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Molecular signaling pathways of diabetic kidney disease; new concepts

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Abstract

Diabetic kidney disease is a main cause of end-stage renal disease (ESRD), therefore, it is important to understand the molecular mechanism underlying diabetic kidney disease. Todays, various factors such as hemodynamic changes, molecular signaling and metabolic pathways have been shown to be involved in its pathogenesis. Excessive glucose influx stimulates cellular signaling pathways, containing advanced glycation end-products (AGEs), oxidative stress conditions, Rho-kinase, the diacylglycerol (DAG)-protein kinase C (PKC) pathway, polyol pathway and hexosamine pathway. In hyperglycemic condition, these factors cooperate with other aggravating factors. Then activated inflammatory processes lead to the development of glomerulosclerosis. The aim is to describe understanding of the signaling pathways in diabetic kidney disease.

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Introduction

Diabetes mellitus is a metabolic disorder that its proportion is increasing in both developed and developing countries. Diabetic kidney disease is one of the critical complications of diabetes mellitus that strongly associates with cardiovascular events. Thus, understanding the molecular mechanisms underlying diabetic kidney disease is critically important while diabetic renal disease is a recognized cause of end-stage kidney failure. Generally, diabetic kidney disease is usually demonstrated by albuminuria, followed by a deterioration of glomerular filtration rate (GFR), which over years causes end-stage kidney disease (ESKD) in most of the individuals with type 1 or type 2 diabetes. The pathological studies show glomerular podocytes injure followed by the continuing, inexorable damaging of the kidney glomeruli, then induces fibrosis, infiltration and tubular atrophy in tubulointerstitial area. Molecular studies explain the molecular signaling mechanisms that result to diabetic kidney disease to find effective modalities and preventative strategies as well (1). Based on evidence, various cell types in the kidney are participating in extension of diabetic kidney disease like mesangial, endothelial cells and also podocytes. For example, signaling abnormalities of mesangial cells inducing matrix protein expression or diminishing matrix metalloproteinase expression have been obviously linked to the pathogenesis of diabetic kidney disease. Furthermore, the signaling abnormalities of podocytes leading to podocyte damage directly contribute to glomerulosclerosis and finally diabetic kidney disease (2). Additionally, based on evidence, damaged podocytes may stimulate mesangial cells to react through augmentation of extracellular matrix (ECM) synthesis or diminution in ECM degradation. However, it is important to elucidate during diabetic kidney disease development what signaling abnormalities in mesangial, endothelial and podocyte cell types occur. Some of these signaling abnormalities and molecular signaling pathways are discussed

Core tip

Excessive glucose influx stimulates cellular signaling pathways, including advanced glycation end-products (AGEs), oxidative stress conditions, Rho-kinase, the diacylglycerol (DAG)-protein kinase C (PKC) pathway, polyol pathway and hexosamine pathway. In hyperglycemic condition, these factors cooperate with other aggravating factors. Then activated inflammatory processes lead to development of glomerulosclerosis.

in this paper.

Materials and Methods

For this review, we used a variety of sources by searching through Web of Science, PubMed, EMBASE, Scopus and directory of open access journals (DOAJ). The search was performed using combinations of the following key words and or their equivalents like; diabetic nephropathy, signaling pathways, metabolic pathway, end-stage kidney disease, diabetic kidney disease, type II diabetes mellitus, diabetic nephropathy, end-stage renal disease, glomerulosclerosis, glomerular filtration rate and podocyte.

Hemodynamic mechanisms

Based on evidence, hyperglycemia increases the blood flow into afferent arterioles, resulting in an increase in glomerular filtration and excess of glomerular pressure. Increasing glomerular pressure is a compensatory mechanism that induces a reduced number of functioning nephrons and an increased GFR of the kidney. Additionally, hyperglycemia and insulin resistance cause activation of angiotensin-converting enzyme2 that plays a pivotal role on the extension of glomerular hyperfiltration. Angiotensin II that has fibrotic effects on glomeruli can stimulate expression of tissue growth factor (TGF-B), activate protein kinase C (PKC) and NF-κB factor in following augment ECM production in mesangial cells (2). Increased glomerular filtration by hyperglycemia can reduce calcium influx into the vascular smooth muscle of the afferent arterioles; therefore, their contraction is suppressed. Additionally, increases of prostaglandin is associated with damaged myogenic responsiveness of the afferent arterioles. In diabetic patients, glucose concentration in the glomerular filtrate is increased, which causes an increased re-absorption of glucose by sodium glucose cotransporter (SGLT) 2 in the proximal tubules. It has been shown that hyperglycemia and TGF-B induce *SGLT2* gene expression in the proximal tubule. Therefore, SGLT2 inhibitors have appeared as a novel therapeutic option against diabetes. Accordingly, SGLT2 inhibitors suppress glomerular hyperfiltration and attenuate albuminuria in diabetic patients (3).

Metabolic mechanisms

The accumulation of metabolites of glucose metabolism pathways has a significant role in the pathogenesis of diabetic renal disease. The various pathways involved in the pathogenesis of diabetic kidney disease such as; polyol pathway, hexosamine pathway, diacylglycerol-protein kinase C (DAG-PKC) pathway, advanced glycation end-products (AGEs) and finally oxidative stress.

Protein kinase C pathway

PKC, a serine/threonine-related protein kinase, involves in various cellular signaling pathways that be activated in the vessels of retina and glomeruli under diabetic situations. PKC is activated by Ca^{2+}, DAG, phospholipids, such as phosphatidylserine and phorbol esters. It has been found that DAG levels are elevated in vascular tissues and glomeruli under diabetic situations due to an augment in the glycolytic intermediate dihydroxyacetone phosphate. Therefore, accumulation of DAG in the cell activates PKC by binding to the DAG binding site in the regulatory domain of PKC (4). Notably, AGEs and oxidative stress can activate PKC in mesangial cells then PKC activates inflammatory signals and fibrotic factors such as endothelin (ET)-1, vascular endothelial growth factor (VEGF), connective tissue growth factor (CTGF) and transforming growth factor (TGF)-βm, thereby enhancing the extension of diabetic nephropathy (5).

Advanced glycation end-products pathways

AGE, as a non-enzymatic glycation of products, is formatted by hyperglycemia that can modify protein function and activate inflammatory signaling pathways. Some studies demonstrate AGEs promote glomerulosclerosis and podocyte abnormalities through NF-κB activation, nitric oxide (NO) and reactive oxygen species (ROS) generation (6).

Polyol pathway/hexosamine pathway

Under hyperglycemic conditions, polyol and hexosamine pathways are reduced glucose to sorbitol by aldose reductase (AR) then converted to fructose by sorbitol dehydrogenase (SDH). Indeed, the polyol pathway contains two enzymes. Firstly, AR which decreases glucose to sorbitol with support of its cofactor NADPH, and secondly SDH which converts sorbitol to fructose with assistance its co-factor NAD+. Therefore, these enzymes decrease the ratio of NADPH/NADP and increase the ratio of NADH/NAD, thus, leading to stopping of glyceraldehyde-3 phosphate dehydrogenase (GAPDH) activity (7). GAPDH is required for the glycolytic conversion of glyceraldehyde 3-phosphate hence, inactivation of GAPDH results in an increase of glyceraldehyde 3-phosphate, which causes production of methylglyoxal, an AGEs precursor and DAG. Thus, a decrease of NADPH causes inhibition of NO synthase (NOS) activity, implying the reason that NOS utilizes NADPH as a coenzyme. Numerous studies show that AR inhibition attenuates high glucose-mediated PKC activation and the TGF-β gene expression in mesangial cells. On the other hand, glucose-6-phosphatase is converted to fructose-6-phophate by hexosamine pathway, and then converted to glucosamine-6-phosphate, and finally uridine 5'-diphospho (UDP)-N-acetyl glucosamine (UDP-GlcNAc) by glutamine fructose-6-phosphate aminotransferase (GFAT) (8). It has been shown that UDPGlcNAc provides O-GlcNAc modification of the serine/threonine residue of protein and competes with phosphorylation, leading to inhibition of the protein function such as insulin signaling pathway. Also, hexosamine pathway induces TGF-β synthesis in mesangial cells thereby induce development of diabetic kidney disease (9).

Nitric oxide signaling

It has been shown that NO produces in high amounts in diabetic glomeruli and can accelerate redox signaling. In addition, it can cause downstream injury to various cells such as endothelial and mesangial cells and also podocytes. In mesangial cells, NO can combine with soluble guanylate cyclase actually and induce activation of fibrotic factors. Some reports demonstrate NO activates presentation of secreted modular calcium binding protein 1 (SMOC-1) that it stimulates TGF-β and CTGF expression in mesangial cells therefore; SMOC-1 is a notable mediator of pro-fibrotic parameter in the mesangial cell (9).

JAK/STAT signaling pathway

Recently it has been detected that activation angiotensin II performs through Janus kinase signal/transducers and activation of transcription (JAK/STAT) signaling pathways. Thus, this pathway may be influential in the glomerular reaction to diabetes. The JAK proteins connect exclusively to cytokine receptors, like interleukins and interferons then activate associated- tyrosine kinases, therefore, activate the cytokine receptor itself (10). Some in vitro studies demonstrate high glucose promotes JAK2 activation that may be connected to activation of JAK2 through ROS, while ROS are induced by high glucose in glomerular mesangial cells. Additionally, ROS stimulate the activity of JAK2 in fibroblasts (9,10).

In addition, hyperglycemia with mediated ROS activates transcription factors like STAT1 and STAT3 then results to tyrosine phosphorylation of JAK2 in mesangial cells. Afterwards, JAK2 activation mediate collagen IV and fibronectin production, transforming growth factor beta (TGF-β) activation and cell growth due to inducing of expression angiotensin II (11). Some reports show *JAK/STAT* genes are presented at higher levels in samples derived from glomeruli, tubules and interstitial area in human diabetic kidney disease (9-11).

Plasminogen activator inhibitor-1 activation

In the plasma and kidney of humans with diabetic kidney disease, levels of plasminogen activator inhibitor (PAI)-1 increases, leading to a decline in plasmin activity due to inhibition of tissue plasminogen activator. On the other hand, protease activity of plasmin decreases, resulting in augment accumulation of ECM proteins, like fibronectin. Hence, inhibition of plasminogen activation may attribute to glomerular modifications of diabetic kidney disease. Likewise, various investigations show hyperglycemia may decrease urokinase plasminogen activator levels and plasmin activity on mesangial cells. In vitro studies show cultured mesangial cell PAI-1 expression augmented by ROS leads to provocation of TGF-β (12). Recent investigations showed that podocyte signaling abnormalities are critical contributors in the pathogenesis of diabetic kidney disease. The podocytes function in various modes is to create and keep the glomerular selectivity barrier. In fact, podocyte foot processes are bridged through a sieve-like slit diaphragm. Podocytes attribute to the synthesis of the glomerular basement membrane (GBM) and podocytes actively crosstalk with glomerular endothelial cells by VEGF (13). In advanced diabetic kidney disease, the total proportion and density of podocytes reduces due to apoptosis and/or detachment from the glomerular basement membrane. Some evidences show that signaling irregularities in diabetic podocytes mostly are including TGF-β family, monocyte chemoattractant protein (MCP)-1/cysteine chemokine receptor (CCR)-2 system and VEGF pathways (10,12).

Increased TGF-β signaling

Hyperglycemia can be activated expression of TGF-β and its receptor TGF-βRII at the podocyte/GBM interface due to modifications in the integrins that prepare adhesion between the two layers which can result to effacement of the foot processes of podocytes and resultant proteinuria. Also, integrin may also attribute to the bio-activation of TGF-β through a conformational change. Furthermore, TGF-β could also participate in glomerular basement membrane thickening and it is a major pro-apoptotic factor in the diabetic podocyte with the apoptosis cascade started once TGF-β concentration surpasses a certain threshold (12).

Finally, TGF-β has a main role on the advanced damage to podocyte in diabetic kidney disease through two mechanisms. First; diminished attachment of the podocyte to the glomerular basement membrane and secondly activation of apoptosis possibly by multiple redundant signaling pathways. Moreover it has been detected that detached podocytes due to apoptosis, decreased podocyte density and presence of apoptotic cells in the kidney and entrance of live podocytes in the urine in diabetic kidney disease (10-12).

Increased MCP-1/CCR2 signaling

MCP-1, a cysteine–cysteine ligand chemokine, is as a mediator of diabetic kidney disease. MCP-1 levels of urinary excretion correlate considerably with proportion of proteinuria in human patients. Recent evidences display MCP-1 may play a significant role in chemical attraction of monocytes and macrophages in kidneys of diabetic individuals that go beyond inflammation (14). Also, in response to metabolic mediators, like AGEs and TGF-β, podocyte MCP-1 production increases. Therefore, the changes of metabolic mediators induce alteration of podocyte function that is a likely explanation for the correlation between MCP-1 and proteinuria in human with diabetic kidney disease (15).

Increased Wnt/β-catenin signaling

Wnt/β-catenin pathway system activity is rapidly increased in diabetic kidney disease. Numerous studies show Wnt/β-catenin pathway is a main element of podocyte dysfunction and albuminuria. On the other hand, the Wnt/β-catenin pathway seems to be attributed to podocyte injury eventually by down regulating nephrin or redistributing(14). The β-catenin function - as a structural

protein - mediates through relating with the cadherin complex and densin at the slit diaphragm. The β-catenin nuclear translocation and signaling are actively moderated by integrin-linked kinase (ILK), while ILK considerably is upregulated in the diabetic podocyte (16). Notably, the ILK/β-catenin pathway may comprise a mechanism by which podocytes sense GBM dysregulation and then react through altering their foot process morphology and finally slit diaphragm arrangement (14,16).

Increased VEGF signaling

Investigations demonstrate that podocytes are the main source VEGF. In renal injuries, VEGF levels are low and are related to impaired angiogenesis with capillary loss (1). In early stages of diabetic kidney disease, VEGF levels and downstream signaling are amplified. However, it seems to be reduced to under normal value with extensive diabetic kidney disease. This early increase in VEGF levels could be due to hyperglycemia or increased signaling through TGF-β, angiotensin II and/or hypoxia-inducible factor-1 (HIF-1). Moreover, this increase has critical impacts on podocyte physiology and pathophysiology (13). After its secretion, VEGF can activate podocytes in an autocrine manner, probably via binding the VEGFR-1 receptor, and induce collagen synthesis via PI3K signaling. Therefore, enhanced VEGF levels induce podocyte GBM matrix protein construction (13).

Rho/Rho-kinase pathway

Rho, a small GTPase binding protein, is localized in the cytosol as a GDP-bound form (inactive form). Under physiological conditions, it is translocated to the cell membrane and can bind into the GTP and make complex form (active form), then activate downstream signaling through Rho-kinase. According to various evidences, numerous factors like hyperglycemia, cytokines and growth factors can activate Rho and increase Rho-kinase activity which connects to the pathogenesis of diabetic nephropathy. In hyperglycemia condition, ROS and PKC levels increase by high glucose-mediated Rho activation and this activation can be inhibited by antioxidants in vascular endothelial cells. Therefore, Rho-kinase is an effector of small-GTPase binding protein that implicates in the pathogenesis of diabetic kidney disease by inducing endothelial dysfunction, podocyte abnormality, excessive ECM production, and finally tubulointerstitial fibrosis, tubular atrophy and mesangial sclerosis in glomeruli (7).

Oxidative stress

Oxidative stress is induced by the imbalance of ROS generation and total antioxidant activity of body. ROS elicits inflammatory signaling pathways that are various sources of ROS production, containing NADPH oxidase and mitochondria. NADPH oxidase is triggered by an augment in the NADH/NAD+ ratio that is induced by increased flux through the polyol pathway. Also, NADPH oxidase activity is increased by chronic hyperglycemia condition and/or free fatty acid-mediated PKC activation. There are some documents that show AGEs can promote ROS generation by modulating catalytic sites in the molecular structure and via AGEs receptors (RAGE) (6). During glucose metabolism, glycolysis transforms glucose molecules to form pyruvate and then enters into the tricarboxylic acid (TCA) cycle, leading to production of ATP through oxidative phosphorylation in the mitochondrial respiratory chain complex. Also, TCA cycle produces NADH and $FADH_2$ which act as electron donors and protons, during oxidative phosphorylation. Then electrons are transferred to molecular oxygen (O2) that O2 is reduced to water and occasionally is converted to superoxide anion (5). In hyperglycemia condition the proton transfers to oxygen radicals, leading to excessive production of superoxide. Therefore, augmentation of superoxide radicals can induce initiation of inflammation signaling pathways (6).

Conclusion

In this review, we demonstrated various signaling pathways such as hemodynamic, metabolic mechanisms and some inflammation signaling pathways underlying diabetic kidney disease. It should be noted that future investigations are mandatory to validate the clinical application of each signaling pathways and management of inhibitor compounds against diabetic kidney disease. In addition to such clinical attempts, future studies are necessary to identify the factor governing these signaling pathways which may provide a novel therapeutic target against diabetic kidney disease.

Authors' contribution

EA searched and gathered the related articles as well as writing. MA prepared the draft. HN edited the final manuscript several times. All authors read and signed the final paper.

Conflicts of interest

The authors declare no conflict of interest.

Ethical considerations

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

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References

1. Badal SS, Danesh FR. Diabetic nephropathy: emerging biomarkers for risk assessment. Diabetes. 2015;64:3063-5.
2. Krolewski AS, Skupien J, Rossing P, Warram JH. Fast renal decline to end-stage renal disease: an unrecognized feature of nephropathy in diabetes. Kidney Int. 2017 Mar 30.
3. Luo X, Wu J, Jing S, Yan LJ. Hyperglycemic stress and carbon stress in diabetic glucotoxicity. Aging Dis. 2016;7:90-110.
4. Oikari S, Makkonen K, Deen AJ, Tyni I, Karna R, Tammi RH, et al. Hexosamine biosynthesis in keratinocytes: roles of GFAT and GNPDA enzymes in the maintenance of UDP-GlcNAc content and hyaluronan synthesis. Glycobiology. 2016;26:710-22.
5. Tobias IS, Kaulich M, Kim PK, Simon N, Jacinto E, Dowdy SF, et al. Protein kinase Czeta exhibits constitutive phosphorylation and phosphatidylinositol-3,4,5-triphosphate-independent regulation. Biochem J. 2016;473:509-23.

6. Aghadavod E, Khodadadi S, Baradaran A, Nasri P, Bahmani M, Rafieian-Kopaei M. Role of oxidative stress and inflammatory factors in diabetic kidney disease. Iran J Kidney Dis. 2016 Nov;10:337-43.
7. Sun L, Dutta RK, Xie P, Kanwar YS. myo-Inositol oxygenase overexpression accentuates generation of reactive oxygen species and Exacerbates Cellular Injury following High Glucose Ambience. J Biol Chem. 2016;291:5688-707.
8. Yao F, Zhang M, Chen L. 5′-Monophosphate-activated protein kinase (AMPK) improves autophagic activity in diabetes and diabetic complications. Acta Pharm Sin B. 2016;6:20-5.
9. Sutariya B, Jhonsa D, Saraf MN. TGF-beta: the connecting link between nephropathy and fibrosis. Immunopharmacol Immunotoxicol. 2016;38:39-49.
10. Thomas MC. Epigenetic Mechanisms in Diabetic Kidney Disease. Curr Diab Rep. 2016;16:31.
11. Wu J, Han J, Hou B, Deng C, Wu H, Shen L. Sulforaphane inhibits TGF-beta-induced epithelial-mesenchymal transition of hepatocellular carcinoma cells via the reactive oxygen species-dependent pathway. Oncol Rep. 2016;35:2977-83.
12. Sutaria A, Liu L, Ahmed Z. Multiple medication (polypharmacy) and chronic kidney disease in patients aged 60 and older: a pharmacoepidemiologic perspective. Ther Adv Cardiovasc Dis. 2016;10:242-50.
13. Hsu YH, Li HH, Sung JM, Chen WY, Hou YC, Weng YH, et al. Interleukin-20 targets podocytes and is upregulated in experimental murine diabetic nephropathy. Exp Mol Med. 2017;49:e310.
14. Meng J, Li L, Zhao Y, Zhou Z, Zhang M, Li D, et al. MicroRNA-196a/b Mitigate Renal Fibrosis by Targeting TGF-beta Receptor 2. J Am Soc Nephrol. 2016;27:3006-21.
15. McClelland AD, Herman-Edelstein M, Komers R, Jha JC, Winbanks CE, Hagiwara S, et al. miR-21 promotes renal fibrosis in diabetic nephropathy by targeting PTEN and SMAD7. Clin Sci (Lond). 2015;129:1237-49.
16. Ng KP, Jain P, Gill PS, Heer G, Townend JN, Freemantle N, et al. Results and lessons from the Spironolactone To Prevent Cardiovascular Events in Early Stage Chronic Kidney Disease (STOP-CKD) randomised controlled trial. BMJ Open. 2016;6(2):e010519.