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Review Article

New perspectives on markers implicated in signalling pathways that advance diabetic nephropathy and its therapeutic approaches

Rahul Sharma[1]*, Jaskaran Singh[2]

[1]Coderite technologies, Punjab, India
[2]Bristol Myers Squib, Hyderabad, India

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***Correspondence:**
Dr. Rahul Sharma,
Email: rahulsharma09sep@gmail.com

ABSTRACT

Diabetic nephropathy is the chronic loss of kidney function occurring due to diabetes mellitus. Due to increased sugar levels, there is disfunctioning of glomeruli, loss of protein in urine, and decrease in the levels of serum albumin that mainly leads to edema. The progression of renal disfunctioning starts when glomerular filtration rate is greater than 90ml/min. A large body of evidence indicates that oxidative stress is the main attributor involved in the progression of macro-vascular complications of diabetes. (ROS), NAD(P)H oxidase, advanced glycation end products (AGE), polyol pathway, uncoupled nitric oxide synthase (NOS), mitochondrial respiratory chain via oxidative phosphorylation, protein kinase C, mitogen-activated protein kinases, cytokines and transcription factors eventually cause increased expression of extracellular matrix (EC) genes with progression to fibrosis and end stage renal disease. Apart from these well-established pathways, major markers in the kidney disease which could work as potential targets has been explored like MCP-1, BMP-7, p38 MAPK, MiR-130b, HSP-27, AKT which further needs more research as they have shown promising results in their early level of studies. The present review aims to investigate the molecular targets involved in diabetic nephropathy, and to comprehend the intricate signalling pathways, such as JAK/STAT, BMP-7–Smad1/5/8 pathway, RhoA/ROCK, caspases, to which the aforementioned markers have either an independent or dependent relationship. If these signalling pathways are properly studied, these markers may aid in the treatment of the disease and its associated secondary effects such as nephropathy.

Keywords: Diabetic nephropathy, Biomarkers, Inflammation, Metabolic changes, Haemodynamic changes, End-stage renal disease

INTRODUCTION

Diabetic nephropathy is one of the major microvascular and macrovascular complication that leads to renal disease progression.[1] This clinical syndrome consists of a progressive reduction in glomerular filtration rate (GFR), hypertension, and persistent albuminuria with an albumin excretion rate greater than 300 mg/d.[2] Increased hyperfiltration of glomerulus followed by microalbuminuria are the early signs of diabetic nephropathy which progresses to the ESRD (End stage renal disease) if microalbuminuria continues to degrade kidney function.[3] A recent study on the prevalence of ESRD associated with diabetic nephropathy from 142 nations, representing 97.3% of the global population, showed a significant increase in the illness's incidence from 375.8 to 1016 million cases.[4] Increased hyperglycaemia leads to formation of free radicals causing oxidative stress and Inflammation that are the first main reasons involved in disrupted pathways like p38 MAPK p42/p44, JAK, STAT, ERK, AKT, TAK SMAD.[5] The main metabolic factors, haemodynamic factors and secondary messengers like advanced glycation end

products, polyols, lipids, angiotensin, PKC, MAPK, ROS cause inflammation that leads to messangial cell expansion and extracellular matrix deposition . All this further leads to glomerular hyperfilteration and renal disease progression, explained in Figure 1.[6] Various biomarkers are categorized according to their origin and pathogenicity of diabetic kidney disease. For example, NGAL falls into the category of tubular biomarkers, while IL-6, IL-8, TNF-α comes under biomarkers of inflammation, and markers such as IgG are the glomerular markers.[7] The aim of this review paper is to update knowledge on novel therapeutic targets and pathways involved in diabetic nephropathy.

VARIOUS BIOMARKERS WITH INVOLVEMENT IN THE DISEASE AND THEIR TARGET THERAPY

In this review various biomarkers are discussed with their involvement in the disease progression through various signalling pathways. Table 1 summarizes the biomarkers included in this section.

MCP-1

MCP-1 (monocyte chemoattractant protein 1) is a small cytokine that belongs to the CC chemokine family.[8] In diabetic nephropathy stimulation of macrophages with MCP-1 results in the activation of ERK and JNK signaling pathways which promote the macrophage release.[9] MCP-1 induces iNOS mRNA and nitric oxide release by peritoneal macrophages, which is regulated through phosphoinositol-3-kinase, PKC, and ERK. This indicates that there is a direct role for MCP-1 in macrophage activation.[10]

Pravastatin-inhibits the activation of extracellular signal-regulated kinase (ERK), NF-κB downstream signalling, and treats fibroblast proliferation in kidney disease and further treats progression of nephropathy. Furthermore, blockade of ERK activity prevents macrophage activity by inhibiting polymerization of globular microfilaments (actin) and TNF-α production.[11] MCP-1 induces a fibrotic response in glomerular mesangial cells.[12] MCP-1 signalling through Chemokine receptor encoded by CCR2 gene on human mesangial cells has shown that fibronectin mRNA and protein synthesis causes TGF-β1 production and activation of NF-κB in glomerular mesangial cells. This is an important aspect in diabetic glomerulosclerosis and causes diabetic nephropathy.[13] So MCP-1 can promote glomerular TGF-β1 production without affecting macrophage accumulation. Furthermore, mesangial expression of MCP-1 is stimulated by TGF-β1, which is the basic mechanism for mesangial matrix accumulation and cause kidney disease.[14]

BMP-7

BMP-7(bone morphogenetic protein) is a protein encoded by BMP-7 gene and is a member of the TGF-β superfamily.[15] Its major function is the transformation of mesenchymal cells into bone.[16] In diabetic nephropathy, BMP-7 function is compromised, podocytes go under high glucose condition that decreases synaptopodin, podocin and BMP-7 gene expression that affects vascular, mesenchymal cells expansion and new protein generation.[17] BMP-7 is not able to rescue the cell from apoptosis caused by the activation of capase-3 downstream signalling. In addition, agonistic action of BMP-7 through Smad-1, -5, -8 signalling ameliorates messengial proliferation and treats renal damage.[18] Recombinant human BMP-7 restores E-cadherin expression and decreases the effect of damage to renal epithelial cells and treatment restores the synaptopodin and podocin function.[19]

A study suggests that BMP-7 cause diabetic nephropathy that decrease DNA synthesis and decreases podocytes and messangial cells.[20] Gremlin is an inhibitor involved in BMP and TGF beta signaling pathway. Inhibition by Gremlin may induce therapeutic effects on the diabetic kidney by allowing the efficient binding of endogenous BMP7 to receptors without inhibition. Gremlin can increase DNA synthesis and cell counts and increase progression of vascular smooth muscle cells (VSMC) through mechanisms that include decreased levels of p27.[21]

RAGE

RAGE (receptor for advanced glycation end products) is a transmembrane receptor of the immunoglobulins. Advance glycation end products have specific binding affinity towards RAGE, other than these, amphotericin, amyloid beta peptide, S100/calgranulins are the other ligands involved.[22] In diabetic nephropathy there is interaction between RAGE and HMGB1 that leads to pro-inflammatory gene activation such as NF-κB and starts inflammation. As RAGE expression is increased, accumulation of at least two ligands - AGEs and S100/calgranulins increases with its expression.[23] RAGE can induce a range of signal transduction pathways including Ras pathways (apoptosis), Rac/Cdc42 and Jak/Stat pathways.[24] Study shows that SRAGE (Endogenous secretory or soluble RAGE) suppressed aortic lesion development, CML-AGE accumulation, AGEs and S100/calgranulins accumulation and suppressed the above-mentioned pathways.[25]

p38 MAP kinase

Through the stimulation of reactive oxygen species (ROS), inflammatory and profibrotic factors such as transforming growth factor (TGF- β), plasminogen activator-1 (PAF-1), TNF- α, p38 MAP Kinase (MAPK) contributes to the pathogenicity of diabetic nephropathy. The mediated effect of p38 MAP Kinase (MAPK) in RPTC (Renal proximal tubular cell) apoptosis, fibrosis and Diabetic nephropathy is mainly triggered by the inhibition of Akt activity during hypergylcaemia.[26] In diabetic nephropathy p38 MAP Kinase (MAPK), (Cytokinin Specific Binding Protein), is in interconnection with Hog1p MAP kinase, which participates in a signalling cascade that leads to activation of cytokines and inflammatory process. High glucose

activates Janus kinase/signal transducers and activators of transcription (JAK/ STAT) in mesangial cells.[27] The studies suggest ROS-dependent activation of p38 MAPK in mesangial cells causes high glucose levels and inflammation in diabetic kidney. NAC or DPI blocks activation of p38 mapk and reduce glucose levels.[28] Antioxidant lithospermate inhibits P38 MAPK activation in STZ induced diabetic rats. Inhibition of JAK2 and STAT1 cause high glucose–induced TGF-1 and fibronectin inhibition.[29]

Table 1: Various biomarkers with transduction pathways involved in diabetic nephropathy.

Biomarker	Molecular therapy	Pathway involved	Out turn of pathway involved
MCP 1(monocyte chemoattractant protein-1) ligand[11]	Pravastatin-inhibits the activation of extracellular signal-regulated kinase (ERK) and NF-Kb.	ERK- JNK Signalling	Activation of macrophages and attraction of monocytes towards kidneys as renal parenchymal cells secrete MCP-1 that stimulates extracellular matrix deposition and release proinflammatory mediators like IL-1, TNF-α
BMP-7[19,55]	Recombinant human BMP-7 (rhBMP-7) lessens the impact to renal epithelium, increases expression of E-cadherin. Recovers podocin and synaptopodin function	BMP-7–Smad1/5/8 pathway	Smad1/5/8 are linked to the elevation of BMP-7 levels, providing a renal protective effect.
RAGE[23,25]	SRAGE- suppressed aortic lesion development and CML-AGE accumulation.	JAK/ STAT Ras pathways	Interaction between HMGB1 and RAGE activates pro-inflammatory genes including NF-κB Increased RAGE expression is correlated with the accumulation of Advanced glycation end products and calgranulins.
TNF-α[32,56]	MMF (mycophenolate mofetil) decreases neutrophil adherence to endothelial cells, reduces IL-6 levels, molecule-1mRNA expression	Caspase- 3 downstream cascade	sodium retention renal hypertrophy. Accumulation of TNF- α Activation of IL-6
RhoA[50]	Fasudil inhibits the RhoA action by decreasing FAK phosphorylation Inhibits β1 integrin activation. Reduce collagenase IV accumulation	RhoA/ROCK	Increased accumulation of collagenase IV, messangial expansion and albuminurea RhoA is involved in actin remodelling those causes decreased glomerular filteration.
Kca3.1[52,54]	TRAM-34 reduces albuminuria renal obstruction and blocks Kca3.1 by reducing reducing expression of TGF-β2 and TβR II and decreasing extracellular matrix deposition	Smad2/3 signalling	Renal fibrosis and urelateral obstruction

Table 2: Evidences for the involvement of biomarkers in clinical and preclinical studies.

Biomarker	Study	Objective	Findings
MCP-1[57]	Clinical	Evaluation of the relationship between diabetic nephropathy and MCP-1	Dysregulated release, as well as activation of leukocytes, and increased MCP-1 concentrations in renal macrophages contributes to increased systemic levels. Subjects under investigation were correlated with UACR levels, ≥ 30 mg/g, were considered for diabetic nephropathy.
RAGE[58]	Clinical	Evaluation of RAGE expression in patients with Diabetic nephropathy in podocytes.	Increased RAGE mRNA expression was found in glomeruli whereas not in tubules or arterial walls in renal biopsy tissue from patients with diabetic nephropathy. Elevated expression of RAGE in the glomerular basement membrane which can cause Heymann nephritis

Continued.

Biomarker	Study	Objective	Findings
p38 MAPK[59]	Clinical	Understanding p38 MAPK signaling to co-relate inflammation and fibrotic mechanisms associated with Type 2 diabetic nephropathy by examining human biopsies using podocytes, cortical tubules and interstitial cells.	Findings revealed that the immunostaining p38 MAPK had undergone phosphorylation in podocytes, cortical tubules and interstitial cells. A similar pattern was observed in macrophages and myofibroblasts. Glomerular endothelial dysfunction. Glomerular hypertrophy, and mesangial cell expansion
RhoA[60]	In vitro	Investigating the role of RhoA/Rho kinase in the progression of diabetic nephropathy using rat (NRK-52E) and human renal tubular epithelial cells (RPTEC).	Findings concluded that In addition to increasing profibrotic growth related factors and alteration of cadherin mediated cell adhesion, RhoA promoted the production of inflammatory cytokines and extracellular matrix proteins. Increased activation of RhoA was linked to changes in the expression of fibronectin, CTGF, collagen- IV, TGF-β and E-cadherin in renal tubular epithelial cells.

TNF-α

There are two different receptors involved, TNF-R1 which is the epithelial cell type, and TNF-R2 which is the myeloid cell type. A number of signal transduction pathways are triggered when TNF-α binds to these receptors. The activation of pathways brings about the expression of cytokines, cell adhesion molecules, transcription factors, and major histocompatibility protein complexes resulting in apoptosis or necrosis.[30] In glomerular capillaries, TNF-α causes the presence of inflammatory cells, which are characterized by glomerular endothelial damage, polymorphonuclear cell accumulation and fibrin accumulation of cell.[31] In diabetic nephropathy due to overexpression of caspase 3 there is accumulation of TNF-α which leads to renal hypertrophy and activation of IL-6. MMF (mycophenolate mofetil) inhibits intercellular adhesion molecule-1 mRNA and surface expression, neutrophil adhesion to endothelial cells, interleukin-6 levels and TNF-a. In addition, MMF may also act on different pathways downstream of TNF- activation.[32]

IgG4

Membranous glomerulo nephropathy, renal fibrosis and tubulointerstitial nephritis are the most prevalent and immediate conditions of IgG-4 related renal disease.[33] When toll like receptors and nucleotide binding oligomerization domain containing protein 2 (NOD2) in monocytes and basophils perceive foreign pathogen associated molecular patterns (PAMPs) and damage associated molecular patterns (DAMPs), CD19+ cells get stimulated to release IgG4.[34]

The serum IgG4 levels gets elevated and contribute in antibody-dependant cell mediated cytotoxicity because they have limited binding affinity towards C1q and Fc receptors, which result in inadequate activation of classic component pathway.[35] In kidney disease, it has been observed that IgG4 was elevated due to decrease in GFR and disfunctioning in the surface density of glomerular basement membrane. Smad1 was associated with the degree of the mesangial cell expansion. All this happens due to infiltration of kidney tissues by lymphocytes and IgG4 secreting plasma cells that leads to fibrosis.[36] Statins have been found to lower uric acid levels and messangial cell hyperplasia and expression of SMAD signaling.[37]

MiR-130b

MiRNAs participating in controlling different grave life processes, specified as cell differentiation, proliferation, necrobiosis and the fix of cell and tissue process. MiR-130b has been seen to be playing a vital role in diabetic nephropathy. It was seen that when miR-130b was introduced, the fibrosis and proliferation of nephrotic cells were markedly enhanced. In human glomerular mesangial cells, miR-130b has functional activity towards TGF- β1 specifically, and the enhanced levels of miR-130b increases the downstream cascades of TGF-β1, t-Smad2/3, p-Smad2/3, and SMAD4 signalling. Increased expressions of collagen type 1, IV, fibronectin and protein levels were seen following an exogenous administration of miR-130b which was correlated with the activity of MiR-130b.[38]

NGAL

An auspicious marker of tubular dysfunction is Neutrophil gelatinase- associated lipocalin (NGAL) which is a flyspeck catalyst to the lipocalin superfamily, consisting of secretory proteins that bind and ship lipophilic molecules.[39] In diabetic nephropathy NGAL levels are elevated as a result of reduced reabsorption in the injured tubules that causes phagocytosis of messangial cells. Urinary NGAL levels have been demonstrated in previous research to rise

in Type 2 diabetes patients before to the development of conventional indicators (eGFR and albuminuria).[40] This suggests that urinary NGAL may be used as a supplemental test for the early detection of diabetic nephropathy. Lisinopril reduced urine-NGAL levels by ACE inhibition leading to decreased albuminurea.[41]

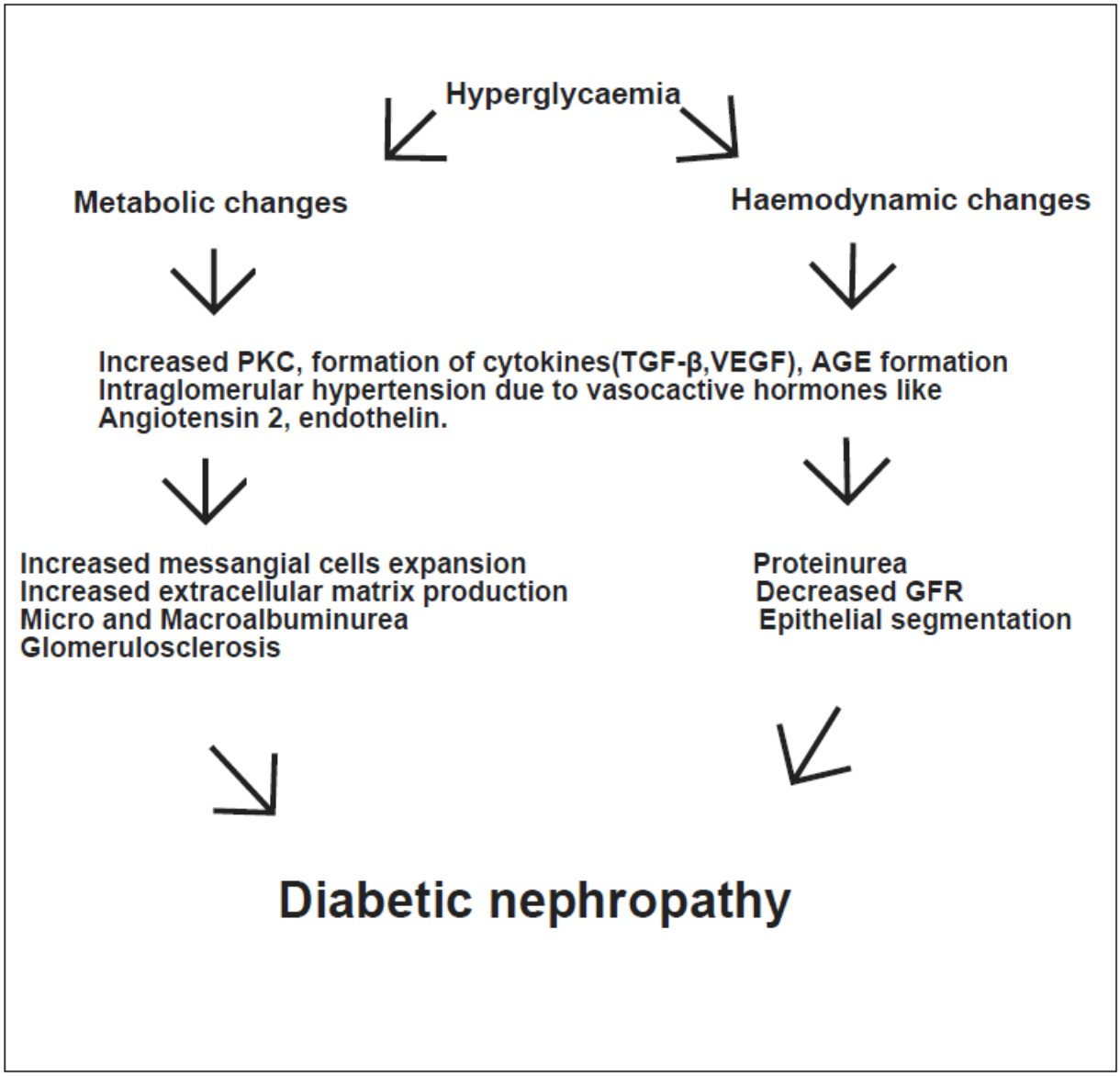

Figure 1: A schematic representation of pathogenesis of diabetic nephropathy.

The key pathways underlying renal damage in diabetes mellitus are depicted in the image. The pathophysiology of diabetic nephropathy is further exacerbated by increased oxidative stress and inflammation, mitochondrial dysfunction brought on by persistent hyperglycemia, changes in metabolism and hemodynamics, and mesangial cell expansion and vasoactive hormones.[6]

M235T

The involvement of M235T is highly included in polymorphism of the AGT gene in which TT genotype is affected in diabetic nephropathy. AGT gene region causes all changes in the M235T polymorphism. Due to M235T polymorphism, angiotensin II is sensitive to both changes in renin and small fluctuations in AGT, AGT gene expression and AGT concentration.[42] The changes lead to vasoconstriction and growth factor for vascular smooth muscle cells, glomerulosclerosis and mesangial cell hypertrophy, cardinal features of diabetic nephropathy.[43]

Interleukins (IL-1 and IL-18)

As the renal expression of IL-1 increases, the synthesis of ICAM-1 and vascular cellular adhesion molecule-1 increases that further enhances expression of ICAM-1 by glomerular mesangial cell expansion and renal tubular epithelium progressing towards nephropathy owing to tubular damage.[44] IL-1 induce transient expression of E-selectin by endothelial cells.[45] IL-1 is also involved in the synthesis of prostaglandin synthesis by mesangial cells.[46] IL-18 has been noticed to increase the production of other

cytokines (including IL-1 and TNF- α), and also increase levels of ICAM-1.[47]

HSP-27

HSP-27(heat shock protein) mainly responsible for thermo tolerance and cytoprotection to cells and is involved in Apaf-1 signalling pathway.[48] HSP-27 present in fibroblasts might affect those in the kidney and be pathophysiologically related to the development of nephropathy in type 1 diabetes mellitus. Increase in expression of HSP-27 in diabetic kidney increase the in phosphorylation of histone H3 that generates ROS and leads to nephropathy. Quercetin and curcumin are a potent inhibitor of HSP-27 that decreased histone3 phosphorylation.[49]

RhoA/ROCK

Numerous signaling pathways are regulated by the small GTPase protein RhoA that belongs to PKA/PKC family and ROCK (Rho kinase), which is an immediate effector of RhoA. The RhoA/ROCK signaling is involved in diabetic nephropathy as it antagonizes the insulin signalling pathways, and due to which it changes the cell size and contractility. Due to increased levels of RhoA there is a significant increase in activity of VEGF (vascular endothelial growth factor) that mainly causes messangial cell expansion leading to vascular endothelial glomerular endothelial cell hyperpermeability.[50] Fasudil, an inhibitor of ROCK (Rho kinase) decreases intercellular FAK phosphorylation, prevents β1 integrin activation and decrease accumulation of collagenase IV which further reduces the extracellular matrix deposition and albuminuria.[51]

KCa3.1

KCa3.1 causes renal fibrosis through increased levels of TGF-β1. The fibrotic effect of KCa3.1 is achieved due to increased expression of TGF-β1, TGF-β receptor II activation and the increased cascade of downstream Smad2/3 signalling that damages fibroblasts, proximal tubule cells and further contributing towards diabetes induced.52 The exact mechanism is still unknown, but it has been noticed that mitochondrial dysfunctioning takes place due to increased expression of TGF-β signaling pathway, which was ameliorated by causing KCa3.1 deficiency in renal tubular cells that inhibits BNIP3 expression, and an anti-fibrotic effect is thus achived due to stablilization of mitochondrial permeability.[53] TRAM 34 works as an ion channel blocker by blocking the activity of KCa3.1.[54] The mechanism of action is described in Table 1.

CONCLUSION

Diabetic nephropathy is an inflammatory disease prompted by a deranged metabolic and haemodynamic processes. Various changes like glomerulosclerosis, thickening of the glomerular basement membrane and mesangial expansion predict disease progression. A complete understanding of these pathways in DN may lead to the discovery of novel therapeutic strategies. The targets that we have discussed need to be explored on a deep bio molecular level as they might link to other targets or pathways that needs exploration. The pathogenicity of kidney disease related to diabetes is multifactorial, and the biomarkers discussed in this article have potential utility in accessing diabetic kidney disease, however, the available data currently hinder their routine application, so there is an immense need to study them for clinical evaluation.

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