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Review Article

AN UPDATE ON DIABETES MELLITUS AND RENAL FUNCTION

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Abstract

Research over the years in the field of diabetes mellitus indicates that kidney is the first organ that will be affected in uncontrolled diabetes, both Type 1 and Type 2. Microalbuminria is the first predictable markers which if not controlled will lead to progressive renal failure leading to ESRD and in such conditions, dialysis and later kidney transplantation is the ultimate choice to reverse kidney failure. Chronic kidney disease in diabetes requires multiple medications leading to more complications and cardiac muscle may be the next target to induce CVD. This review article presents up-to-date information available to link Type 2 DM to Renal functions and will be useful to research scholars to extend further research in this field.

Keywords: T2DM, DKD, ESRD, DN, CVD.

Introduction

Type 2 Diabetes Mellitus (T2DM) is the most common form of Diabetes Mellitus (DM) characterized by hyperglycemia, insulin resistance and relative insulin deficiency [1]. T2DM results from interaction between genetic, environmental and behavioral risk factors [2]. People living with T2DM are more vulnerable to various forms of both short- and long-term complications, which often lead to their premature death [3].High levels of blood glucose in DM make the kidneys to filter more amount of blood in order to excrete into urine. This extra work is hard on the filters and later a small amount of protein will be lost in the urine known as microalbuminuria. When kidney disease is diagnosed early, during microalbuminuria, several treatments are possible and if the kidney disease is diagnosed during macroalbuminuria, End-Stage Renal Disease (ESRD) will be the outcome forcingan individual either for a kidney transplant or dialysis [4]

The incidence and prevalence of DM have grown significantly throughout the world, due to the increase in T2DM. This overall increase in the number of people with diabetes has a major impact on development of diabetic kidney disease (DKD), one of the most frequent complications of both types of diabetes. DKD is the leading cause of ESRD, accounting for approximately 50% of cases in the developed world andis the single strongest predictor of mortality in patients with diabetes. It is a prototypical disease of gene and environmental interactions [5]. Tight glucose control significantly decreases DKD incidence, indicating that hyperglycemia-induced metabolic alterations, including changes in energy utilization and mitochondrial dysfunction, play critical roles in disease initiation. Blood pressure control, especially with medications that inhibit the angiotensin system, is the only effective way to slow disease progression. Inflammation, cell hypertrophy and dedifferentiation by the activation of classic pathways of regeneration further contribute to disease progression [6].

DM and chronic kidney disease (CKD) require multiple medications for their management. Many of the anticipated effects of these medications are altered by the physiologic changes that occur in CKD. Failure to individualize drug dosing in this population may lead to

toxicity or decreased therapeutic response, leading to treatment failure. At times this can be challenging for a multitude of reasons, including the limitations of available calculations for estimating renal function, inconsistent dosing recommendations and dose for some medications. Clinicians caring for these patients need to consider an approach of individualized drug therapy that will ensure optimal outcomes [7]. The screening and early diagnosis of DKD is based on the measurement of urinary albumin excretion and the detection of microalbuminuria, the first clinical sign of DKD. The management of DKD is based on the general recommendations in the treatment of patients with diabetes, including optimal glycaemic and blood pressure control, adequate lipid management and abolishing smoking, in addition to the lowering of albuminuria [8].

In recent years, advances in high-throughput laboratory techniques and computational analyses, coupled with the establishment of multicenter consortia have helped to identify genetic loci that are replicated across multiple populations. Several genome-wide association studies (GWAS) have been conducted for DKD with further meta-analysis of GWAS and comprehensive "single gene" meta-analyses now published. Meta-analyses and integrated-omics pathway studies are being used to help elucidate underlying genetic risks. Epigenetic phenomena are increasingly recognized as important drivers of disease risk, and several epigenome-wide association studies have now been completed [9].DKD occurs in 25%-40% of patients with diabetes. Family history, smoking, glycemic, blood pressure and plasma lipid level control are established factors for identifying people at greatest risk of DKD development and progression. Absolute albumin excretion rate (AER) and glomerular filtration rate (GFR) measurements also are important, although AER categorization generally lacks the necessary specificity and sensitivity, and estimates of declining GFR are compromised by methodological limitations for GFRs in the normal-to-high range. Emerging risk markers for progressive loss of kidney function include markers of oxidation and inflammation, profibrotic cytokines, uric acid, advanced glycation end products, functional and structural markers of vascular dysfunction, kidney structural changes and tubular biomarkers. Among these, the most promising are serum uric acid and soluble tumor necrosis factor receptor (type 1 and type 2) levels, especially in relation to GFR changes [10].

DM is the single largest contributor for the increased prevalence of CKD and episodes of acute kidney injury (AKI) increase the risk of advanced CKD in diabetic patients. The diabetic tubular growth and the associated molecular signature (including up regulation of TGF-β, senescence and inflammation) set up the development of diabetic nephropathy and renal failure in part by increasing the susceptibility to AKI, which further promotes hypoxia and apoptosis. Considering the strong association between AKI episodes and the cumulative risk of developing advanced CKD in diabetes, strategies that reduce AKI in these patients are expected to help reduce the growing burden of ESRD [11]. New-onset diabetes mellitus after transplantation(NODAT) has been described in approximately 30% of non-diabetic kidney-transplant recipients after many years ofpost-transplantation. DM in patients with kidney transplantation constitutes a major comorbidity and has significant impact on the patients and allografts' outcome. In addition to the major comorbidity and mortality that result from cardiovascular and other DM complications, long standing DM after kidney-transplant has significant pathological injury to the allograft, which results in lowering the allografts and the patients' survivals [12].

Kidney transplantation is being performed more frequently for individuals with ESRD due to improved survival and quality of life compared to long-term dialysis. Though rates decrease after transplantation, cardiovascular disease (CVD) remains the most common cause of death after kidney transplant. NODAT, a common complication following kidney transplantation and pre-transplant diabetes both significantly increase the risk for CVD. Several other risk factors for CVD in kidney transplant recipients have been identified; however, optimal therapy for controlling the risk factors of CVD after kidney transplantation, including NODAT and pre-transplant diabetes, is not well defined [13]. Diabetic nephropathy (DN) is a major cause of morbidity and mortality in patients with both types of diabetes and the leading cause of ESRDworldwide [14].Glomerular dysfunction plays a critical role in DN, but deterioration of renal function also correlates with tubular alterations. DN is characterized by glycogen accumulation in tubules. The enhanced expression of suggests the participation of muscle glycogen synthase (MGS) in renal metabolic changes associated with diabetes. Human kidney2 (HK2) renal cell line exhibited an intrinsic ability to synthesize glycogen, which was enhanced after over-expression of protein targeting to glycogen. A correlation between increased glycogen amount and cell death was observed. Based on a previous transcriptome study on human DKD, significant differences in the expression of genes involved in glycogen metabolism were analyzed. Glucose is the main modulator of MGS activity in HK2 cells, suggesting that blood glucose control is the best approach to modulate renal glycogen-induced damage during long-term diabetes [15].

DN is a severe microvascular complication frequently associated with both T1 and T2DM, is a leading cause of renal failure. The condition can also lead to accelerated CVD and macrovascular complications. Currently available therapies have not been fully efficacious in the treatment of DN, suggesting that further understanding of the molecular mechanisms underlying the pathogenesis of DN is necessary for the improved management of this disease. Although key signal transduction and gene regulation mechanisms have been identified, especially those related to the effects of hyperglycaemia, transforming growth factor β1 and angiotensin II, progress in functional genomics, high-throughput sequencing technology, epigenetics and systems biology approaches have greatly expanded our knowledge and uncovered new molecular mechanisms and factors involved in DN. These mechanisms include DNA methylation, chromatin histone modifications, novel transcripts and functional noncoding RNAs, such as microRNAs and long noncoding RNAs [16].Podocytes are differentiated cells necessary for the development and maintenance of the glomerular basement membrane and the capillary tufts, as well as the function of the glomerular filtration barrier. The epithelial glomerular cells express a local renin angiotensin system (RAS) that varies in different pathological situations such as hyperglycemia or mechanical stress. RAS components have been shown to be altered in the diabetic podocytopathy, and their modulation may modify diabetic nephropathy progression. Podocytes are a direct target for angiotensin II - mediated injury by altered expression and distribution of podocyte proteins. Furthermore, angiotensin II promotes podocyte injury indirectly by inducing cellular hypertrophy, increased apoptosis and changes in the anionic charge of glomerular basement membrane. RAS blockade has been shown to decrease the level of proteinuria and delay the progression of CKD [17].

Numerous drugs with different mechanisms of action and different pharmacologic profiles are being used with the aim of improving glycemic control in patients with T2DM. Therapeutic options for patients with T2DM and CKD are limited because a reduced glomerular filtration rate results in the accumulation of certain drugs and/or their metabolites. Conventional oral hypoglycemic agents, such as sulfonylurea are not suitable due to the risk of prolonged hypoglycemia; furthermore, metformin is contraindicated for moderate to advanced CKD. Therefore, in order to achieve good glycemic control, insulin injection therapy remains the mainstay of treatment in diabetic patients with moderate to advanced CKD, particularly in that receiving dialysis therapy [18]. Metformin is globally accepted as the first choice in practically all therapeutic algorithms for diabetic subjects. The advantages of metformin are low risk of hypoglycaemia, modest weight loss, effectiveness and low cost. Data of UK prospective diabetic study indicates that treatment based on metformin results in less total as well cardiovascular mortality. Metformin remains the drug of choice for patients with diabetes and CKD provided that their estimated Glomerular Filtration Rate (eGFR) remains above 30 mL/min per square meter. For diabetic patients with eGFR between 30-60 mL/min per square meter more frequent monitoring of renal function and dose reduction of metformin is needed. The use of sulfonylureas, glinides and insulin carry a higher risk of hypoglycemia in these patients and must be very careful. Lower doses and slower titration of the dose is needed and therefore it is better to avoid sulfonylureas with active hepatic metabolites as they are excreted in urine. Very useful drugs for this group of patients emerge dipeptidyl peptidase 4 inhibitors. These drugs do not cause hypoglycemia and most of them except linagliptin require dose reduction in various stages of renal disease [19].

Accurate assessment of cardiovascular (CV) risk is a prerequisite for devising effective therapeutic strategies in patients with T2DM as it allows to refine prognosis and treatment targets as well as the cost-benefit ratio for specific pharmacological interventions. The presence of subclinical vascular organ damage plays a well-known role in determining overall risk and a wider use of low cost, easy to perform diagnostic tools to stratify CV risk is very much needed. Besides their well-known prognostic value for progression to ESRD, subclinical renal abnormalities such as microalbuminuria and/or a slight reduction in eGFR, have been shown to be powerful independent predictors of CVD in patients with T2DM. Through the combined evaluation of these two biomarkers of CKD, clinicians can usefully and reliably get a perspective on global and CV outcome of their diabetic patients [20].

The Renal Insufficiency And Cardiovascular Events (RIACE) of Italian Multicentre Study is an ongoing observational survey that examines the role of eGFR as an independent predictor of CV and renal outcomes in a very large Italian subjects with T2DM, which has concluded that non-albuminuric renal impairment is the predominant clinical phenotype in patients, particularly women with reduced eGFR; concordance between CKD and diabetic retinopathy is low, with only a minority of patients with renal dysfunction presenting with any or advanced retinal lesions; the non-albuminuric form is associated with a significant prevalence of CVD, especially at the level of the coronary vascular bed; CKD is associated with HbA1c variability more than with average HbA1c, whereas retinopathy and CVD are not; in elderly individuals with moderate-to-severe eGFR reduction, use of agents which are not recommended such as sulphonylureas and metformin is still frequent;

though complications are generally more prevalent in men (except non-albuminuric renal impairment) women show a less favorable CVD risk profile and achieve therapeutic targets to a lesser extent than men, despite the fact that treatment intensity is not lower. These data update existing information on the natural history of CKD in patients with T2DM[21].

Increased urinary albumin excretion (UAE) is a marker of renal and cardiovascular risk in patients with T2DM. An early study reports that albuminuria may be a better marker of kidney disease progression than of CV risk in the obese T2DM patient accurately demonstrate the link albuminuria - renal risk and albuminuria - CV risk in the obese T2DM patient and additional studies using very strict criteria of selection and judgment are needed [22]. A study from Austria states that mortality and incidence of renal replacement therapy increased in each quartile of baseline HbA1c, with the lowest rates in the quartile with HbA1c ≤6.5%. In people with established T1DM who were observed for almost three decades, the overall mortality was 24% and the incidence of renal replacement therapy was 8.6%, with a 21.8% combined incidence rate of the other hard endpoints in the surviving people. A clear linear relationship between early glycemic control and the later development of ESRD and mortality has been found [23].

In contrast to T1DM, the incidence of non-diabetic renal disease (NDRD) is very high in T2DM patients. A wide spectrum of non-diabetic nephropathy (NDN) including both glomerular and tubulointerstitial lesions are reported in patients with T2DM and their precise diagnosis requires histological examination of kidney tissue. Renal biopsy studies suggest that 25-50% of patients with T2DM had glomerular lesions unrelated to or in addition to DN. Histological studies confirm that NDRD can occur in isolated form withoutDN or superimposed on DN. DN can occur in the absence of retinopathy and chance of getting diabetic and non-diabetic renal lesions are nearly equal in T2DM patient in the absence of diabetic retinopathy [24].

The spectrum of renal disease in patients with diabetes encompasses both DKD (including albuminuric and non-albuminuric phenotypes) and non-diabetic kidney disease(NDKD), which could manifest as varying degrees of renal insufficiency and albuminuria, with heterogeneity in histology reported on renal biopsy. For patients with diabetes and proteinuria, the finding of NDKD alone or superimposed on the changes of DN is increasingly reported. It is important to identify NDKD as some forms are treatable, sometimes leading to remission. Clinical indications for a heightened suspicion of NDKD and hence consideration for renal biopsy in patients with diabetes and nephropathy include absence of diabetic retinopathy, short duration of diabetes, atypical chronology, presence of haematuria or other systemic disease and the nephrotic syndrome [25]. A wide spectrum of NDRD is reported to occur in patients with T2DM. It has been estimated that up to one-third of all diabetic patients who present with proteinuria are suffering from NDRD. Performing renal biopsy in diabetics with no extra renal end organ damage other than nephropathy helps to diagnose and treat NDRD and this is the first report from Pakistan documenting the prevalence of NDRD in patients with T2DM [26].

NODAT is defined as diabetes which developed after organ transplantation. NODAT occurs in approximately 16-20% of recipients one year after kidney transplantation and is the main factor for the increased mortality and morbidity, increased medical costs, progressive graft failure and decreased patients' quality of life. Determination of phenotypic risk factors allows to define the scale of the risk of NODAT and can be helpful in detecting patients at risk of post-transplant diabetes. Overweight and obesity are well-known phenotypic risk factors that can be modified by lifestyle-change intervention. Adequate education about the principles of healthy lifestyle is one of the most important prevention factors. The medical staff should organize health education which should begin long before the planned transplantation, even at the stage of predialysis treatment or dialysis and be continued after transplantation. Early assessment of the risk of developing glucose metabolism disorders also allows the selection of immunosuppressive therapy less likely to affect carbohydrate metabolism [27]. Lifestyle modification and a conventional anti-diabetic approach, as in the T2DMguidelines, are also recommended in NODAT management [28].

Conclusion

This review article contains many research findings during the last decade. Chronic and Diabetic kidney diseases are on the increase worldwide, more prevalent in a developing country like India. Some of the screening tests like albumin excretion rate, estimated GFR, basic kidney function tests, lipid profile for evaluating CVD must be the order of laboratory diagnosis for screening kidney function and finally renal biopsy will be the ultimate goal to evaluate renal dysfunctions. The contents of this review article will certainly help research scholars to explore the possibility of bringing laboratory diagnosis as the best method for kidney diseases induced by uncontrolled diabetes mellitus.

Conflicts of Interest

The authors have no conflict of interest.

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