose metabolism. A comprehensive meta-analysis of 19 studies

involving 2245 patients found no significant differences post-RDN in fasting glucose (weighted mean difference: 0.19 mmol/L; 95% confidence interval [CI]: -0.37–0.00), insulin (standardized mean difference [SMD]: 0.01; 95% CI: -0.41–0.39), HbA1c (SMD: 0.05; 95% CI: -0.17–0.07), or HOMA-IR (SMD: 0.29; 95% CI: -0.72–0.14), indicating modest or no overall benefit for glycemic control.^[63] Trials such as SYMPPLICITY HTN-3 and Prague-15 similarly reported neutral outcomes on HbA1c and fasting glucose, particularly in diabetic subgroups.^[48] These findings highlight the translational gap from preclinical models and underscore the need for further research focused on T2DM-specific cohorts.

Limitations and future directions

Despite promising preclinical and early clinical evidence, the application of RDN in T2DM faces several key limitations. Most mechanistic insights derive from animal models (e.g., STZ-induced diabetic rats and obese canine models), which demonstrate reductions in sympathetic activity, SGLT2 expression, gluconeogenesis, and improved insulin sensitivity; however, these findings may not fully translate to humans due to species differences in sympathetic regulation and glucose homeostasis. Human studies remain limited in scale, often involving small cohorts (typically $n < 50$) with short follow-up periods (3–12 months), restricting assessment of long-term glycemic durability, such as sustained HbA1c reductions or prevention of diabetic complications. Heterogeneity in RDN techniques – radiofrequency, ultrasound, or chemical ablation – further complicates direct comparisons, while

procedural variability (e.g., incomplete nerve ablation or operator experience) may contribute to inconsistent metabolic outcomes. Publication bias favors positive results, whereas larger sham-controlled hypertension trials (e.g., SPYRAL HTN-ON MED expansion phase) have shown modest or neutral effects on BP and limited metabolic data. Adverse events, though generally infrequent (e.g., renal artery stenosis <1%–2%), remain underreported in T2DM-specific contexts, and data in advanced chronic kidney disease or polymorbid patients are sparse.^[8,10,48,50]

Future directions should prioritize large-scale, multicenter randomized controlled trials with extended follow-up (>2–5 years) to evaluate RDN's impact on primary glycemic endpoints (fasting glucose, HOMA-IR, HbA1c) in T2DM populations, ideally stratified by baseline sympathetic activity or IR severity. Integration of multiorgan denervation approaches (e.g., hepatic + renal) and advanced imaging for denervation verification may enhance efficacy. Ongoing registries and postapproval studies following 2023 FDA approvals will clarify real-world safety, metabolic benefits beyond hypertension, and potential nephroprotective effects in diabetic nephropathy. Until robust evidence accumulates, RDN should remain investigational for T2DM management. Preclinical models show robust RDN effects on glucose metabolism, but clinical trials often report modest benefits due to human variability, comorbidities, and incomplete denervation. This translational gap warrants further investigation.^[8,10,48,50]

CONCLUSION

Catheter-based RDN has emerged as a promising treatment for patients with resistant hypertension, showing significant and sustained BP reduction. While many studies show benefits, trials like SYMPPLICITY HTN-3 reported modest or neutral BP reductions, possibly due to procedural inconsistencies. Recent studies also highlight its beneficial effects on glucose metabolism, which could be clinically significant given that impaired glucose tolerance increases cardiovascular risks. RDN targets renal sympathetic nerves, which contribute to IR and glucose metabolism impairment in hypertension and related conditions like T2DM and PCOS. By reducing sympathetic activity, RDN may mitigate hyperinsulinemia-induced hypertension, improve fasting glucose, and enhance insulin sensitivity, independent of body weight or antihypertensive therapy changes. In PCOS, RDN has shown improved insulin sensitivity, reduced sympathetic activity, and better renal function markers, such as glomerular hyperfiltration and albuminuria. Animal studies further confirm that RDN can slow diabetic nephropathy progression by reducing fibrotic markers and preserving glomerular integrity. However, its long-term

impact on glycemic control, such as HbA1c, remains unclear due to limited study durations and physiological factors. While RDN offers a potential nonpharmacological approach to manage IR and metabolic disorders, current evidence primarily comes from experimental and small-scale clinical studies. Larger trials are needed to validate these effects in T2DM populations and assess RDN's role in preventing diabetes or its complications.

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Conflicts of interest

There are no conflicts of interest.

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