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Food Science & Nutrition Technology
ISSN: 2574-2701

The Role of Podocyte Apoptosis and the Involvement of SIRT1 in Diabetic Nephropathy

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Mini Review
Volume 11 Issue 1
Received Date: May 19, 2026
Published Date: May 27, 2026
DOI: 10.23880/fsnt-16000367

Abstract

Diabetic nephropathy is the most common chronic microvascular complication of diabetes and the role of podocytes in diabetic nephropathy has been extensively investigated in recent years. Podocytes, along with endothelial cells and the glomerular basement membrane, are crucial components of the glomerular filtration barrier, and podocyte damage and dysfunction are associated with diabetic nephropathy. In particular, dysfunction of the podocyte foot-like processes, particularly as a result of apoptosis, affects the glomerular filtration rate and causes proteinuria. This mini-review examines the mechanisms of podocyte apoptosis and discusses the latest findings on podocyte-related diabetic nephropathy, particularly the involvement of SIRT1.

Keywords: Podocytes; Apoptosis; Diabetic nephropathy

What is SIRT1?

Six types of sirtuin (SIRT) have been identified [1]. SIRTs are nicotinamide adenine dinucleotide (NAD+)-dependent deacetylators that function as intracellular regulators of transcriptional activity. Under conditions of excessive nutrient supply, when the NAD+/NADH ratio decreases, levels of renal SIRT1 are reduced in diabetic patients and experimental models of diabetes. A mouse model with specific Sirt1 knockdown exhibits severe albuminuria and mitochondrial dysfunction, demonstrating the importance of SIRT1 to renal function [2-6]. Therefore, this review focuses on sirt1 and discusses its role in inducing apoptosis in podocytes in diabetic nephropathy.

Food and Diabetic Nephropathy

Yuan, et al. [7] reported that the plant-derived compound diosgenin has a protective effect on podocyte injury in diabetic nephropathy by enhancing podocyte survival, suppressing inflammatory injury, and weakening insulin resistance. They also showed that diosgenin activates the AMPK/SIRT1/NFκB signaling pathway. These findings indicate that diosgenin may suppress diabetic nephropathy.

Puerarin is the active ingredient in Radix puerariae and a major compound used in traditional Chinese medicine used to treat patients with diabetic nephropathy. Li et al. [8] showed that in streptozocin-induced diabetic mice, puerarin protects

podocytes from diabetic damage through the upregulation of HMOX1 and SIRT1-mediated autophagy.

Li, et al. [9] reported effects of the traditional Chinese medicine, baicalin (5,6,7-trihydroxyflavone), using cell-based methods. Baicalin is in the Chinese Pharmacopoeia and is a major flavonoid purified from the roots of Astragalus membranaceus. Treatment with baicalin after hyperglycemic stimulation decreased the rate of apoptosis and increased the survival of podocytes. Furthermore, in diabetic nephropathy, the effects of baicalin are associated with the SIRT1/NFκB signaling pathway.

Chang, et al. [10] investigated the role of Tanshen-Weining formula, a traditional Chinese medicine, using db/db mice, a model of type II diabetes. Apoptosis activity and levels of cleaved caspase-3 were elevated in the kidneys of db/db mice compared with non-diabetic mice and Tanshen-Weining formula suppressed these effects. Podocyte damage in db/db kidneys was reduced by Tanshen-Weining formula. The levels of podosin and nephrin in the kidneys of db/db mice were reduced compared with those in the kidneys of non-diabetic mice, and podocalyxin was increased in the urine of db/db mice compared with non-diabetic mice. After treatment of db/db mice with Tanshen-Weining formula, levels of podosin and nephrin increased in the kidneys and urinary podocalyxin was suppressed. db/db mice had lower SIRT1 levels and higher HIF1α levels in the kidney compared with non-diabetic mice, but Tanshen-Weining formula promoted SIRT1 and inhibited HIF1α in the kidneys of db/db mice. Furthermore, SIRT1 levels were reduced in podocytes of db/db mice compared with those in non-diabetic mice and Tanschen-Weining formula normalized this reduction.

Xue, et al. [11] investigated Lou, et al. [12] generated a diabetic nephropathy mouse model by combining streptozotocin with a high-fat diet. The mouse model showed increased levels of fasting blood glucose, glycated hemoglobin, triglycerides, total cholesterol, and inflammatory cytokines, decreased levels of nephrin and podosin, increased rates of apoptosis, and enhanced oxidative stress. Administration of cholagin, an ellagitannin from the Tanninaceae family of medicinal plants, improved all these measures. Furthermore, cholagin increased levels of SIRT1 and AMPK, inhibited reactive oxygen species and oxidative stress, and increased autophagy in hyperglycemia-induced podocytes. These findings indicate that cholagin mitigates podocyte damage by regulating autophagy through the SIRT1-AMPK pathway.

The effect of mogroside IIIE, a cucarbitan-type compound isolated from Siraitia grosvenori, on MPC-5 cells under normal glucose or hyperglycemic conditions. Mogroside IIIE enhanced the viability of hyperglycemic MPC-5 cells, and reduced levels of inflammatory cytokines and oxidative stress-related markers. Furthermore, hyperglycemia-induced podocyte apoptosis was inhibited after MG IIIE intervention: BCL2 levels were upregulated, BAX levels were downregulated, and cleaved caspase 3 and caspase 9 were observed. Mogroside IIIE also activated AMPK/SIRT1 signaling.

Thus, AMPK/SIRT1 signaling in podocytes is important in the onset and progression of diabetic nephropathy, and suppressing this mechanism appears to be a key factor in the progression of complications from diabetes to nephropathy.

Medicine and Diabetic Nephropathy

Obstruction of the renin-angiotensin II system prevents or delays albuminuria in diabetic patients. Gu et al., [13] investigated the inhibitory mechanism of the angiotensin receptor blocker, olmesartan, on albuminuria in a mouse model of diabetic nephropathy and reported that olmesartan suppressed the increased number of apoptotic cells and decreased the number of podocytes in diabetic glomeruli. Furthermore, in vitro studies revealed that olmesartan prevented angiotensin II/p38/SIRT1-induced podocyte apoptosis, while slightly suppressing the prevention of high-glucose/AMPK/SIRT1-induced podocyte apoptosis. This represents a novel mechanism of action for olmesartan.

Zhuang, et al. [14] investigated the mechanism by which metformin, a first-line hypoglycemic agent for the treatment of type 2 diabetes, protects renal podocytes under high-glucose conditions and the association between miR-34a and SIRT1 in diabetic nephropathy. Microarray and RT-qPCR analyses revealed that miR-34a is downregulated in hyperglycemic podocytes, concomitant with decreased cell viability and induction of apoptosis. Metformin administration to hyperglycemic podocytes upregulated miR-34a, suppressed apoptosis, and restored cell viability. A dual luciferase reporter assay showed that the SIRT1 3′-UTR is a direct target of miR-34a. Further studies showed increased levels of SIRT1 in hyperglycemic-exposed podocytes, while metformin treatment decreased SIRT1 levels. Furthermore, upregulation of miR-34a reduced SIRT1 levels, while inhibition of miR-34a increased intracellular SIRT1 levels. These observations indicate that metformin-induced miR-34a suppresses podocyte apoptosis by acting on SIRT1 under hyperglycemic conditions.

Since it has been shown that drugs can also affect the AMPK/SIRT1 mechanism, it is expected that these research findings will be confirmed and applied in the future.

Conclusion

The mechanism of podocyte apoptosis in diabetic nephropathy has been elucidated through animal model and in vitro studies, and the effects of herbal medicines and other drugs on this mechanism are now being investigated. Further investigation and confirmation of results are crucial for the development of these drugs. In addition, well-designed and rigorously controlled clinical trials are essential to evaluate safety, efficacy, and long-term effects of drug candidates in diverse patient populations. Clinical data are indispensable to confirm whether the benefits observed in preclinical models translate to meaningful outcomes in humans. If validated by rigorous clinical evidence, these treatments have the potential to provide novel treatment options.

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