UNIT NO. 4

UNDERSTANDING PATIENTS WITH DIABETIC NEPHROPATHY AND ITS CURRENT DAY MANAGEMENT IN PRIMARY CARE

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ABSTRACT

There are two groups of diabetic patients that we may encounter in our clinic practice, be it primary or tertiary care facilities. Type I Diabetes Mellitus (DM) is characterized by insulin deficiency at the onset of the disease and Type II DM is characterized by insulin insensitivity (inability of cells to utilize glucose properly despite adequate insulin). Type I DM is an autoimmune disease against the insulin producing beta cells in the pancreas and tends to occur in the younger lean population (usually before age 30). Type II DM on the contrary is more common in the older obese population (though recent trend showed an alarming increase of type II DM even amongst teens albeit obese teens). There are presently more teens suffering from type II DM than type I DM worldwide.

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DIABETIC NEPHROPATHY

Diabetic kidney disease or diabetic nephropathy is a distinct pathological condition seen in both types of DM. Not all diabetic patients with chronic kidney disease (CKD) have diabetic nephropathy as a cause. DM can also cause kidney damage via other disease processes. They may suffer from repeated urinary tract infections and these episodes may lead to recurrent and chronic pyelonephritis that may damage and decrease renal mass. For those complicated by neurogenic bladder, painless obstructive uropathy may be present long before diagnosis is made causing asymptomatic progressive renal impairment. Many diabetics share similar cardiovascular (CV) risks factors such as hypertension and dyslipidaemia. Together, all these factors may lead to diffuse small vessel disease and a condition known as ischemic nephropathy (recurrent renal ischemia and infarctions). Diabetic nephropathy and ischemic nephropathy accounts for the majority of CKD in the diabetic population.

DIAGNOSIS

Diabetic nephropathy is usually diagnosed by screening blood and urine tests. It must be remembered that as type I DM is diagnosed at the onset of disease, nephropathy is not seen in the first decade of the disease. However, the situation is quite the opposite for type II DM. Many with type II DM may have had undiagnosed DM for significant period of time and present with complications of DM when DM was first diagnosed. Hence, all patients with type II DM must be screened for possible kidney disease from day one of diagnosis of DM.

The clinical diagnosis of DM nephropathy is not complex. We understand hyperglycemia initially leads to nephromegaly and hyperfiltration. Many in the early stages of the disease may have higher than normal glomerular filtration rate (GFR) or hyperfiltration. Hyperfiltration is induced by a rise in intraglomerular pressure (this is the pressure within each glomerulus in the kidney). It has been shown experimentally that hemodynamic changes occur in diabetic patients leading to vasodilation of the afferent (pre-capillary) glomerular arteriole. Hyperfiltration eventually is associated with structural change and damage to the kidneys. Renal histology of early changes include mesangial expansion and glomerular basement membrane thickening.

MICROALBUMINURIA

An early clinical manifestation of diabetic nephropathy is microalbuminuria – a very small quantity (hence the term micro) of albumin leaking into the urine. The normal rate of albumin excretion in the urine is less than 20mg/day (15 ug/min). Microalbuminuria is defined as 30-300 mg/day of albuminuria (20-200 ug/min). Screening for microalbuminuria is the best mean of detecting possible early diabetic nephropathy. This can be done with a spot urine (preferably early morning first void) sample. It can be sent to the lab for urinary albumin-creatinine ratio or tested in the clinic using a special strip that can detect albuminuria in this range. Usual dipstick used in clinic can only detect macroalbuminuria – quantity of albuminuria exceeding 300mg/day or 200ug/min. 24 hour urine collection is the gold standard but it may not be practical for many especially older patients (who are forgetful and / or may have incontinence). In addition to predicting risk for eventual overt diabetic nephropathy, presence of microalbuminuria is also associated with risk of cardiovascular disease. The small quantity of albuminuria is thought to reflect endothelial dysfunction and not just renal disease. Many best practice guidelines advocate for early detection of microalbuminuria in diabetic patients including our Ministry of Health guidelines.

MACROALBUMINURIA

Progression of microalbuminuria to macroalbuminuria is estimated to be in the range of 2.5-3% /year. Onset of

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macroalbuminuria is usually associated with reduction in renal function (or GFR). Some long term observational studies have noted a decline of close to 1ml/min/month in diabetics with macroalbuminuria. This phase of disease is usually associated with histological changes that include glomerular sclerosis and typically in diabetic nephropathy a form of nodular glomerulosclerosis (known as Kimmelstiel-Wilson lesion). If the condition is left untreated, progression to end stage diabetic kidney disease will be the inevitable consequence.

It is important to know that albuminuria may occur in other forms of renal disease apart from diabetic nephropathy and this may also be the case in a diabetic patient. Albuminuria that occurs very early (less than 5 years) in the course of DM type I is not due to diabetic nephropathy. A patient who presents with sudden nephrotic syndrome with preserved (normal) GFR is likely suffering from a form of glomerulonephritis. This also applies to a patient with albuminuria but with significant hematuria (diabetic nephropathy is classically a solely proteinuric/albuminuric disease). A patient with acute sudden decline in renal function will also require further evaluation beyond a presumed diagnosis of diabetic nephropathy. Any other associated features not expected in a diabetic will also be a cause for suspecting that it is not diabetic nephropathy. Presence of diabetic retinopathy supports a diagnosis of diabetic nephropathy but absence does not rule it out completely in DM type II patients as concordance of both these microvascular complications are lower in DM type II.

TREATMENT STRATEGY

Having screened or make a diagnosis, the next step is crucial. Executing the right treatment strategy will reduce the risk of worsening kidney disease. If the condition is diagnosed early when patient is still in the microalbuminuria phase, treatment has been shown to regress microalbuminuria to normoalbuminuria. This can occur both in patients with type I DM and recently in type II DM as well. Patients who are able to regress to normoalbuminuria have much lower risk of morbidity and mortality related to cardiovascular and renal events. Even if treatment does not lead to regression to normoalbuminuria, it can retard and reduce progression to macroalbuminuria and overt renal disease. For those already with macroalbuminuria, it is still not too late and treatment can provide benefit as shown in many large randomized trials.

The remainder of this review will center on the treatment of diabetic nephropathy and its related CV risks, particularly glycemic control and rigorous blood pressure therapy using agents that impair the renin-angiotensin axis at various levels. Maintaining ideal body weight and smoking cessation are two lifestyle issues that can contribute to improve renal and CV outcomes in a diabetic patient. Although never easy to modify long standing lifestyle behavioral pattern, it must continuously be discussed and encouraged.

Glycemic control has been well proven to prevent onset and delay progression of diabetic related renal complications. It can at least partially reverse glomerular hypertrophy and hyperfiltration – both hallmarks of early diabetic kidney disease. It can delay the appearance of albuminuria and reduce degree of albuminuria for those with preexiting significant albuminuria. Achieving euglycemia should always be the aim for all diabetic patients, perhaps with the only exception for those very elderly and those with advanced renal impairment. Past studies demonstrated efficacy using insulin in type I DM and various oral diabetic agents in type II DM. The strongest evidence of reversibility is in patients receiving pancreatic transplantation (curative treatment) showing glomerular structural improvement after ten years post transplant. Choice of therapy to achieve normoglycemia is less important than the ability to reach target glycemic control. A target HbA1c of 7% is very reasonable although in a recent large trial of intensive glycemic control, achieved HbA1c of 6.5% was associated with better outcome especially in preventing development of overt diabetic nephropathy.

It must be noted that in patients with already advanced diabetic nephropathy with GFR less than 30 ml/min/1.73m2, treatment target will have to be more circumspect. Diabetic patients with advanced renal impairment are at much higher risk of suffering hypoglycemia. Long acting sulphonylureas especially those that are cleared by the kidneys and metformin is no longer suitable except under close supervision in selected group of patients. Short acting agents that are predominantly cleared by the liver are suitable for use. Newer class oral agents like DPP-4 inhibitors can be used with dose adjustment. Insulin is always safe in the appropriate dose whatever the renal function.

As mentioned earlier, extensive studies in diabetic animals suggest that intraglomerular hypertension and glomerular hypertrophy play an important role, being present early in the disease. Decreasing intraglomerular hypertension with moderation in dietary protein intake and use of agents that blocks the renin-angiotensin axis is highly effective in diabetic patient. Angiotensin converting enzyme inhibitors (ACEI) and angiotensin receptor blocker (ARB) are two proven classes of anti-hypertensive agents that not only lower systemic blood pressure but also specifically vasodilate the efferent glomerular arteriole. This leads to lowering of intraglomerular pressure and preservation of the affected glomeruli. Clinically, it is assume that intraglomerular pressure is lowered when the albumin leakage is lessened. ACEI and ARB have both been shown in randomized controlled clinical trials to reduce albuminuria significantly along with reduction in the rate of reaching end stage renal failure. ACEI and ARB represent the present day standard of care for diabetic nephropathy – both early disease (microalbuminuric phase) and overt disease (macroalbuminuria).

Two other classes of anti-hypertensive also exert influence on the renin-angiotensin (-aldosterone) axis. Aldosterone antagonist has been shown to reduce albuminuria in diabetic nephropathy when used alone or when combined with ACEI or ARB. Aliskerin is a direct renin inhibitor (DRI) – a new class

of anti-hypertensive. It has been shown that combining aliskerin with an ARB is more effective in reducing albuminuria than with ARB alone. There have also been advocates by some experts to use supra-high doses of ACEI or ARB to achieve even more albumin reduction. This is usually achieved with doses that are 3-4 times higher than the highest approved dose for use to treat hypertension. Although successful in reducing albuminuria, there have been no studies for renal protection (decreasing risk of GFR decline and dialysis onset).

Combining an ACEI with an ARB has superiority in reducing albuminuria when compared with either alone. However there is insufficient evidence to demonstrate disease retardation and preservation of GFR. In addition, combination therapy with ACEI and ARB may potentially carry a higher incidence of adverse effects in certain subset of patients. Typically it is when albuminuria is not controlled with a single renin-angiotensin blocking agent that a second will be added on. It should not be used in diabetic with little albuminuria. When combination therapy is tried, it must be ensured that the blood pressure does not drop too precipitously. Combination of an ACEI or ARB with aldosterone antagonist or DRI have also been used successfully in reducing albuminuria but no present longer term evidence as yet on retarding disease progression. Major studies are ongoing to test if such combinations will lead to better prognosis.

Strict blood pressure control is of utmost importance in retarding diabetic nephropathy and other complications consequent of diabetes. Every 10 mmHg reduction will reduce diabetic complications by 12%; the lowest risk was seen in those with systolic blood pressure below 120 mmHg. Those with heavy proteinuria will need their blood pressure reduced to a greater degree. However it was also observed that those with systolic blood pressure below 120 mmHg had surprisingly increased risk of cardiovascular adverse events. This may be due to the fact that those with low blood pressure may have higher rate of pre existing cardiac disease, hence the observed trend in the opposite direction. However, it does not change the approach to lower blood pressure at least to below 130/80 mmHg especially for those with significant albuminuria. For the many diabetic patients that are seen, cardiac surveillance and evaluation should always be considered and necessary intervention taken.

PRIMARY PREVENTION

Another emerging area of interest is primary prevention of diabetic nephropathy. It is of great significance if we can prevent onset of albuminuria (and diabetic nephropathy) in a diabetic who has normoalbuminuria. The majority of diabetic patients will first present to primary care and if prevention strategy can be implemented early in the course of disease, future outcome can be improved. There have been studies looking at this in both normotensive and hypertensive diabetic patients. Studies involving normotensive diabetic patients were not conclusive for prevention of onset of microalbuminuria. However, in hypertensive diabetic patients there have been positive studies using either ACEI or ARB. It is appropriate to consider starting ACEI or ARB in a diabetic patient who requires anti-hypertensive for the prevention of the onset of microalbuminuria.

Adverse events in the treatment of diabetic nephropathy using renin-angiotensin blocking agents relates most commonly to sudden decline in renal function and hyperkalemia. The best means of avoiding an adverse patient event is to monitor closely each time a therapy is started or dose adjusted (especially higher). If the sudden decline in renal function cannot be explained by new or concomitant risk factors, then early referral to the specialist is mandatory.

Weight reduction can reduce proteinuria in obese diabetics. Obesity itself is a potential cause for chronic kidney disease apart from diabetic related kidney disease. A mean weight lose of 4% body weight was associated with significant reduction in proteinuria amongst diabetics (with BMI > 27kg/m2). All overweight or obese diabetic patients should have some form of directed or supervised weight loss program that includes dietary intervention, behavioral and exercise therapist.

The strength of evidence for lipid reduction in the prevention or retardation of diabetic nephropathy is not very strong. There are trials reporting that lowering LDL-C will reduce proteinuria and slow the loss of GFR. But since diabetic are at high risk for CV disease, lowering LDL-C should be routinely practiced.

CKD not only possibly leads to end stage kidney failure requiring dialysis or transplant but also is associated with risk for CV disease. Many CV risk factors are present in a diabetic patient with chronic kidney disease. Traditional risk factors such as DM itself, hypertension, dyslipidaemia and vascular calcification are well known and seen frequently in a diabetic population. Diabetic patients with kidney disease especially those with more advanced renal impairment are associated with consequences that adversely impact the CV health such as anemia and abnormal calcium-phosphate metabolism. Further, it has been shown that renal impairment itself is a CV disease risk equivalent just as DM is. Patient with significantly reduced GFR (less than 60 ml/min/1.73m2) and heavy proteinuria (more than 1g/day) are at higher risk than either alone. As such, all diabetic nephropathy patients will need to be screened for CV disease (history, physical exam and ECG as initial assessment). All other established CV risk factors (such as DM, hypertension, obesity, smoking and lipids) will need evaluation and intervention.

Although the strength of evidence for secondary prevention of CV disease in a population with existing CKD (DM nephropathy) is not as robust as those with no CKD, it is prudent to manage these risks. Most large clinical trials on lowering LDL-C and CV risk excluded patients with significant chronic kidney disease or included only small numbers in the overall study population. Meta-analysis that pooled various studies over the years did show a significant reduction in CV events for those taking statin to lower LDL-C. Another study with substantial population with diabetic and GFR of less than 60 ml/min/1.73m2, demonstrated

that there was greater magnitude of risk reduction in those with low GFR than those with normal GFR. A prospective randomized trial is underway presently to evaluate specifically the issue of LDL-C lowering in a CKD population for CV risk reduction. We do know that statin appears safe for patients with CKD from large trials done so far.

Treatment of blood pressure is effective in protecting against progressive renal failure and also CV disease. Although blood pressure and reduction in CV risks is well established in the non kidney disease population, it is less well studied in population with CKD. One major trial provided post hoc analysis of the subset of patients with GFR less than 60 ml/min/1.73m2 showed risk reduction of all major CV events. It did not however specifically study patients with DM nephropathy. Use of ACEI or ARB as anti-hypertensive agents of choice has clearly benefited many patients (DM or not) from the CV perspective.

Overall, the management of CV disease in a diabetic population has to deal with the usual non CKD risks and in addition, CKD related risks (correction of anemia and calcium phosphate metabolism). Some of the treatment strategies outlined for DM nephropathy will also improve CV outcome. Hence, it is about treating the patient with DM nephropathy and not just the nephropathy itself.

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LEARNING POINTS

- **Not all diabetic patients with chronic kidney disease (CKD) have diabetic nephropathy as a cause. DM can also cause kidney damage via other disease processes.**
- **All patients with type II DM must be screened for possible kidney disease from day one of diagnosis of DM.**
- **Screening for microalbuminuria is the best mean of detecting possible early diabetic nephropathy. This can be done with a spot urine (preferably early morning first void) sample.**
- **Strict blood pressure control is of utmost importance in retarding diabetic nephropathy and other complications consequent of diabetes.**