# Currently, dn; however, this method has some drawbacks.

Business, Management

Currently, diabetic nephropathy (DN) is the most common cause of end-stage renal disease(ESRD) worldwide, and approximately 40% of patients require renal replacementtherapy. Early identification of patients who are prone to develop renalcomplications would be an important step for their better management during theclinical course of this disease process (Parving et al., 2001)Early stages of DN are characterized byhyperfiltration, nephron enlargement and mesangial cell hypertrophy, whichlater on progress to glomerulosclerosis (Satchell et al., 2008).

Microalbuminuria has been the standard method for diagnosis of early stagesof DN; however, this method has some drawbacks. Microalbuminuria can developwhen advanced changes have already set in as assessed by renal biopsyexamination. Also, the immunoassay that measures microalbuminuria can onlydetect the immunoreactive form of albumin, and its nonimmunoreactive forms areundetectable by this method (Liu et al., 2011). MicroRNAscomprise 21 to 23 nucleotides, and bind to the 3?-untranslated regions (UTRs)of their target mRNAs in a stable manner. Micro RNAs modulate a wide range ofbiological functions, including oncogenesis, apoptosis, cardiac development andinsulin secretion (Chen et al.

, 2012). Upregulationof several miRNAs can occur in diabetic kidney. These miRNAs bind to the 3’UTRof renoprotective genes leading to their decreased expression.

And in turn, these upregulated miRNAs contribute to the pathogenesis of DN (Hao et al., 2014). Severalkey factors are overexpressed in DN, such as TGF-? 2, COL1, COL4, and NADPHoxidase subunit 4 (NOX4). These DN-

inducing factors can result in ECMaccumulation, renal fibrosis, and oxidative stress, all of which contribute tothe pathogenesis of DN. Furthermore, these factors are also targets for severalmiRNAs that are downregulated in DN. Therefore, it is reasonable that thesedownregulated miRNAs are DN inhibiting miRNAs which lead to the decrease ofthese DN inducing factors (Hao et al., 2014). Underdiabetic conditions, miR-216a was up regulated, followed by the inhibition of Ybox binding protein 1 which led to increased expression of TGF-? stimulatedclone 22, eventually resulting in high production of COL1? 2 in MMCs (Kato et al.

, 2010). MicroRNA-21 (miR-21) is considered a profibrotic microRNA; theexact mechanism of how miR-21 participates in diabetic renal injury may berelated to: The activation of TGF-? signaling during diabeticconditions and phosphatase and tensin homolog (PTEN) which is one of potentialtargets of miR-21 and a negative regulator of epithelial-to-mesenchymaltransition. Suppressionof PTEN by miR-21 is shown to induce phosphatidylinositide 3-kinases (PI3K) andAkt activity, and subsequently induces metalloproteinase-2 (MMP-2) expressionwhich control ECM turnover during fibrosis. Consequently, upregulation of Aktpathway could be another mechanism for miR-21 to contribute in diabetic kidneyinjury.

The reciprocal regulation of PTEN levels and Akt1 substrate activity bymiR-21 mediates critical pathologic features of diabetic kidney disease (Liet al., 2014). MicroRNA-377 (miR-377) inducesfibronectin (extracellular cellular matrix protein) expression in MCs throughthe downregulation of manganese superoxide dismutase and p21-activated kinase.

Fibronectin is not a direct target of miR-377; however, miR-377 first targets the expression of protein-activated kinase 1(PAK1) and manganese superoxidedismutase (MnSOD), which lead to elevated fibronectin expression and hencecontribute to DN (Kantharidis et al., 2011). MicroRNA-93 (miR-93) is a keyregulator of vascular endothelial growth factor (VEGF) signaling in thekidneys. It has a modulatory effect on VEGF expression and its downstreamsignaling, which may play a role in the pathogenesis of diabetic nephropathy. SinceVEGF targets collagen IV and fibronectin, the repression of miR-93 duringdiabetic kidney disease may lead to the production of collagen and fibronectinthat are known to increase in DN (Liet al., 2014). MicroRNA 25 (miR-25) levelwas significantly reduced both in kidneys from diabetic rats and in highglucose-treated mesangial cells, accompanied by the increases in NOX4 (NADPHoxidase subunit 4) expression levels.

An inhibitor ofmiR-25 effectivelyincreased NOX4 levels. Luciferase assays showed that miR-25 directly bound tothe 3’UTR of NOX4 mRNA. These data indicate that miR-25 may be a DN-protectivemolecule through inhibiting NOX4 (Fu et al., 2010). Objective: The aim of the current work was to study differential expressionsof miR-21, miR-93, miR-216a, miR-25 and miR-377 and their possible underlyingrole in the development of nephropathy in patients with type 1 diabetic.