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WHAT IS NEW IN DIABETIC KIDNEY DISEASE?

CURRENT UPDATE- BANGALADESH

DM-NEPHROPATHY

Diabetic nephropathy is a clinical syndrome characterized by the following :

- **Persistent albuminuria (>300 mg/d or >200 µg/min) that is confirmed on at least 2 occasions 3-6 months apart**
- **Progressive decline in the glomerular filtration rate (GFR)**
- **Elevated arterial blood pressure**

PROTENURIA

- ***Proteinuria was first recognized in diabetes mellitus in the late 18th century. In the 1930s, Kimmelstiel and Wilson described the classic lesions of nodular glomerulosclerosis in diabetes associated with proteinuria and hypertension.***

- ***By the 1950s, kidney disease was clearly recognized as a common complication of diabetes, with as many as 50% of patients with diabetes of more than 20 years having this complication.***

DM-NEPHROPATHY

- **Currently, diabetic nephropathy is the leading cause of chronic kidney disease in the United States and other Western societies.**
- **It is also one of the most significant long-term complications in terms of morbidity and mortality for individual patients with diabetes.**
- **Diabetes is responsible for 30-40% of all end-stage renal disease (ESRD) cases in the United States.**

DM-NEPHROPATHY

- ***Generally, diabetic nephropathy is considered after a routine urinalysis and screening for microalbuminuria in the setting of diabetes. Patients may have physical findings associated with long-standing diabetes mellitus.***

- ***Good evidence suggests that early treatment delays or prevents the onset of diabetic nephropathy or diabetic kidney disease. This has consistently been shown in both type 1 and type 2 diabetes mellitus.***

ATYPICAL-DM NEPHROPATHY

- **Recently, attention has been called to atypical presentations of diabetic nephropathy with dissociation of proteinuria from reduced kidney function.**
- **Also noted is that microalbuminuria is not always predictive of diabetic nephropathy. Nevertheless, a majority of the cases of diabetic nephropathy presents with proteinuria, which progressively gets worse as the disease progresses, and is almost uniformly associated with hypertension.**

PATHOPHYSIOLOGY

Three major histologic changes occur in the glomeruli of persons with diabetic nephropathy.

- **First, mesangial expansion is directly induced by hyperglycemia, perhaps via increased matrix production or glycation of matrix proteins.**
- **Second, thickening of the glomerular basement membrane (GBM) occurs.**
- **Third, glomerular sclerosis is caused by intraglomerular hypertension (induced by dilatation of the afferent renal artery or from ischemic injury induced by hyaline narrowing of the vessels supplying the glomeruli).**
- **These different histologic patterns appear to have similar prognostic significance.**

DIABETIC GLOMERULOPATHY

- **The key change in diabetic glomerulopathy is augmentation of extracellular matrix.**
- **The earliest morphologic abnormality in diabetic nephropathy is the thickening of the GBM and expansion of the mesangium due to accumulation of extracellular matrix.**

PATHOGENISIS-DM NEPHROPATHY

- **Simple schema for the pathogenesis of diabetic nephropathy.**

  Light microscopy findings show an increase in the solid spaces of the tuft, most frequently observed as coarse branching of solid (positive periodic-acid Schiff reaction) material (diffuse diabetic glomerulopathy).
- **Large acellular accumulations also may be observed within these areas. These are circular on section and are known as the Kimmelstiel-Wilson lesions/nodules.**

IF-MICROSCOPY

- ***Immunofluorescence microscopy may reveal deposition of albumin, immunoglobulins, fibrin, and other plasma proteins along the GBM in a linear pattern, most likely as a result of exudation from the blood vessels, but this is not immunopathogenetic or diagnostic and does not imply an immunologic pathophysiology.***
- ***The renal vasculature typically displays evidence of atherosclerosis, usually due to concomitant hyperlipidemia and hypertensive arteriosclerosis.***

ELECTRON MICROSCOPY

- **Electron microscopy provides a more detailed definition of the structures involved.**
- **In advanced disease, the mesangial regions occupy a large proportion of the tuft, with prominent matrix content.**
- **Further, the basement membrane in the capillary walls (ie, the peripheral basement membrane) is thicker than normal.**

DM-NEPHROPATHY-SEVERITY

- **The severity of diabetic glomerulopathy is estimated by the thickness of the peripheral basement membrane and mesangium and matrix expressed as a fraction of appropriate spaces (eg, volume fraction of mesangium/glomerulus, matrix/mesangium, or matrix/glomerulus).**

DM NEPHROPATHY VERSUS CHRONIC RENAL INSUFFICIENCY

- **The glomeruli and kidneys are typically normal or increased in size initially, thus distinguishing diabetic nephropathy from most other forms of chronic renal insufficiency, wherein renal size is reduced (except renal amyloidosis and polycystic kidney disease).**

OVERT DM NEPHROPATHY/HT

- **In addition to the renal hemodynamic alterations, patients with overt diabetic nephropathy (dipstick-positive proteinuria and decreasing glomerular filtration rate [GFR]) generally develop systemic hypertension.**
- **Hypertension is an adverse factor in all progressive renal diseases and seems especially so in diabetic nephropathy.**
- **The deleterious effects of hypertension are likely directed at the vasculature and microvasculature.**

HT-ASSOCIATION

- **Evidence suggests that hypertension associated with obesity, metabolic syndrome, and diabetes may play an important role in the pathogenesis of diabetic nephropathy.**
- **Central obesity, metabolic syndrome, and diabetes lead to increased blood pressure.**

CENTRAL OBESITY

- **Central obesity induces→ hypertension initially by →increasing renal tubular reabsorption of sodium and causing a hypertensive shift of renal-pressure natriuresis through multiple mechanisms→ including**
- **A.activation of the sympathetic nervous system and renin-angiotensin-aldosterone system,**
- **B. as well as physical compression of the kidneys.**
- **C.Hypertension, along with increases in intraglomerular capillary pressure and the metabolic abnormalities (eg, dyslipidemia, hyperglycemia) likely interact to accelerate renal injury.**

DM NEPHROPATHY FEATURES

- **Similar to obesity-associated glomerular hyperfiltration, renal vasodilation, increases in the glomerular filtration rate and intraglomerular capillary pressure, and increased blood pressure also are characteristics of diabetic nephropathy.**
- **Increased systolic blood pressure further exacerbates the disease progression to proteinuria and a decline in the glomerular filtration rate, leading to end-stage kidney disease.**

ETIOLOGY-DM-NEPHROPATHY

- **Etiology**
  The exact cause of diabetic nephropathy is unknown, but various postulated mechanisms are hyperglycemia (causing hyperfiltration and renal injury), advanced glycation products, and activation of cytokines.
- **Many investigators now agree that diabetes is an autoimmune disorder, with overlapping pathophysiologies contributing to both type 1 and type 2 diabetes; and recent research highlights the pivotal role of innate immunity (toll-like receptors) and regulatory T-cells (Treg)**

MECHANISM –HYPERGLYCEMIA ?

- **Glycemic control reflects the balance between dietary intake and gluconeogenesis and tissue uptake or utilization through storage as glycogen or fat and oxidation.**
- **This balance is regulated by insulin production from the β cells in the pancreas.**
- **Insulin regulates serum glucose through its actions on liver, skeletal muscle, and fat tissue.**
- **When there is insulin resistance, insulin cannot suppress hepatic gluconeogenesis, which leads to hyperglycemia. Simultaneously, insulin resistance in the adipose tissue and skeletal muscle leads to increased lipolysis and reduction in disposal of glucose causing hyperlipidemia in addition to hyperglycemia.**

CYTOKINES

Evidence suggests that when there is insulin resistance, the pancreas is forced to increase its insulin output, which stresses the β cells, eventually resulting in β-cell exhaustion.

The high blood glucose levels and high levels of saturated fatty acids create an inflammatory medium, resulting in activation of the innate immune system,which results in activation of the nuclear transcription factors-kappa B (NF-κB), and release of inflammatory mediators,
including, interleukin (IL)–1β and tumor necrosis factor (TNF)–α, promoting systemic insulin resistance and
β-cell damage as a result of autoimmune insulitis.

Hyperglycemia and high serum levels of free fatty acids and IL-1 lead to glucotoxicity, lipotoxicity, and IL-1 toxicity, resulting in apoptotic β-cell death.

TGF-B/VEGF

- **Hyperglycemia also increases the expression of transforming growth factor-β (TGF-β) in the glomeruli and of matrix proteins, specifically stimulated by this cytokine.**
- **TGF-β and vascular endothelial growth factor (VEGF) may contribute to the cellular hypertrophy and enhanced collagen synthesis and may induce the vascular changes observed in persons with diabetic nephropathy.**
- **Hyperglycemia also may activate protein kinase C, which may contribute to renal disease and other vascular complications of diabetes.**

FAMILIAL/GENETIC

- **Familial or perhaps even genetic factors also play a role. Certain ethnic groups, particularly African Americans, persons of Hispanic origin, and American Indians, may be particularly disposed to renal disease as a complication of diabetes.**
- **It has been argued that the genetic predisposition to diabetes that is so frequent in Western societies, and even more so in minorities, reflects the fact that in the past, insulin resistance conferred a survival advantage (the so-called thrifty genotype hypothesis).**

POLYMORPHISM

- **Some evidence has accrued for a polymorphism in the gene for angiotensin-converting enzyme (ACE) in either predisposing to nephropathy or accelerating its course.**
- **However, definitive genetic markers have yet to be identified. More recently, the role of epigenetic modification in the pathogenesis of diabetic nephropathy has been highlighted.**

FOLIC ACID –DM NEPHROPATHY

- ***A study by Bherwani et al suggested that an association exists between decreased serum folic acid levels and diabetic nephropathy. In the study, which involved 100 patients with diabetes mellitus, including 50 with diabetic nephropathy and 50 without it, multivariate logistic regression analysis indicated that reduced folic acid levels increased the risk of diabetic nephropathy by 19.9%.***

EPIDEMIOLOGY

- ***Epidemiology***
  Since the 1950s, kidney disease has been clearly recognized as a common complication of diabetes mellitus (DM), with as many as 50% of patients with DM of more than 20 years' duration having this complication.

RISK OF DEVELOPMENT DM-NEPHROPATHY

- **The risk for the development of diabetic nephropathy is low in a normoalbuminuric patient with diabetes' duration of greater than 30 years. Patients who have no proteinuria after 20-25 years have a risk of developing overt renal disease of only approximately 1% per year.**
- **In terms of diabetic kidney disease in the United States, the prevalence increased from 1988-2008 in proportion to the prevalence of diabetes. Among people with diabetes, the prevalence of diabetic kidney disease remained stable.**

STATISTICS

- **International statistics**
  Striking epidemiologic differences exist even among European countries. In some European countries, particularly Germany, the proportion of patients admitted for renal replacement therapy exceeds the figures reported from the United States.
- **In Heidelberg (southwest Germany), 59% of patients admitted for renal replacement therapy in 1995 had diabetes and 90% of those had type 2 DM. An increase in end-stage renal disease (ESRD) from type 2 DM has been noted even in countries with notoriously low incidences of type 2 DM, such as Denmark and Australia. Exact incidence and prevalence from Asia are not readily available.**
- **A study from the Netherlands suggested that diabetic nephropathy is underdiagnosed. Using renal tissue specimens from autopsies, Klessens et al found histopathologic changes associated with diabetic nephropathy in 106 of 168 patients with type 1 or type 2 diabetes. However, 20 of the 106 patients did not during their lifetime present with the clinical manifestations of diabetic nephropathy.**

STUDY-CHINA

- **A retrospective study from China, by Fan and Wang, indicated that in type 2 diabetes patients with renal injury, there is a high prevalence of nondiabetic renal disease (NDRD).**
- **The investigators found that among 88 patients with type 2 diabetes who underwent renal biopsy, the incidence of NDRD was 72.73%, compared with 20.46% for diabetic nephropathy and 6.82% for diabetic nephropathy complicated with NDRD.**
- **Membranous nephropathy, immunoglobulin A (IgA) nephropathy, and focal segmental glomerulosclerosis were the most common NDRDs identified.**

SEX/AGE-DISTRIBUTION

- **Sex distribution for diabetic nephropathy**
  Diabetic nephropathy affects males and females equally.
- **Age distribution for diabetic nephropathy**
  Diabetic nephropathy rarely develops before 10 years' duration of type 1 DM.
- **The peak incidence (3%/y) is usually found in persons who have had diabetes for 10-20 years. The mean age of patients who reach end-stage kidney disease is about 60 years.**
- **Although in general, the incidence of diabetic kidney disease is higher among elderly persons who have had type 2 diabetes for a longer generation, the role of age in the development of diabetic kidney disease is unclear.**
- **In Pima Indians with type 2 diabetes, the onset of diabetes at a younger age was associated with a higher risk of progression to end-stage kidney disease.**

PREVALENCE

- **Prevalence of diabetic nephropathy by race**
- **The severity and incidence of diabetic nephropathy are especially great in blacks (the frequency being 3- to 6-fold higher than it is in whites), Mexican Americans, and Pima Indians with type 2 DM.**
- **The relatively high frequency of the condition in these genetically disparate populations suggests that socioeconomic factors, such as diet, poor control of hyperglycemia, hypertension, and obesity, have a primary role in the development of diabetic nephropathy. It also indicates that familial clustering may be occurring in these populations.**

AGE/PROGNOSIS

- **By age 20 years, as many as half of all Pima Indians with diabetes have developed diabetic nephropathy, with 15% of these individuals having progressed to ESRD.**

- **Prognosis**
- **Diabetic nephropathy accounts for significant morbidity and mortality.**

- **Proteinuria is a predictor of morbidity and mortality.**
- **The overall prevalence of microalbuminuria and macroalbuminuria in both types of diabetes is approximately 30-35%. Microalbuminuria independently predicts cardiovascular morbidity, and microalbuminuria and macroalbuminuria increase mortality from any cause in diabetes mellitus.**
- **Microalbuminuria is also associated with increased risk of coronary and peripheral vascular disease and death from cardiovascular disease in the general nondiabetic population.**

PROTEINURIA &MORTALITY

- **Patients in whom proteinuria has not developed have a low and stable relative mortality rate, whereas patients with proteinuria have a 40-fold higher relative mortality rate.**
- **Patients with type 1 DM and proteinuria have the characteristic bell-shaped relationship between diabetes duration/age and relative mortality, with maximal relative mortality in the age interval of 34-38 years (as reported in 110 females and 80 males).**

ESRD

- **ESRD is the major cause of death, accounting for 59-66% of deaths in patients with type 1 DM and nephropathy. In a prospective study in Germany, the 5-year survival rate was less than 10% in the elderly population with type 2 DM and no more than 40% in the younger population with type 1 DM.**

- **The cumulative incidence of ESRD in patients with proteinuria and type 1 DM is 50% 10 years after the onset of proteinuria, compared with 3-11% 10 years after the onset of proteinuria in European patients with type 2 DM.**

VARIOUS STUDIES

- **A study by Zhang et al suggested that the presence of diabetic retinopathy is an independent risk factor for the advancement of diabetic nephropathy to ESRD in patients with type 2 DM.**

A study by Jiang et al indicated that a higher number of comorbidities in patients with type 2 DM increases the likelihood that diabetic nephropathy will progress. Dividing the study's patients into four groups—low comorbidity/low treatment, low comorbidity/high treatment, moderate comorbidity/high insulin use, and high comorbidity/moderate treatment—the investigators found the subjects' 5-year diabetic nephropathy progression rates to be 11.8%, 18%, 16.5%, and 27.7%, respectively.

OTHER STUDIES

- **A study by Rosolowsky et al reported that despite renoprotective treatment, including transplantation and dialysis, patients with type 1 diabetes and macroalbuminuria remain at high risk for ESRD.**

- **Although both type 1 and type 2 DM lead to ESRD, the great majority of patients are those with type 2 diabetes. The fraction of patients with type 1 DM who develop renal failure seems to have declined over the past several decades. However, 20-40% still have this complication.**
- **On the other hand, only 10-20% of patients with type 2 DM develop uremia due to diabetes. Their nearly equal contribution to the total number of patients with diabetes who develop kidney failure results from the higher prevalence of type 2 DM (5- to 10-fold).**

CVD

- ***Cardiovascular disease is also a major cause of death (15-25%) in persons with nephropathy and type 1 DM, despite their relatively young age at death.***

METFORMIN IN RENAL DISEASE

- **What are the current recommendations regarding metformin use in renal disease?**

- **FDA recently changed the guidance regarding the appropriate prescription of metformin in response to a citizen's petition, and the new labeling guidance is that metformin can be continued down to an eGFR of 30 mL/min.**
- **Now, the reason that this guidance changed is that it's been observed in many, many large observational studies and hundreds of thousands of patients that there are extremely few adverse outcomes in patients on metformin until the creatinine clearance really is below 30.**

METFORMIN DOSE ADJUSTMENT

- **What do I do, what do many people do in practice? Many people feel that it's prudent to reduce the dose of metformin when the creatinine clearance drops to 45, so between 30 and 45 the dose can be reduced from 1000 mg twice a day, perhaps to 500 mg twice a day, and of course in patients who have unstable renal function who are at risk for acute kidney injury, who are at risk for infection or have rapid changes in their clinical status, caution is warranted, perhaps increased monitoring or even discontinuation of metformin.**
- **But for people who really are in very steady state, with an eGFR in the kind of 35 to 40 range, not only is it safe to continue metformin, it may be safer to continue metformin than it is to select an alternate glucose-lowering medication.**
- **-----ADA-JUNE-29-2018- INTERVIEW WITH DEBORAH WEXIER**

NEW MARKERS-?

- **Are there any new markers besides the microalbumin/creatinine ratio to identify and track renal disease in patients with diabetes?**

- **There are actually a number of other markers of acute kidney injury and stage renal disease, but in clinical practice we still rely on the creatinine, particularly the creatinine clearance or glomerular filtration rate, as well as the urine microalbumin to creatinine ratio,extremely important marker**

New BIO-MARKERS

- ***Apart from Albuminuria and Non Albuminuria Diabetes Kidney disease.***
- ***Tubular biomarkers reported as predictors of Diabetes Kidney disease consist of cystatin C, kidney injury molecule-1microglobuin,N-acetyl-Beta-D-glucosaminidase, and liver-type fatty-acid binding protein.***
- ***Serveral studies show that these markers are not only more sensitive, but are much earlier predictors of diabetic nephropathy than microalbuminuria.***
- ***Although their advantages over microalbuminuria are evidence-based, majority still need to be validated for diagnostic purposes.***
- ***Ref:international Journal of Nephrology and Kidney Failure-19 March. 2018.***

CKD/DKD

- **it's important to recognize that there's also an entity of chronic kidney disease and diabetic kidney disease without microalbuminuria that can be just as problematic and something really to be concerned about. You don't always get the warning sign of microalbuminuria before a patient's progressed to more advanced diabetic kidney disease.**

- **The entity of diabetic kidney disease without microalbuminuria is an increasingly prevalent problem and just as concerning.**

MEDICATIONS-?

- **Are there any medications other than ACE Inhibitors or angiotensin receptor blockers that can help ameliorate diabetic nephropathy?**

- **Physiology of how SGLT2 inhibitors may be beneficial for the kidney in an additive affect to angiotensin receptor blockers and ACE inhibitors.**
- **One of the great things about SGLT2 inhibitors is that they decrease intraglomerular pressure and decrease, actually cause afferent arteriolar vasoconstriction.**
- **As a result they're really protecting the glomerulus against the hyperfiltration that's seen in diabetic kidney disease, and as people probably know, a blockade of the renin-angiotensin system leads to dilation of the efferent arteriole which also decreases the pressure in the macula densa.**
- **So, there's a possibility that combining these two drugs together could lead to decreased pressure across the glomerulus and be very protective in restoring normal physiology in people with diabetic kidney disease.**

CREATINE BUMP

- **we often do see a creatinine bump in the use of angiotensin receptor blockade or in the use of SGLT2 inhibitors and that may be a physiologic increase in creatinine that's related to decreased GFR, but what that really represents is sort of a functional improvement in the pressure across the glomerulus.**
- **It can be very hard to tell whether that represents true acute kidney injury or in fact the intended goal of therapy, and therefore, it is important to carefully monitor patients on dual blockade, but that over the long term, when used properly, this has been seen in clinical trials to have benefit on diabetic kidney disease and offers very exciting potential for the future.**

GUIDELINES-?

- **Are there guidelines for lowering the dose of insulin in a patient with deteriorating renal function?**

- **The big challenges we face is how to manage insulin in a patient with progressive kidney disease.**
- **There's a lot of factors at play. As kidney disease progresses, insulin resistance can increase.**
- **Also, as kidney disease progresses, insulin clearance decreases, so it really can be quite hard to predict whether one needs to increase or decrease the insulin.**
- **Also, this is often a time in the course of people's illness where there's a lot of other competing demands, multimorbidity, chronic illness, sometimes erratic dietary intake, and so actually, the most important thing is to pay very close attention in patients on complex insulin regimens and to be very proactive in adjusting them.**

CREAININE/HYPOGLYCEMIA

- ***Even small increases in the creatinine dramatically increase the risk of hypoglycemia because the kidney is responsible for about 30% of gluconeogenesis.***
- ***Monitoring the patient, having the patient do careful self-monitoring, and making sure the patient understands how to adjust his or her own insulin in anticipation of changes in diet and activity is the most important strategy***

ANGPLT2

- **Conclusions**
- **ANGPTL2 might be directly involved in podocyte dysfunction and independently associated with the progression of DKD stages.**
- **ANGPTL2 directly increased albumin permeability through the translocation of zonula occludens-1 from the membrane to the cytosol via activation of focal adhesion kinase.**
- **Angiopoietin-like protein 2 (ANGPTL2) is a circulating, proinflammatory protein.**

- **Ref.Toshihisa Ishii etal**
- **The Journal of Clinical Endocrinology & Metabolism, Volume 104, Issue 1, 1 January 2019**

QUIZ-URINE CLUSTERINE

- **Urine clusterin in diabetic patients with eGFR ≥60 mL/min/1.732 correlates with:**
- **A.Both answers are correct**
- **B.Neither answer is correct**
- **C.Development of CKD stage 3 or greater**
- **D.Persistence/progression of albuminuria**

- **Answer Explanation:**
- **Both answers are correct. The increase of urine clusterin along with albuminuria could be an independent predictive marker for the progression of diabetic kidney disease in type 2 diabetes.**
- **Kim SS, et al. Clin Endocrinol (Oxf). 2017 Apr 23. [Epub ahead of print]**

NEPRILYSIN INHIBITORS IN CKD

- **Do Neprilysin Inhibitors Have a Role in Patients With CKD?**
- **Tejas P. Desai, MD**

- **December 14, 2018**

- **What Are Your Thoughts on Neprilysin Inhibitors for CKD?**
- **Despite the current negative findings, I wonder whether neprilysin inhibition can still have a role in patients with proteinuric kidney disease. While the majority of patients enrolled were assumed to have diabetic kidney disease, the mean proteinuria was 310 mg/g.**
- **I also wonder whether a longer duration of treatment is required to see a difference in eGFR. I don't think we should shut the door on neprilysin inhibitors just yet as they relate to renal protection.**

CLUSTERING OF DM

- **Emma Ahlqvist, PhD, of Lund University in Sweden, and colleagues in the Lancet Diabetes & Endocrinology**

- **The five unique subgroups based on severity and underlying disease mechanism analysis -- reported by Emma Ahlqvist, PhD, of Lund University in Sweden, and colleagues in the Lancet Diabetes & Endocrinology -- were:**
- **Cluster 1: Severe autoimmune diabetes (SAID)**
- **Cluster 2: Severe insulin-deficient diabetes (SIDD)**
- **Cluster 3: Severe insulin-resistant diabetes (SIRD)**
- **Cluster 4: Mild obesity-related diabetes (MOD)**
- **Cluster 5: Mild age-related diabetes (MARD).**

- **cluster 3, which had the highest degrees of insulin resistance, showed a significantly higher risk for diabetic kidney disease than the other groups. Those in the severely insulin-deficient cluster had the highest risk for diabetic retinopathy.**

CIGARETTE SMOKING AND DM

- **Cigarette smoking as a risk factor for diabetic : A systematic review and meta-analysis of prospective cohort studies**
- **Dan Liao,et**
- **Conclusions**
- **The present study highlighted that smoking was an independent risk factor for DN, especially in patients with T1DM. This is the first meta-analysis of prospective cohort studies to discuss the relationship between smoking and DN.**
- **Ref:PLoS ONE 14(2): e0210213. doi:10.1371/journal.pone.0210213**

The Familiarity of Rapid Renal Decline in Diabetes

- **We estimated GFR (eGFR) from serum creatinine measurements obtained from 15,612 patients with diabetes at the University of Utah Health Sciences Center and established their renal function trajectories.**

FAMILIALITY OF RAPID RENAL DECLINE IN DIABETES

- **Familial analysis showed that rapid renal decline aggregates in these families and is associated with its increased risk among first-degree relatives. Further study of these families is necessary to understand the magnitude of the influence of shared familial factors, including environmental and genetic factors, on rapid renal decline in diabetes.**
- **Ref:Diabetes 2019 Feb; 68(2): 420-429.**
- **Scott G. Frodsham etal**
- **Received 31 July 2018 and accepted 5 November 2018**

THANK YOU…