An Update on Etiopathogenesis of Diabetic Kidney Disease and Their Therapeutic Implications-A Systematic Review

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Abstract

As we all know Diabetic Kidney Disease (DKD) represents the commonest etiology for Chronic Kidney Disease (CKD) along with end-stage renal Disease (ESRD). Earlier we have reviewed in detail the role of epigenetic modifications in the case of DKD and the medications undergoing trial regarding that like Apabetalone, Apelin, curcumin analogs, sodium, butyrate, the role of bromodomain extra terminal (BET) Proteins, roles of different histone acetylases like KDM6A (alias UTX), enhancer of Zeme Homolog 2 (EZH2) methylases, besides how to avoid propagation of CKD in general. As far as the natural history of DKD goes it is inclusive of glomerular hyperfiltration, propagative albuminuria along with reducing glomerular filtration rate (GFR), and finally renal failure.

We already possess the information that DKD is correlated with metabolic alterations that occur secondary to hyperglycemia causing glomerular hypertrophy, glomerulosclerosis, tubulointerstitial inflammation as well as fibrosis. Here we have updated other etiological factors like part of the Cannabinoid receptor (CB1) in DKD, and the role of Pyroptosis that is further being explored, along with an update regarding how hyperglycemia brings about epigenetic modifications.

Initially, it was believed that with the advent of sodium–glucose cotransporter 2 (SGLT2) inhibitors both cardiovascular outcomes (CVOT) as well renal outcomes improved. Nevertheless, all of these are efficacious just if an early diagnosis of DKD is made, however, nothing works in avoidance of the propagation of DKD. Numerous trials are going on with regards to Bardoxolone Methyl Treatment along with credence trials regarding Canagliflozin, positive actions of incretins might be renoprotective.

Further Hypoxia-inducible factor prolyl hydroxylaseampering agents having been approved for renal anemia are undergoing trials. Moreover, certain ACE2 inhibitors or angiotensin blockers are being worked out. Once it is realized which of these drugs works then the combination of SGLT2 inhibitors can be tried with proven positive actions of these drugs.

Keywords: DKD • Epigenetic Modifications Pyroptosis • Inflammation • Glomerulosclerosis • Fibrosis • SGLT2 Inhibitors

Introduction

At present the incidence of Diabetes mellitus (DM) is escalating with 400 million worldwide living with it. These quantities are anticipated to escalate to 600 million by the year 2035 [1]. People of all ages are impacted by DM, regardless of sex, ethnicity, education status, or income. Of these DM

patients 20% are anticipated to propagate Diabetic Kidney Disease (DKD) that gets impacted by genetic as well as environmental factors besides induction by microvascular along with macrovascular alterations along with

inclusive of extracellular matrix [ECM] besides fibrosis of Kidney glomeruli accrual as well as interstitium [2-5]. At the time of initiation DKD patients canonically display microalbuminuria with greater than 30-300 mg albumin excretion daily at the latter phases of the disease; the time this slowly gets converted to macroalbuminuria with over 300mg albumin excretion [6]. The hazard ratio regarding all-cause mortality in the case of DKD patients is, documented to be 1.83 in contrast to 1.46 for patients with normoalbuminuria [7]. In total complicated crosstalk amongst metabolic events, epigenetics along with no epigenetic modes, transcriptional control is implicated in the generation along with propagation of DKD. In this last decade, only agents like Sodium–glucose cotransporter 2(SGLT2) hampering agents Identification of these agents having effectiveness against hypoglycemia besides enhancement of Kidney results [8]. Additionally, endothelin-1 has been correlated with vasoconstriction, Kidney damage, mesangial hyperplasia, glomerulosclerosis, and fibrosis along with Inflammation, hence endothelin-1 receptor antagonists have been speculated as probable therapeutic agents for DKD [9]. Here our focus was on generated along with probable approaches with the objective of reducing the worsening of renal function as well as treatment of the particular significant complications in patients whose presentation is with DKD subsequent to reviewing epigenetic modifications in DKD, Vitamin C in AKI avoidance of CKD, the role of Vitamin D in renal diseases [10-15].

Impact of Hyperglycemia on Diabetes-Modulated Cellular Changes

In view of the uncontrolled expression of glucose transporter quantities of extracellular glucose would finally escalate intracellular quantities of glucose which leads to switching the glucose to the fructose-6 phosphate along with glucose hexosamine metabolic pathways [16, 17]. Hence hyperglycemia in general escalates quantities of advanced glycation end-products (AGE) along with Reactive oxygen species (ROS) that are intricately correlated with the generation of DKD. The generation of AGE takes place by non-enzymatic glycation reactions amongst reducing sugars, amino acids, lipids, or DNA along with are correlated with quantities of ROS formation [18]. Generation of ROS takes place at the time of mitochondrial Oxidative metabolism along with subsequent exposure to xenobiotics as well as cytokines via the reactions catalyzed by nicotinamide adenine nucleotide phosphate (NADPH) oxidases, nitric oxide synthase (NOS) along with xanthine oxidase as well as escalated ROS result in Oxidative stress(OS), along with cell demise. Prior studies illustrated that restricting the generation, of AGE) along with ROS is efficacious in reducing the rate of DKD propagation [19, 20]. Additionally, we already have the knowledge that ROS possess the capacity of activating Janus kinase / Signal Transducers and Activators of Transcription (JAK/STATs) pathway with an experiment in a mouse model studies illustrated that selectively expressing JAK2in glomerular podocyte escalated the functional along with pathological properties of DKD [21]. Furthermore, significantly escalated quantities of numerous JAK-STAT family members have been visualized [22].

Diabetic complications can ensue at the time of high glucose quantities secondary to escalated ROS generation [23]. The basic factors implicated in the generation of escalated ROS are the electron transport chain (ETC), as

well as electron leakage of NADH dehydrogenase in the mitochondria [24]. Elimination of mitochondrial regulation influences renal health in view of mitochondria being the main sources of ROS generation, apoptosis along with metabolism. This robust escalated ROS results in DNA injury, that in turn causes induction of GADPH poly ADP ribose polymerase (PARP) for hampering glyceraldehyde 3 phosphate dehydrogenase (GADPH) function, which causes the accrual of glycolytic metabolites. Following this generation of polyol, hexosamine, and diacylglycerol (DAG), activation of the protein kinase C (PKC) pathway as well as the formation of AGEs take place [25-27]. The crosstalk amongst AGEs along with their receptors RAGE facilitates the overgeneration of ROS in addition to activation of nuclear factor KB (NFκB) that causes upregulation of inflammation-associated genes, thus escalated tumor necrosis factor-alpha (TNFα), interleukin-6 (IL-6) as well as monocyte chemoattractant protein 1(MCP1) [28]. In addition to the OS, endoplasmic reticulum (ER) stress, along with inflammatory events induction take place due to hyperglycemia, besides reduction of NO accessibility along with dysfunctional angiogenesis which can result in endothelial impairment in the Kidneys [29]. Besides Hexosamine metabolic pathways activation by greater glucose quantities possess the capacity of altering signal transduction, gene transcription, and cell survival along with proteasome modulated breakdown as well as facilitates hyperglycemia stimulated vascular injury [30]. Moreover, greater glucose quantities result in accrual of ECM, besides upregulating the expression of DKK1, Kremen-2 receptor, transforming growth factor beta (TGF-β), along with fibrotic factors in mesangial cells, that finally enhances injury to the glomerular filtration barrier to result in DKD [31, 32].

Both DKD in addition to DM patients possesses greater proneness to inimical cardiovascular results, partially in view of Renin-Angiotensin-Aldosterone System (RAAS) activation. RAAS controls BP, salt balance, and fluid homeostasis, along with blockade of RAAS with an angiotensin-converting enzyme (ACE2) hampering agent or angiotensin receptor blockers(ARB) utilization is commonly done regarding modifications of hyperfiltration states besides postponement of Renal disease generation along with propagation [33, 34].

Agents that can result in improvement of hypertension (like lisinopril), as well as hyperglycemia (empagliflozin), was further illustrated to cause recovery of physiological along with histopathological examination(HPE) characteristics of Kidney Disease in a mouse model of hypertension aggravated propagative DKD [35]. Furthermore, treatment using N-acetyl-seryl-aspartyl-lysylproline (Ac-SDKP), which represents a naturally present immunomodulatory along with angiogenic enzyme basically generated via enzymatic hydrolysis implicating meprin α along with prolyl oligopeptidase has been illustrated to partly result in recovery of end-organ injury by reduction of inflammation as well as fibrosis along with facilitation of angiogenesis [36]. The advantageous action of mineralocorticoids receptor antagonists (MRAs) and eplerenone on renal outcome parameters like proteinuria have been observed for a certain time, with trials of generation of MRAs in the form of adjunctive treatments for reducing the risk of DKD going on [37]. Dipeptidyl Peptidase -4 (DPP-4) Inhibitors in general employed for the treatment of T2D have further been illustrated to avoid Diabetic Renal damage by different modes like hampering of DPP-4 by linagliptin decreases obesity correlated insulin resistance (IR) along with inflammation via the control of M1/M2 macrophages status besides ameliorating OS along with Diabetic Renal damage [38].

Glycosuria results in osmotic diuresis and usually takes place in the case of DM patients, once the quantities of glucose filtration become greater than the ability of renal tubular reabsorption. Sodium–glucose cotransporter 2 (SGLT2) hampering agents reflect a class of oral Diabetic medicines that possess the capacity of changing the physiology of the nephron, along with glucose reduction by eliminating sugar from the body via urine. Moreover, SGLT2) hampering agents can aid in restoring function to SIRT3, a mitochondrial NAD+-based deacetylase that can hamper EMT along with Renal fibrosis, which is repressed by escalated glucose quantities. Therapy with hampering agents which block acetylation-modulated STAT3 binding has further been illustrated to decrease proteinuria in db/db mouse models [39].

Genetic pathways correlated with DKD

Glomeruli represent the main filtration units of the Kidney and are comprised of capillary blood vessels structurally that possess the capacity of filtering plasma along with generating urine [40]. Every glomerulus is comprised of mesangial cells, podocytes, and tubular cells along with a basement membrane (BM), all work in concert for the sustenance of normal filtration functions (Figure1) [41]. Mesangial cells constituted 30-40% of total cells in the glomerulus as well as account for the elimination of immune complexes besides proteins from the blood which get trapped in the BM [42, 43]. Podocytes reflect remarkably specialized epithelial cells which cover the outer surface of the BM [44]. In adults, they undergo terminal differentiation, however, do not undergo replication. The sequelae of this are over 20% podocyte deletion or dysfunction of the glomerular filtration barrier can irreversibly injure a glomerulus, resulting in proteinuria [45]. We possess the information that hyperglycemia can cause apoptosis, detached glomerular BM besides elimination of glomerular podocytes, mesangial hypertrophy, matrix accrual as well as BM thickening, all of which are a cornerstone in early DKD which finally propagates to glomerular fibrosis besides proteinuria (figure1) [46, 47].

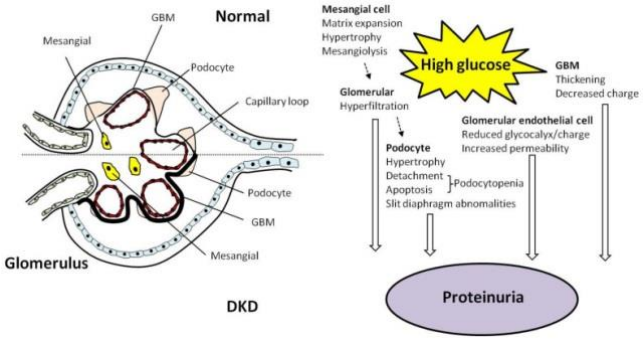

Figure 1: Courtesy ref no-41-Characteristic glomerular changes and mechanisms of proteinuria in diabetic kidney disease. Characteristic glomerular changes in diabetic kidney disease (DKD) include glomerular basement membrane (GBM) thickening and mesangial expansion (due to increased mesangial matrix and increased mesangial cell size caused by hypertrophy). These changes are driven by hyperglycemia, and can ultimately lead to proteinuria if left unaddressed. Dashed arrows indicate mesangial expansion leading to glomerular hyperfiltration.

Part of Hyperglycemia in Glomerular Fibrosis

Long-time damage along with abdominal wound repair events along with escalated ECM laying down reflect the major stimulators of renal fibrosis. Myofibroblasts are believed to be the primarily activated fibroblast phenotype in the case of renal fibrosis [48]. Knowledge regarding numerous sources of fibroblasts generating matrix inclusive of activated resident fibroblasts, differentiated pericytes, enrollment of circulating fibroblasts, besides mesenchymal cells transformed from macrophages, obtained from renal tubular epithelial cells via EMT or converted from endothelial cells via endothelial–mesenchymal transition (EndMT) [49]. Additionally, inflammatory cells along with inflammatory cytokines in addition to the correlated signaling pathways, all being major actors in the activation of fibroblasts [50].

Dense fibrosis of the glomerular micro milieu, in particular, mesangial cells is a landmark of DKD, along with the fibrosis of the mesangial cells is intricately correlated with the activation of the TGF-β1 signaling pathway, which facilitates the activation of fibroblasts, besides aberrant generation of the profibrotic matrix in mesangial cells [51]. Additionally, TGF-β1 facilitates the proliferation, and differentiation of renal cells along with the generation of ECM [52], as well as renal tubular epithelial cells EMT, which is necessary for the formation of tubulointerstitial fibrosis [53]. Probably these inimical alterations in mesangial cells, endothelial cells along with podocytes might be correlated. Hyperglycemia has further been associated with the breakdown of the podocytes-glucocorticoid receptor signaling pathway as per our knowledge for further stimulating EndMT along with resulting in glomerular fibrosis in the case of DM.

Moreover, glomerular fibrosis activates the Wnt/β-catenin signaling, which manipulates TGF-β1 modulated fibrosis in mesangial cells [54]. This can further cause activation of glycogen synthase kinase 3 β (GSK3β) signaling along with induction of apoptosis in mesangial cells [55, 56]. A prior study illustrated that GSK3β phosphorylation reduced the activation of fibroblasts as well as the generation of fibrosis in mice, however, this was hampered by Wnt/β-catenin signaling [57]. Conversely, the hampering of Wnt signaling by DKK1 decreased β-catenin phosphorylation besides ameliorating TGF-β1 expression for reducing mesangial cells fibrosis [31].

Cannabinoid receptor1 (CBR1) is another factor implicated in DKD, that activates the Peroxisome Proliferator-Activated Receptor γ receptor2 (PPARγ2), followed by binding of adipocyte particular nuclear hormones to PPARγ2, with subsequent activation of transcription genes implicated in adipogenesis, inclusive of, αP2, Fibroblast growth factor 21 (FGF21), FGF1 along with CD36, along with facilitates the insulin sensitization in lipid metabolism [55, 56]. A prior study illustrated that over-expression of PPARs is intricately correlated with Metabolic Syndrome (MetS) causing alterations in lipid metabolism besides accrual of body fat, inducing DKD along with the robustness of the disease [57]. At the time hyperglycemic situations, CBR1 inimically impacts metabolism, and escalated insulin resistance (IR), causing augmentation of DKD. Moreover, CBR1 facilitates the expression of proteins correlated with Kidney fibrosis that results in deterioration of DKD inclusive of Ras, extracellular signal–regulated kinase (ERK1/2), transcription factor c-Jun, inflammation controller SOCS3(Suppressor of cytokines signaling 3) along with proinflammatory cytokines IL-1β as well as fibrotic matrix fibronectin [58].

Hyperglycemia induction of Glomerular Impairment along with Proteinuria

Proteinuria implicates a situation of enhanced protein quantities in the urine along with an indicator of Kidney injury. Information exists regarding hyperglycemia-stimulated mitochondrial fission escalates the generation of ROS that results in proteinuria along with facilitating the apoptosis as well as podocytes in Kidney microvascular endothelial cells [59]. The modulation of this event is brought about by dynamin- relatedprotein1 (Drp1) [59]. A prior study illustrated that translocation of Drp1into the mitochondria get modulated through phosphorylation along with enrolment by Rho-correlated-coiled coil containing protein kinase 1 (ROCK1), which reasons out regarding how the ROCK1 expression in Diabetic mice facilitates the glomerular apoptosis along with mitochondrial ROS generation. Furthermore, hyperglycemia-stimulated expression of renal hedgehog interacting protein (Hhip) in glomerular endothelial cells might aid in fibrosis along with apoptosis of these kinds of cells [60]. Hhip quantities are escalated in early DKD of Diabetic mice as well as humans, prior to the generation of microalbuminuria [61]. Other than mitochondrial fission, Notch signaling pathway activation has further been associated with the facilitation of the generation of glomerular diseases inclusive of proteinuria. The intracellular domain of Notch 1 is the knowledge we possess regarding activating vascular endothelial growth factors (VEGF) causing podocyte apoptosis along with proteinuria [62]. A prior study further illustrated that hampering this pathway further confers protection in rats with proteinuria [63].

The other signaling pathways correlated with proteinuria are the Wnt/β-catenin signaling pathways; enhancement of Wnt/β-catenin transcripts along with proteins have been encountered in the podocytes of patients with DKD along with mouse models, whereas the stability of expression of Wnt/β-catenin genes in the podocytes of transgenic mice was illustrated to stimulate proteinuria [64]. Additionally, hyperactivation of the mammalian target of rapamycin (mTOR) stimulates podocyte hypertrophy besides apoptosis of podocytes that exacerbates glomerular disease along with proteinuria [65]. Moreover, information is there regarding nephrin expression is implicated in the generation of hyperglycemia-stimulated albuminuria [66]. Nephrin represents a transmembrane protein possessing extracellular domains which aid in the communication of foot processes of podocytes, being necessary for the appropriate working of the renal filtration barrier. Podocytes possess actin cytoskeleton architecture along with remodeling of actin cytoskeleton along with a breakdown of this architecture results in the reduction of nephrin expression like Rac1, Cdc42 are controllers of dynamics of the actin cytoskeleton, with depletion of their genes decreased nephrin expression along with stimulated albuminuria in mice [67-69].

Hyperglycemia along with Albuminuria in Renal Tubular Cell Fibrosis

DKD is intricately correlated with the generation of fibrosis of the renal tubular epithelial cell, the epithelial cells residing at the outer renal tubular layer whose function is the reabsorption of glucose, and amino acids besides other constituents of urine [70, 71]. A prior study illustrated that renal tubular cell fibrosis can result subsequent to exposure to greater quantities of glucose or albumin, which was intricately correlated with the enhanced expression of MCP-1, PAI-1, along with TGF-β1, secondary to hyperglycemia stimulated ROS generation [72]. Repression of these genes can aid in the avoidance of these profibrotic genes [73]. Additionally, renal tubular epithelial cell fibrosis is intricately correlated with albuminuria that in turn causes activation of the unfolded protein response (UPR) for induction of apoptosis [74-75]. Hampering of apoptosis might enhance autophagy in tubular epithelial cells, resulting in the deterioration of inflammation in addition to fibrosis [76-77]. Moreover, renal tubular epithelial cell polarity gets eliminated secondary to hyperglycemia, besides their acquisition of migration as well as invasive characteristics [78]. These result in escalated expression of fibronectin along with α smooth muscle actin (SMA) as well as a reduction in expression of E cadherin leading to fibrosis.

Endothelial Cell in Diabetes associated renal fibrosis

Fibrosis constitutes a property of propagative Chronic Kidney Disease (CKD) secondary to any cause that finally leads to renal failure (figure2). Numerous newer signaling molecules that control renal fibrosis have been revealed recently. Glucocorticoid receptor (GR) represents a nuclear hormone receptor that modulates steroid hormones along with in general gets expressed in maximum cell kinds, inclusive of the Kidney. The part of GR in cardiovascular disease (CVD) along with renal diseases is complicated. Endothelial GR negatively controls vascular inflammation in the case of the model of sepsis along with atherosclerosis [79]. Elimination of endothelial GR can stimulate upregulation of the Wnt signaling pathways that in turn facilitates renal fibrosis [80]. Hence endothelial GR is necessary for the form of antifibrotic molecules in DM.

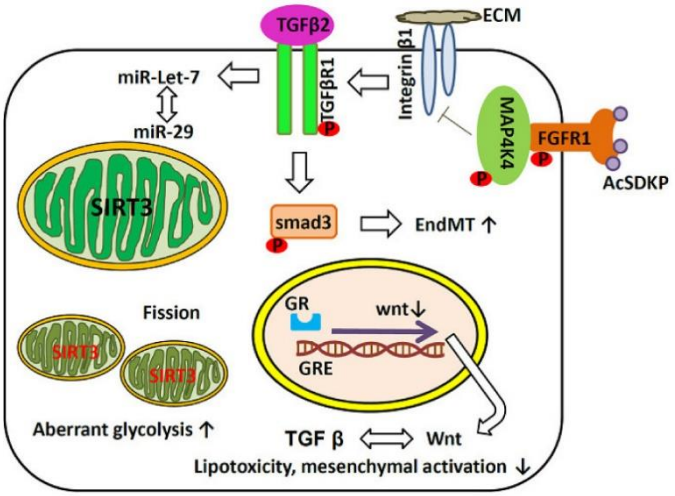

Figure 2: Courtesy ref no-41-Endothelial cell dysfunction in renal fibrosis. AcSDKP: N-acetyl-seryl-aspartyl-proline; ECM: extracellular matrix; EndMT: endothelial-to-mesenchymal transition; FGFR: fibroblast growth factor receptor; GR: glucocorticoid receptor; GRE: glucocorticoid response element; TGF-β: transforming growth factor-β; MAP4K4: mitogen-activated protein kinase kinase kinase kinase 4. Red SIRT3 indicates deficiency and black SIRT3 indicates sufficiency. ↑: Increase in the expression level; ↓: Decrease in the expression level.

Transgenic mice possessing decreased STAT3 activation capacity revealed lesser proteinuria, mesangial cell expansion, cell proliferation, macrophage infiltration, inflammation, and aberrant matrix generation on treatment with streptozocin (STZ) for diabetes [81]. Mitochondrial SIRT3 represents an NAD+-based deacetylase which basically possesses antioxidant action for the avoidance of aging-correlated diseases) [82]. A deficiency of SIRT3 can result in dysfunctional insulin liberation, escalated mitochondrial protein acetylation along with enhances mitochondrial OS [83]. Utilization of cellular NAD+- for deacetylation by SIRT1 of variable proteins, is implicated in mitochondrial bio generation, Oxidative stress (OS), inflammatory apoptosis along with autophagy. Hampering of acetylation of NFKB through SIRT1 activation causes recovery of inflammation in diabetic mice [84]. In hyperglycemic situations, downregulation of 5'AMP-activatedproteinkinase (AMPK)/ SIRT1 /PGC-1α stimulates hypertrophy, ROS, along with mitochondrial as well as autophagy impairment, all of which facilitate the formation of DKD. AMPK causes SIRT1 upregulation by escalating cellular NAD+- quantities [85]. Identification of both AMPK along with SIRT1 has been done in the form of intracellular energy sensors, that find out along with react to AMP/ATP along with NAD+/ NADH ratios respectively besides are activated at the time of energy expenditure situations along with in activated in DM [86].

Furthermore, we possess the knowledge that FGF signaling sustains endothelial barrier function besides endothelial cell survival through binding with associated FGFR [87]. The Ac-SDKP1- FGFR-MAP4K4 axis possesses a significant part in tackling EndMT-correlated fibrotic conditions [88]. Regarding a target for Ac-SDKP1, endothelial FGFR is necessary for the form of a core anti-fibrotic molecule [89].

Aberrant Transcriptional Control results in DKD

Transcriptional regulation is key regarding the sustenance of cellular homeostasis. Nevertheless, hyperglycemia transcriptionally stimulates the expression of particular genes that get constitutively expressed despite following the regulation of hyperglycemia which can aid in the generation of Kidney Injury in DKD patients [90].

Dyscontrolled Transcriptional Factors along with DKD

The binding of transcriptional factors usually takes place in particular sequences in promoters for controlling transcription along with at the time of escalated glucose quantities numerous signal transduction pathways activation takes place for controlling transcription that might impact the production of DKD. That there is a key part of Wnt signaling in podocyte fibrosis is well acknowledged for example, greater glucose quantities activate Wnt signal transduction that results in β-catenin phosphorylation. This phosphorylated β-catenin subsequently activates the transcription of Snail 1, Matrix Metalloproteinases (MMPs) 7, besides facilitation of podocyte dedifferentiation along with mesenchymal conversion leading to podocyte fibrosis [91,92]. Caudal type homeobox transcription factor2(CDX2) possesses the capacity of activating transcription factor2 cystic fibrosis transmembrane conductance regulator(CFTR) for repressing Wnt signaling as well as avoidance of fibrosis [93]. A prior study illustrated that CDX2) expression caused recovery of renal tubular damage in DKD patients along with mouse DKD model [94].

ROS possesses a significant part in the generation of tubulointerstitial fibrosis that results subsequent to the activation of myofibroblasts [95]. A transcription factor possessing an antioxidant part, nuclear factor erythroid-2-related factor-2((Nrf2) causes transcription of glutathione peroxidase (GPx), to enhance Oxidative stress (OS), along with apoptosis that results in continued damage with renal fibrosis as well as DKD [96]. Nrf2 expression takes place integrally, nevertheless, its breakdown occurs by the NRF2-Kelch-like ECH-associated protein (Keap1) through the ubiquitin-proteasome pathway [97]. In view of Keap1 possessing Reactive cysteine residues which can generate crosslinking with oxidants along with electrophiles (alias accept or donate electrons) for sensing the cellular Oxidative stress (OS), during situations of OS, stabilization of NRF2 occurs. NRF2 possesses a central part in conferring protection to renal cells from Oxidative injury by activating the genes that encode glutathione as well as NADPH for tackling OS [98]. Additionally, it possesses the capacity of activating the pentose phosphate pathway via the generation of NADPH which might be correlated with nephroprotection from Oxidative injury [98].

Another transcription factor that is intricately correlated with DKD is FoxO1. Numerous genes which are controlled by FoxO1 are acknowledged to avoid renal FoxO1 tubulointerstitial fibrosis as well as apoptosis, both of which possess a significant part in the pathogenesis of DKD [98]. Escalated glucose quantities facilitate FoxO1 phosphorylation in Kidneys for activating transcription of genes implicated in gluconeogenesis along with glycogenolysis, thus resulting in proteinuria, besides renal fibrosis [99, 100]. Hampering, the working of FoxO1 by natural products or synthetic substances was illustrated to ameliorate renal cell injury in the presence of escalated glucose quantities [101]. Another transcription factor that is correlated with DKD is Dachschund homolog1 (DACH). DACH results in the enrolment of Pax transactivation domain interacting protein in podocytes (PTIP) for suppressing transcription in DACH podocytes which need DACH-sequence particular DNA binding as well as decreased histone methylation H3 at K4 for activating the transcription of NELL2 along with enhanced podocytes damage [102].

Impact of Genes Controlled by Kruppel-like Factors in DKD

Kruppel-like factors (KLFs) represent a group of transcription factors inclusive of a minimum of 27 proteins. Numerous of these KLF members inclusive of KLF2, KLF4, KLF5, KLF6 along with KLF15 possess the capacity of activating genes in glomerular endothelial cells or podocytes for the avoidance of fibrosis, despite KLF10 apparently possessing inimical actions on the Kidney [103-107].

Reno Protective Actions of KLFs

The activation of a tight junction protein called occludin is brought about by KLF2 for the avoidance of the generation of gaps amongst endothelial cells, besides the sustenance of the intactness of the endothelial barrier [108]. At the time of escalated glucose quantities, repression of expression of KLF2 takes place by FoxO1 that resulting in injury to the glomerular endothelial cells as well as podocytes [105, 109]. Reduction of GpC methylation at the nephrin promoter occurs with an expression of KLF4, along with other epithelial markers [104], for conferring protection to the Kidney at the time of normal situations, however, escalated glucose quantities result in reduction of KLF4 messenger ribonucleic acid (mRNA) quantities besides escalated expression of migration inhibitory factor (MIF) along with MCP-1 in an event modulated by TGF-β1 along with canonically repressed by KLF4 [109]. TGF-β1 acts as a crucial guide in the formation of renal fibrosis, with TGF-β1 expression facilitating the generation as well as propagation of renal disease, whereas further causes activation of expression of Twist1 or Snail for prolonging of G2/M cell cycle arrest along with facilitating renal fibrosis [110-112]. KLF4 functions to repress cell proliferation along with differentiation stimulated by TGF-β1 [113]. Additionally, KLF 5 significantly ameliorates the expression of Bax, caspase3, caspase 8, and caspase-9 in podocytes by blockade of mitogen-activated protein kinase (MAPK) pathways [114]. A prior study validated that controlling P38-stimulated apoptosis along with hampering apoptosis through MAPK pathways might be an efficacious approach to decrease renal fibrosis [115,116].

Cytochrome-c-oxidase (COX) possesses a crucial part in the controlling of aerobic energy generation through the mitochondrial respiratory electron transport chain (ETC). In the case of podocytes KLF 6 controls mitochondrial function via the COX assembly gene (SCO2) that modulates the balance amongst mitochondrial respiration as well as a glycolytic pathway for the avoidance of mitochondrial impairment along with podocyte apoptosis [103]. Furthermore, KLF 15 hampers TGF-β1 via the ERK/ MAPK, and JNK/ MAPK pathways [117], as well as is the crucial controller of podocytes differentiation along with confers protection of the podocytes against injury [118].

KLF 10 results in Kidney injury in DKD

KLF 10 possesses numerous parts in podocyte impairment along with damage. TGF-β1, bone morphogenetic protein-2(BMP-2), along with epidermal growth factors (EGF), induce KLF 10 expression, which possesses a significant part in the transcription of genes like Smad, that is implicated in cell proliferation, apoptosis as well as differentiation [119]. KLF 10 further hampers the expression of nephrin via crosstalk with DNA methyltransferase1 (DNMT1) for methylation of nephrin promoter1 (figure 3) [108]. Additionally, KLF 10 suppresses the transcription of numerous genes in particular expressed in podocytes inclusive of the ones encoding Wilms tumor 1 protein (WT1), podocin, synaptophysin as well as nephrin finally causing activation of expression of Lysine, particularly demethylase (KDM6A) that is necessary for the sustenance of Kidney function like a controller of podocytes differentiation for facilitating global epigenetic reprogramming, resulting in abnormal gene expression [108, 120]. Lastly KLF 10 stimulated expression of KDM6A results in induction of proteinuria, besides irreversible Kidney injury in case of Diabetic situations [108].

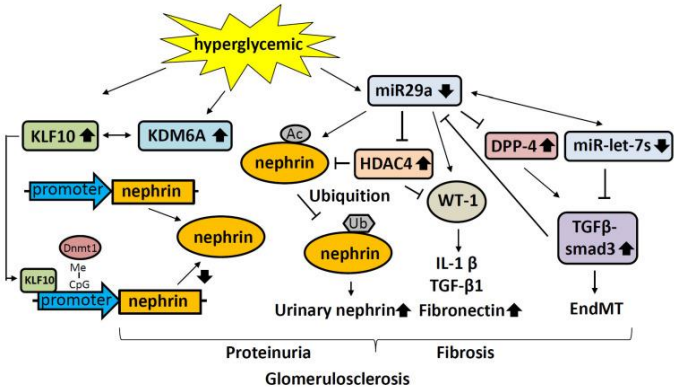

Figure 3: Hyperglycemia-induced nephrin modification induces glomerulosclerosis. Ac: acetylation; Dnmt1: DNA methyltransferase 1; EndMT: endothelial-to-mesenchymal transition; HDAC4: histone deacetylase 4; IL-1β: Interleukin-1β; KDM6A: lysine-specific demethylase; KLF 10: Krüppel-like factor 10; Me: methylation; TGF-β: Transforming growth factor β; Ub: ubiquitination; WT1: Wilms' tumor 1 protein. ↑: Increase in the expression level; ↓: Decrease in the expression level.

Epigenetic Modifications along with pathogenesis of DKD

Histone acetylation at H3 along with H4 is acknowledged to decrease the positive charge of chromatin, by which promoters become available to transcription factors regarding transcriptional activation [121]. On the other hand, deacetylation possesses an opposite action which results in transcriptional suppression [122]. The catalysis of these events takes place respectively by Histone acetylases (HATs), along with histone deacetylases (HDACs) [123]. Histone methylation along with demethylation by Histone methyltransferases (HMTs), along with demethylase of the CpG islands in promoters are further acknowledged to respectively suppress along with cause activation of gene expression [124].

DNA Methylation is correlated with DKD

DNA methylation is a suppressive epigenetic modification that is believed to be responsible for the pathogenesis of DKD. The methylation of cytosine in the CpG islands of promoters is correlated with transcriptional repression [124]. A microarray evaluation of cytosine methylation in human Kidney tubules documented Kidney structural injury alter cytosine methylation along with the extent of Kidney fibrosis [125]. Moreover, another study observed how there was escalated expression of DNMT1 in the peripheral blood mononuclear cells in DKD patients with enhanced DNMT1 possessing the capacity of activating the mTOR pathway along with inflammation [126].

The RAS protein activator like 1 (RASAL1) gene encodes a hamper or of RAS protein along with hyperglycemia is acknowledged to result in hypermethylation of RASAL that is correlated with the continuation of fibroblast activation along with renal fibrosis [127]. TGF-β1 facilitates the expression of DNMT1 along with DNMT3 for induction of hypermethylation as well as suppression of transcription of RASAL1, leading to activation of fibrogenesis [128]. Fibronectin is another protein correlated with the generation of Kidney fibrosis [129]. Subsequent to renal damage, a repair event is initiated along with following fibronectin in the ECM reflecting the 1st protein that gets deposited along with its accrual at the time of fibrogenesis [129]. Fibronectin accrual is intricately correlated with fibrosis [129]. A prior study illustrated that methylation quantities of the MMP9 gene promoter in patients with DKD were decreased resulting in escalated expression of fibronectin [130]. Hypomethylation of hampering agents of MMPs (TIMP2) as well as AKR11 genes that encode aldose reductase are further correlated with proteinuria in the case of patients with early DKD [131].

DKD is correlated with Histone Post-Translational Modifications

Histone acetylation relaxes the chromatin structure damage along with promoting the binding of transcription factors to promoters for activating transcription. On the other hand, methylation possesses a reverse action of suppression of transcription. Hyperglycemia in general impacts these events to result in Kidney conditions [133].

Histone Acetylation is implicated in DKD Pathogenesis

Histone acetylation is implicated in the propagation of DKD [134,135]. A prior study demonstrated that acetylation of H3K9 was enhanced in the Kidneys of DKD patients [134]. In the meantime, acetylation of Histone H3 along with H4 are acknowledged to activate transcription of Cola1, connective tissue growth factors(CTGF) plasminogen activatorinhibitor1 (PAI-1), P2I, Lacm1, FN1, TNF-α, COX2, along with MCP1 that can facilitate DKD generation [136]. Besides Histone acetyltransferase (HAT), histone deacetylases (HDACs) control gene expression epigenetically by elimination of acetyl groups from histones to suppress transcription, which can facilitate DKD generation also. Like the expression of nephrin that confers protection to podocytes from injury secondary to hyperglycemia gets repressed by HDAC4. A prior study further demonstrated that nephrin expression was escalated subsequent to miR 29a, which results in a reduction of expression of HDAC4, leading to escalated nephrin expression (Figure3) [137].

Differentiation of myofibroblasts is an event that generates terminally differentiated myofibroblasts and is implicated in tissue repair [138]. Myofibroblasts lead to the accrual of interstitial constituents like collagen along with fibronectin at the time of wound repair along with express escalated quantities of α smooth muscle actin (αSMA) [139]. These cells are finally engulfed in stress fibers [139]. TGF-β1 modulates the turnover of ECM for facilitating myofibroblasts differentiation in the Kidney is well established. A prior study demonstrated that HDAC4 is needed for TGF-β1 stimulated myofibroblastic differentiation, since hampering histone deacetylation by trichostatin A or silencing the expression of HDAC4 hampered the transcription of αSMA gene that displays a crucial part of histone acetylation in renal fibrosis [140]. Furthermore, SIRT3, a histone deacetylase in the mitochondria impacts glycolysis as well as fibrosis via the control of PKM2 dimer along with HIF-α quantities, besides modulating STAT3 phosphorylation for impacting abnormal glycolysis in tubules [141].

Histone Methylation is implicated in DKD Pathogenesis

Histone methylation comprises monomethylation, monomethyl, and dimethyl, along with trimethyl kinds, besides the degree of Histone methylation which modulates gene transcription as well as impacts DKD pathogenesis [136,142]. SUV39H represents a histone methyltransferase catalyzing the methylation of K9 residues in H3 with dimethyl or trimethyl groups in the repressive mark H3K9m3. Hyperglycemia has been illustrated to reduce the expression of SUV39H for facilitating the generation of renal fibrosis [143]. Prior studies illustrated that DKD generation is correlated with escalated transcription of proinflammatory or profibrotic genes in view of the reduction of methylation of histone H3 at the promoters of these genes [135,144]. That p21 (WAF1) gets transcribed at escalated quantities subsequent to acute Kidney damage along with hampering of SUV39H expression was observed to ameliorate hyperglycemia stimulated fibronectin as well as p21 (WAF1) expression along with augmenting hyperglycemia stimulated cell hypertrophy [145,146]. Amelioration of SUV39H expression in turn represses escalated glucose quantities stimulated expression of fibronectin as well as p21 (WAF1) [146]. This overexpression of SUV39H along with H3K9 methylation in the case of DKD patients has been observed to decrease Kidney inflammation along with cell apoptosis [147].

Noncoding RNAs are implicated in the DKD Pathogenesis

Noncoding RNAs are further implicated in the propagation of DKD inflammation along with fibrosis [148]. It has been acknowledged that long noncoding RNAs (lnc RNAs) take part in both the start as well as propagation of DKD by the direct impact of pathogenic actions or by indirect modulation of particular renal pathways(like TGF-β1, nuclear factor κB (NFκB), STAT3, as well as GSK-3β signaling [149]. Hence lnc RNAs might have the probability of working as biomarkers regarding early diagnosis or prognostic follow-up or in the form of therapeutic targets with the idea of reducing the rate of propagation or even reverting the fully generated DKD. Escalated glucose quantities have been illustrated to escalate the expression of miR34a, which stimulates mesangial proliferation along with mesangial proliferation glomerular hypertrophy via hampering of the growth arrest-specific -1(GAS1) [150]. GAS1 is implicated in glomerular cell proliferation along with activation, being expressed in the Kidney at the time of pathological situations [151]. Furthermore, hampering of miR196a activation stimulates mesangial hypertrophy by activation of cyclin-dependent –kinase2 (Cdk2) inhibitors1 based p27kip, hence avoidance of cell cycle arrest in the G1 phase [152]. MiR93 expression further escalates the expression of mitogen along with stress-activated kinase 2 (Msk2) that in turn modulates Msk2chromatin remodeling along with podocytes gene transcription to result in DKD [153].

CB1R gets expressed in Kidney as already detailed, along with activation of CB1R expression by hyperglycemia leads to renal damage along with nephropathy [137]. In the case of a transfection system miR29a was observed to repress the expression of CB1R in the mesangial cells of escalated glucose quantities-stressed mice, hence blocking the expression of proinflammatory as well as profibrotic mediators for ameliorating renal hypertrophy [154]. Moreover, curcumin is acknowledged to possess advantageous actions for the reduction of the robustness of DKD in view of this natural substance facilitating the expression of curcumin miR29a to

hamper CB1R[155]. Conversely, the reduction of expression of miR29a ameliorates DKK1- Wnt/β-catenin signaling as well as facilitates apoptosis along with laying down of ECM for impacting Kidney fibrosis [32]. Furthermore, miR29c as per our knowledge activates Rho kinase by targeting Sprouty homolog1 (Spry) that is correlated with ECM accrual. Moreover, podocyte apoptosis is regulated by miR29c as well as miR21, with the escalation of miR29c facilitating the assembly of fibronectin along with apoptosis [156]. Noncoding RNA miR-let-7, reduces ECM protein expression via a mode implicating TGF-β1/Smad3 pathway, in addition to DPP-4 hampering as well as facilitating peptide Ac-SDKP expression resulting in renal protection by controlling the interaction between miR29 along with miR-let-7 [157,158].

EMT along with EndMT events possess a key part in the generation of fibrosis in the Kidney. Noncoding RNA miR21 reflects a downstream target of Smad3 that activates transcription of miR21once TGF-β1 is present [159]. MiR21 further hampers profibrotic signals along with attenuates glomerular damage stimulated by TGF-β1 along with hyperglycemia [160]. TGF-β1stimulates signal circuit augmentation along with activation of a chronic state of profibrotic as well as can control the expression of miR 192, miR 200s, miR 21, along with miR 130b in mesangial cells, miR93is implicated in TGF-β1stimulated EMT along with renal fibrogenesis, whereas downregulation of miR23a hampers escalated glucose-stimulated EMT along with renal fibrogenesis [160-162]. Studies have illustrated that miR192 quantities are escalated in glomeruli that were obtained from streptozocin (STZ), injected mice in addition to db/db mice [163]. Additionally, miR 200s are in abundance in Kidney, with their expression getting stimulated by OS. These miR 200 were illustrated to control mesenchymal-epithelial transition (MET) via modulating the E-cadherin transcriptional suppressor zinc finger-E-box binding homeobox1 (ZEB1) [164]. Nevertheless, the miR 130b-SNAILaxis works to facilitate EMT along with propagation to escalate tubulointerstitial fibrosis in DKD [165].

Escalated glucose quantities further facilitate the expression of TGF-β1 for activating the expression of miR 377 that represses the expression of p21-activated kinase (PAK) as well as superoxide dismutase (SOD), thus escalating fibronectin protein generation [166]. TGF-β1 decreases the expression of antifibrotic miRNAs (miR 29s along with let7), that target various collagen isoforms in mesangial cells. Other miRNAs that confer protection are inclusive of miR 26a which hamper TGF-β1 stimulated ECM protein expression in DKD patients, as well as miR 146athat gets upregulated in early DKD for decreasing the expression of proinflammatory cytokines like IL-1β along with IL-18 [167-169].

Role of Pyroptosis in DKD

Pyroptosis has been recently found to be a kind of programmed cell death (PCD) as reviewed by us earlier [170]. With research propagation with regards to DKD, researchers have paid escalated attention to establishing the part of pyroptosis in the pathogenesis of DKD, concentrated in three pathways of pyroptosis development; namely i) the classical inflammasome, ii) non-classical inflammasome, besides ii) caspase-3-modulated inflammasome pathways [171]. The molecular and pathophysiological modes of the pyroptosis-correlated inflammasome pathway in the generation of DKD were summarized in their review. Activation of the diabetes-modulated pyroptosis correlated inflammasomes, like nucleotide-binding oligomerization domain-like receptor protein 3 (NLRP3), in Toll-like receptor 4 (TLR4), caspase-1, interleukin (IL)-1β, and the IL-18 axis, possess a necessary part in DKD lesions [172]. By hampering activation of the TLR4 along with NLRP3 inflammasomes, the generation of caspase-1, IL-1β, and IL-18 is hampered, hence resulting in improvement of the pathological alterations correlated with DKD. Studies utilizing escalated glucose-stimulated–cell models, high-fat diet/streptozotocin-induced DKD animal models, along with human biopsies would aid in the estimation of spatial along with temporal expression of DKD inflammatory constituents. Recent studies have validated the association between the pyroptosis-correlated inflammasome pathway as well as kidney disease. Nevertheless, these studies are comparatively superficial currently, and the modes require further evaluation. Associating these observations with disease activity along with prognosis would contribute to new ideas for DKD research [171].

Progress in treatment along with future plans

DKD is the major etiology of ESKD. Nevertheless, just RAAS with multidisciplinary therapies is efficacious for DKD. In 2019, sodium-glucose cotransporter 2 (SGLT2) hampering agents illustrated effectiveness against DKD in Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) trial, adding a new treatment dimension. Nevertheless, the propagation of DKD has not been fully regulated. The patients with transient exposure to hyperglycemia generate diabetic complications, inclusive of DKD, despite subsequent normalization of their blood glucose. Temporary hyperglycemia causes advanced glycation end product (AGE) accrual along with epigenetic alterations in the form of metabolic memory. The drugs that enhance metabolic memory are awaited, and AGE inhibitors and histone modification inhibitors are the concentration of clinical along with basic research. Additionally, incretin-associated drugs illustrated a renoprotective capacity in numerous clinical trials, along with these trials with the renal outcome as their primary endpoint are currently ongoing. Hypoxia-inducible factor prolyl hydroxylase inhibitors recently approved for renal anemia might be renoprotective since they show benefit in tubulointerstitial hypoxia. Furthermore, NF-E2–related factor 2 activators improved the glomerular filtration rate of DKD patients in Bardoxolone Methyl Treatment: Renal Function in chronic kidney disease/Type 2 Diabetes (BEAM) Trial and Phase II Study of Bardoxolone Methyl in Patients with Chronic Kidney Disease and Type 2 Diabetes (TSUBAKI) trial. Hence, subsequent to SGLT2 hampering agents, numerous innovative agents could be utilized along with them in treating DKD. Future studies are anticipated to provide new insights regarding epigenetic modifications as per the review by Yamazaki (see Figure 4 along with Figure 5).

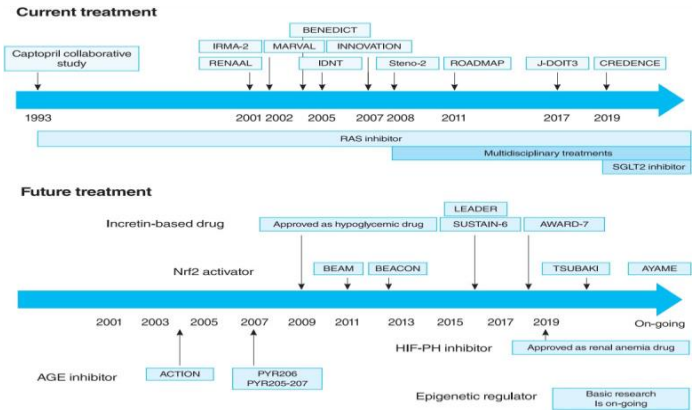

Fig 4: The time course of current treatments. BENEDICT, Bergamo Nephrologic Diabetes Complications Trial; IRMA-2, Irbesartan in Patients with Type 2 Diabetes and Microalbuminuria Study; MARVAL, Microalbuminuria reduction with valsartan; INNOVATION, Incident to overt: Angiotensin II receptor blocker, Telmisartan, Investigation On type II diabetic Nephropathy; RENAAL, Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan; IDNT, Irbesartan in Diabetic Nephropathy Trial; ROADMAP, Randomized Olmesartan and Diabetes Microalbuminuria Prevention; J-DOIT3, Japan Diabetes Optimal Integrated Treatment study for 3 major risk factors of cardiovascular disease; CREDENCE, Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation; RAS, renin-angiotensin system; SGLT2, sodium-glucose cotransporter 2 [173].

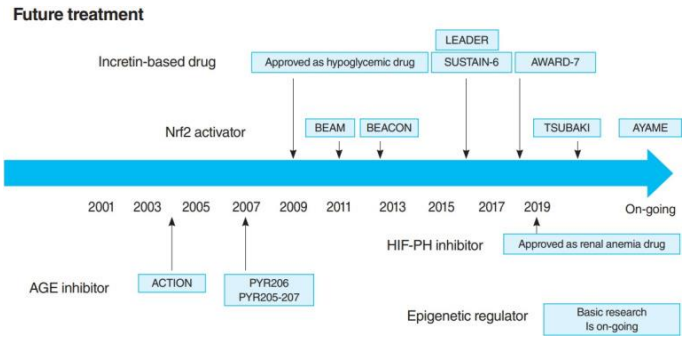

Fig 5: The time course of current treatments. BENEDICT, Bergamo Nephrologic Diabetes Complications Trial; IRMA-2, Irbesartan in Patients with Type 2 Diabetes and Microalbuminuria Study; MARVAL, Microalbuminuria reduction with valsartan; INNOVATION, Incident to overt:

Angiotensin II receptor blocker, Telmisartan, Investigation On type II diabetic Nephropathy; RENAAL, Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan; IDNT, Irbesartan in Diabetic Nephropathy Trial; ROADMAP, Randomized Olmesartan and Diabetes Microalbuminuria Prevention; J-DOIT3, Japan Diabetes Optimal Integrated Treatment study for 3 major risk factors of cardiovascular disease; CREDENCE, Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation; RAS, renin-angiotensin system; SGLT2, sodium-glucose cotransporter 2 [173].

Here we conducted a systematic review utilizing search engines PubMed, google scholar; Web of Science; Embase; Cochrane review library utilizing the MeSH terms like CKD propagation; risk factors; eGFR; Diabetic Kidney Disease (DKD; other etiologies of CKD; epithelial–mesenchymal transition (EMT); FSGS; proteinuria; Preventing Acute Kidney injury (AKI); etiology for AKI; glomerulosclerosis; glomerulopathy; epigenetics role in DKD; DNA methylation; Histone post-translational modifications; curcumin analogs; miRNAs from 1970'S till date in2022. We found a total of 3,500 articles on DKD of which we selected 173 articles for this review. No meta-analysis was done.

Conclusion

Hence as summarized above how hyperglycemia gets modulated by certain cytokines, growth factors, along with non-epigenetic modes which these latter are the crucial guides for DKD, that implicates Wnt /β-catenin signaling, ER Stress, escalated ROS, RAAS activation, overload of albumin as well as extra generation of inflammatory mediators. Nevertheless, epigenetic modes like DNA methylation, Histone post-translational modifications in addition to non-coding RNA further possess a key part in the pathogenesis of DKD, just like the events of inflammation along with fibrogenesis (Figure 6). That early stage DKD benefits from multidisciplinary therapy however with the propagation no definitive efficacious therapy is accessible. With the ongoing trials as highlighted above gradually we might be able to tackle these however in the meantime the above insight might aid treating physicians in the diagnosis of early DKD at a stage that is simpler regarding management or comparatively reduce the rate of propagation of Diabetic nephropathy to attain improved results.

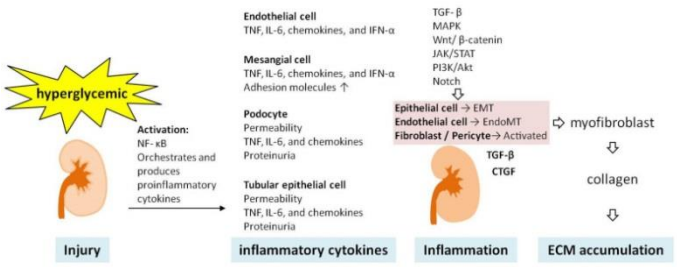

Figure 6: Mechanisms driving renal inflammation and fibrosis. ECM: extracellular matrix; EMT: epithelial–mesenchymal transition; EndoMT: endothelial–mesenchymal transition; IFN-α: interferon alpha; IL-6, interleukin 6; JAK/STAT: Janus kinase signal transducers and activators of transcription; MAPK: mitogen-activated protein kinase; TGF-β: transforming growth factor-beta; TNF, tumor necrosis factor [41].

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