Vascular Complications of Diabetes- Retinal and Renal Changes in Diabetic Foot

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ABSTRACT

BACKGROUND
Diabetes mellitus is a major medical problem throughout the world, especially in India. It causes an array of systemic complications, which has considerable impact on both the patient and society because it typically affects individuals in their productive years. Diabetic foot is one of the major complications with both micro and macro vascular components to it. In this background we did a prospective study to establish its relationship with diabetic retinopathy and nephropathy, if any.

METHODS
Among the diabetic foot patients admitted in surgical wards we graded the lesion based on Wagner’s classification. These patients underwent retinal examination to grade retinopathy. Blood Urea Nitrogen (BUN), serum creatinine and renal ultrasound were done to grade Nephropathy. The result was later analysed to look for any relations between the variables.

RESULTS
The present study showed a significant relationship of diabetic foot with duration of diabetes. 46.7% of patients were in the stage of micro albuminuría and 36.7% in macro albuminuría. 35% patients had moderate non proliferative retinopathy and 30% had severe non proliferative retinopathy.

CONCLUSIONS
This study did not show strong association between diabetic foot, DR and DN in patients with T2DM but majority of the subjects had all 3 diseases in different grades. There was strong association with disease duration, which calls for multpronged approach to the problem.

KEYWORDS
Diabetic Foot, Diabetic Retinopathy, Diabetic Nephropathy, Macrovascular, Microvascular
BACKGROUND

Diabetes is a global health issue and adds to economic burden in a developing country like India. Kerala, though much developed in health sector compared to other states has a huge burden of diabetics, with a prevalence of 17% against the national average of 8%. Both microvascular and macrovascular complications follow diabetes, mainly type (T2DM). Most common microvascular complications include Diabetic Retinopathy (DR), Diabetic Nephropathy (DN) and Neuropathy. Macrovascular diseases include Ischemic heart disease, cerebrovascular disease and Peripheral vascular occlusive disease (PVOD). Diabetic foot is combination of both microvascular secondary to neuropathy and macrovascular secondary to PVOD. Diabetic foot being one of the commonest diseases admitted in surgical ward, we tried to analyse the stages of retinopathy and nephropathy in these patients and compare with the stage of diabetic foot. Diabetes mellitus is a contributory factor in more than 50% of lower limb amputations in united states (data in India needs to be elucidated) relative risk of amputation is 40% higher in patients with diabetes. Ophthalmic complications of diabetes include corneal abnormalities, glaucoma, iris neovascularisation, cataracts and neuropathies. However the most common and potentially most binding of these is diabetic retinopathy. Pathophysiology of diabetic retinopathy remains unclear, but several theories have been postulated to explain the typical course and history of the disease. Growth hormone appears to play a causative role in the development and progression of diabetic retinopathy as reported by Poulsen. He describes reversal of retinopathy in a lady with juvenile onset DM who had post-partum haemorrhagic necrosis of the pituitary gland (Sheehan syndrome). Increased erythrocyte aggregation, decreased RBC deformability, increased platelet aggregation and adhesion are seen in hyperglycaemic state and this causes sluggish circulation, endothelial damage and focal capillary occlusion. This is a forerunner of retinal ischemia, which in turn contributes to the development of diabetic retinopathy. WHO has stated that India will become the hub of diabetic population in the coming decades, with worldwide about 366 million people suffering from diabetes. According to National Urban Diabetes Study conducted in the year 2000 the prevalence of Type 2 diabetes in the population above 40 years is around 23.8% in 6 major cities in India. A study by Chennai rural epidemiology estimated it to be 30.1%.

METHODS

All diabetic foot patients admitted in surgical wards were included in the study. Patients who were admitted in surgical wards for diabetic foot ulcers were graded according to Wagner’s ulcer classification system. Diabetic foot is graded from grade 0 to grade 5. Grade 0 No open lesions, grade 1 as superficial diabetic ulcer. It becomes stage 2 when the ulcer extends in to ligament or tendon without osteomyelitis or abscess formation. When ulcer goes deeper with features of joint sepsis, abscess or bone infection (osteomyelitis) it becomes stage 3. When there is localized gangrene like of the single toe or partial fore foot or heel it progresses to next stage and grade 5 having extensive gangrenous involvement of the entire foot. Evaluation of foot ulcer involves examination of the ulcer along with neurological and vascular status. For neurological assessment Semmes-Weinstein monofilaments helps to determine the presence of “protective sensation,” (sensitivity to the 10-g monofilament). Also, a tuning fork was used to differentiate the sensation gradient between the toe and ankle. Gentle probing can detect sinus tract formation, undermining of the ulcer margins, and dissection of the ulcer into the tendon sheaths, bone or joints. On probing the ulcer and it hits a bone, it is highly suspicious for osteomyelitis. If the cellulitis extends beyond 2 cm from ulcer perimeter, or if there is deep abscess, osteomyelitis, or critical ischemia, there is a high probability for limb loss. Vascular examination was carried out including capillary filling time (a capillary filling time of more than 5 seconds was considered as delayed), examination of pedal pulses, arterial Doppler evaluation when pedal pulses were not palpable. Examination of the wound included; size, location, base, depth, shape and border. Foot x-ray was used to rule out osteomyelitis. Signs of infection like cellulites, odour and purulent discharge is looked for and if necessary, discharge sent for culture and sensitivity and initiated with appropriate antibiotic.

Diabetic Nephropathy

Grading for Diabetic Nephropathy

- No evidence of Diabetic nephropathy.
- Stage of micro albuminuria, urine Albumin excretion (UAER) 30-300 mg/24 hrs.).
- Stage of overt diabetic nephropathy with clinical proteinuria (UAER >300 mg/24 hrs.).
- Stage of Acute renal failure. (elevated serum urea and Creatinine).
- Stage of Chronic renal failure (previous or present requirement of dialysis for renal support).

Presence of Nephropathy was elucidated by urine analysis for proteinuria (24 hr urine was collected and sent to lab to look for albuminuria); blood for Blood Urea Nitrogen (BUN) and serum Creatinine and Ultrasound KUB was done to look for renal changes of diabetes. In the early diabetic nephropathy, GFR and renal volume are increased while in the chronic phase the kidney volume is progressively reduced. Grading of nephropathy was done as Stage 0-not having nephropathy, Stage 1 with hyperfiltration, Stage 2 urine microalbuminuria (urinary albumin 30-300 mg/24 hrs.), stage 3- macroalbuminuria (urinary albumin >300 mg/24 hrs.), Stage 4 -acute renal failure with elevated Serum Creatinine and BUN and stage 5- End stage kidney disease with previous or present requirement of dialysis.

All the patients in the study group underwent retinal examination by an ophthalmologist to grade the level of
Grading for Diabetic Retinopathy
Retinal examination of the patients are done with the help of an ophthalmologist and the grading done as-
- Early diabetic retinopathy.
- Mild non proliferative diabetic retinopathy.
- Moderate non proliferative retinopathy.
- Severe non proliferative retinopathy.
- Advanced proliferative changes.

Exclusion Criteria
- Chronic renal failure patients.
- Patients with known case of diabetic retinopathy or other unrelated retinal disease.
- Patients who have undergone A.K. / B.K. amputations.
- Bed ridden patients.
- Patients with known diabetic nephropathy or on dialysis probably for other renal disease.

Interventional Criteria
The study does not involve any kind of intervention at any stage of the disease process, in clinical or laboratory investigations or in the treatment offered to the patient. The patient on admission to surgical ward is accessed for retinopathy and nephropathy and standard treatment provided.

Ethical Considerations
Ethical approval was obtained from the Institution Ethics Committee prior to the commencement of the study. Informed consent was obtained from all patients at the time of admission.

RESULTS
Out of the 60 patients who qualified for the study only 1 patient belonged to grade 0 of Wagner classification. Majority of patients (48.3%) patients had grade 2 diabetic foot followed by grade 3 (26.7%). 35% patients had grade 2 retinopathy (moderate non proliferative retinopathy) and 30% had severe non proliferative retinopathy. 46.7% patients were in the stage of microalbuminuria and 36.7% patients in stage of macroalbuminuria. Different parameters were correlated to look for relation between the variables, viz., Age of the patient, grade of diabetic foot, duration of diabetes and grades of retinal and renal changes. It showed that there was a significant relation between the grade of the foot, duration of diabetes and the grade of nephropathy (Figure 1, Figure 2). The study obtained an R square value of 11.9% which showed the study as significant. There was a significant correlation between the grade of diabetic foot and nephropathy. Diabetic foot grade did not have any direct relation with the grade of retinopathy, neither was any relation between the age of the patient and grade of diabetic foot. There was a significant correlation between the duration of diabetes and grade of diabetic foot.

DISCUSSION
50-60% of patients with diabetes are affected with neuropathy and is seen in up to 80% of patients with diabetic foot ulcer. Ischemia with microvascular dysfunction,
infection and neuropathy join hands and promote tissue necrosis, to ulceration and finally to gangrene. Diabetic nephropathy is one of the major causes of chronic kidney disease and it is also the most common cause of dialysis among all kidney disease.\textsuperscript{10} It is a clinical syndrome characterized by persistent albuminuria (>300 mg/day), a relentless decline in glomerular filtration rate and elevated arterial blood pressure. Diabetes is responsible for 30 to 40% of all end stage renal disease. Blood pressure must be restricted to 125/75 in stage 4 nephropathy to prevent the progression to overt nephropathy.\textsuperscript{11} In our study group of diabetic foot patients, an alarming portion of patients were in the stage of microalbuminuria progressing to renal failure without any knowledge of the same. More than this 46.7% of patients were in the stage of microalbuminuria and in this stage treatment with angiotensin receptor blockers and ACE inhibitors where shown to delay the progression of nephropathy.\textsuperscript{12} In a study with angiotensin receptor blocker irbesartan, over 2 year period, was found to lower the progression to overt nephropathy in patients with albuminuria.\textsuperscript{13} Nephropathy in the stage of microalbuminuria, close to half of the patients in our study group, comes to light only when the patient with diabetes goes for some foot ulcer or other medical problems. Though a definite correlation between the grade of diabetic foot and nephropathy could be established in the present study, we found that there is a definite correlation with the duration of diabetes.

Out of the 60 patients all 56 were in some stage of retinopathy. The prevalence of DR in India is estimated to be around 12% to around 22.4%.\textsuperscript{14} The association of serious corona ry artery disease has been well established with proliferative retinopathy in patients with NIDDM. Auni Juutilainen et al. in their study has shown that mortality in patients with diabetic proliferative retinopathy and coronary artery disease was independent of conventional risk factors of CAD, glycaemic control, proteinuria and duration of diabetes.\textsuperscript{15} Renal disease as evidenced by proteinuria and elevated BUN/ Creatinine levels is an excellent predictor of the presence of retinopathy. Viz a viz glomerular lesions were significantly associated with retinopathy and was a independent risk factor for renal outcomes in patients with diabetic nephropathy.\textsuperscript{16} In patients with type 2 DM, it has been shown that conventional risk factors like obesity and poor glycaemic control may increase the chances of death partly through endothelial dysfunction, increased inflammatory activity and (micro) albuminuria.\textsuperscript{17} Aggressive treatment of diabetic nephropathy may have beneficial effect on the progression of diabetic retinopathy and neovascular glaucoma.\textsuperscript{18} Diabetic nephropathy is the leading cause of chronic renal failure worldwide. It is one of the most significant long term complications in terms of morbidity and mortality for individual patients with diabetes. 30 to 40% of all end stage renal disease cases are secondary to diabetes. Proteinuria was recognized as early as 18th century in patients with diabetes. Kimmelstiel and Wilson first described the classic lesions of nodular glomerular sclerosis in diabetes and established its association with Proteinuria and hypertension.\textsuperscript{19} The key change in diabetic glomerulopathy is augmentation of extracellular material.\textsuperscript{20} Thickening of the glomerular basement membrane and expansion of the mesangium due to accumulation of extracellular matrix are the earliest morphological abnormality in DM. Kimmelstiel-Wilson lesions/nodules are seen in light microscopy. The aetiology of diabetic nephropathy is not known. Postulations include hyperglycaemia (causing hyper filtration and renal injury), advanced glycosylation products, and activation of cytokines. Hyperglycaemia increases the expression of transforming growth factor -beta (TGF-beta) in the glomeruli and of matrix proteins specifically stimulated by this cytokine.\textsuperscript{19} TGF-may contribute to both the cellular hypertrophy and enhance collagen synthesis observed in patients with diabetic nephropathy.

NICE guidelines for delaying the progression of macrovascular diseases in the setting of microvascular disease suggested statins for the primary prevention of cardiovascular disease and also for the secondary prevention of cardiovascular disease irrespective of baseline lipid values along with low dose aspirin.\textsuperscript{20}

**CONCLUSIONS**

Whether to conclude or begin is a question. Though this study did not show strong association between diabetic foot, DR and DN in patients with T2DM, majority of the subjects had all 3 diseases in different grades. Many studies have shown that mortality with microvascular and macrovascular complications is on the rise. India marching towards the second half of 21\textsuperscript{st} century and expecting the highest number of diabetic patients globally needs more focused work on the management of diabetes and delaying the progression of its complications by unifying current treatments for diabetic foot ulcer, diabetic nephropathy, retinopathy and also in other subset of patients like cardiovascular diseases. Further studies to understand the molecular mechanisms and pathogenesis of microvascular complications of diabetes are necessary. For now, in order to have a positive impact on T2DM patients’ quality of life, diabetic microvascular complications should be detected early by screening with retinal examination and renal function tests and appropriate treatment instituted. All diabetic patients approaching for specific health related issues should be screened for the usual complications and followed up appropriately; multicentric randomized controlled trial is suggested to have wider evaluation.

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