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

Prajeesh Thiru Chaithanya[1], Sreejayan Meethala Parambil[2], Rajan Puthiadath[3]

[1]Assistant Professor, Department of Cardiovascular and Thoracic Surgery, Government Medical College, Kozhikode, Kerala. [2]Additional Professor, Department of General Surgery, Government Medical College, Kozhikode, Kerala. [3]Senior Consultant, General Surgeon, Malabar Institute of Medical Sciences, Kozhikode, Kerala.

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 albuminuria and 36.7% in macro albuminuria. 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 multipronged approach to the problem.

KEYWORDS

Diabetic Foot, Diabetic Retinopathy, Diabetic Nephropathy, Macrovascular, Microvascular

Corresponding Author:
Dr. Prajeesh Thiru Chaithanya,
Harichaithanyam, Amat Road,
Kovoor MLA Road, Kozhikode- 673017,
Kerala.
E-mail: tcprajeesh@gmail.com
DOI: 10.18410/jebmh/2020/58

Financial or Other Competing Interests: None.

How to Cite This Article:
Prajeesh TC, Sreejayan MP, Rajan P. Vascular complications of diabetes-retinal and renal changes in diabetic foot. J. Evid. Based Med. Healthc. 2020; 7(6), 275-279. DOI: 10.18410/jebmh/2020/58

Submission 31-12-2019,
Peer Review 05-01-2020,
Acceptance 12-01-2020,
Published 06-02-2020.

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).[1] 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.[2] 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.[3] 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.[4] A study by Chennai rural epidemiology estimated it to be 30.1%.[5]

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.[6] 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.[7]

All the patients in the study group underwent retinal examination by an ophthalmologist to grade the level of

retinopathy and staged from no diabetic retinopathy to advanced proliferative changes in the retina.[8]

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.

Around 20% of newly detected diabetics are found to have diabetic retinopathy. Patients on insulin treatment are more likely to have retinopathy compared to pts on diet control and oral hypoglycemic.[9]

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.

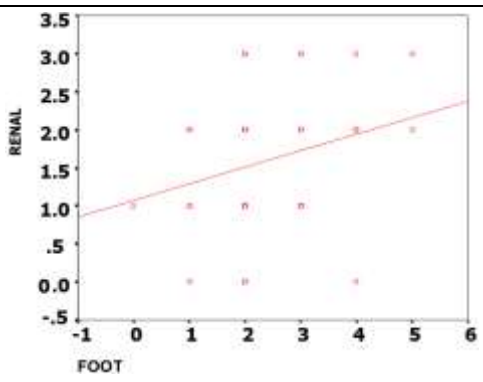

Figure 1. Relation between Grade of Nephropathy and Diabetic Foot

p value=> 0.050

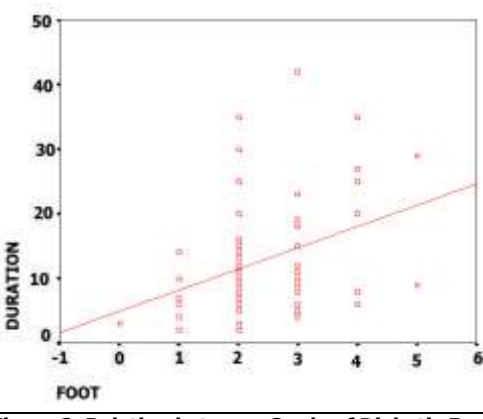

Figure 2. Relation between Grade of Diabetic Foot and Duration of Diabetes

p value = 0.015

An ANOVA test was done to see whether the relation between the grade of diabetic foot and the grade of nephropathy was due to the common relation with the duration of diabetes. The result showed that the relation between the duration of diabetes and the grade of diabetic foot was constant, while the relation between grade of foot and nephropathy was variable and dependent on the duration of diabetes, showing that the significance between the two was related to the duration of the primary disease. 50% of the patients in our study group were above 50ys of age. Only 6 patients did not have retinopathy and 2 patients had proliferative retinopathy. 4 patients were free of nephropathy.

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.[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.[11] In our study group of diabetic foot patients, an alarming portion of patients were in the stage of macroalbuminuria 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.[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.[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%.[14] The association of serious coronary 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.[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.[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.[17] Aggressive treatment of diabetic nephropathy may have beneficial effect on the progression of diabetic retinopathy and neovascular glaucoma.[16] 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.[18] The key change in diabetic glomerulopathy is augmentation of extracellular material.[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.[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.[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 21st 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.

REFERENCES

[1] Poulsen JE. Recovery from retinopathy in a case of diabetes with Simmonds' disease. Diabetes 1953;2(1):7-12.
[2] Tarr JM, Kaul K, Chopra M, et al. Pathophysiology of diabetic retinopathy. ISRN Ophthalmol 2013;2013:1-13.

[3] Wild S, Roglic G, Green A, et al. Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. Diabetes Care 2004;27(5):1047-1053.
[4] Ramachandran A, Snehalatha C, Kapur A, et al. High prevalence of diabetes and impaired glucose tolerance in India: National Urban Diabetes Survey. Diabetologia 2001;44(9):1094-1101.
[5] Mohan V, Deepa M, Deepa R, et al. Secular trends in the prevalence of diabetes and impaired glucose tolerance in urban South India--the Chennai Urban Rural Epidemiology Study (CURES-17). Diabetologia 2006;49(6):1175-1178.
[6] Fiorini F, Barozzi L. The role of ultrasonography in the study of medical nephropathy. J Ultrasound 2007;10(4):161-167.
[7] Moosa MR, Van Der Walt I, Naicker S, et al. Important causes of chronic kidney disease in South Africa. S Afr Med J 2015;105(4):1-8.
[8] Classification of Diabetic Retinopathy from Fluorescein Angiograms. ETDRS Report Number 11. Early Treatment Diabetic Retinopathy Study Research Group. Ophthalmology 1991;98(5 Suppl):807-822.
[9] Klein R, Klein BE, Moss SE, et al. The Wisconsin Epidemiologic Study of Diabetic Retinopathy: III. Prevalence and risk of diabetic retinopathy when age at diagnosis is 30 or more years. Arch Ophthalmol 1984;102(4):527-532.
[10] Lakshminarayana GR, Sheetal LG, Mathew A, et al. Hemodialysis outcomes and practice patterns in end-stage renal disease: experience from a Tertiary Care Hospital in Kerala. Indian J Nephrol 2017;27(1):51-57.
[11] Nazar CMJ. Diabetic nephropathy; principles of diagnosis and treatment of diabetic kidney disease. J Nephropharmacol 2014;3(1):15-20.
[12] Baltatzi M, Savopoulos C, Hatzitolios A. Role of angiotensin converting enzyme inhibitors and angiotensin receptor blockers in hypertension of chronic kidney disease and renoprotection. Study results. Hippokratia 2011;15(Suppl 1):27-32.
[13] Wardle EN. How does hyperglycaemia predispose to diabetic nephropathy? QJM 1996;89(12):943-951.
[14] Raman R, Rani PK, Reddi Rachepalle S, et al. Prevalence of diabetic retinopathy in India: Sankara Nethralaya Diabetic Retinopathy Epidemiology and Molecular Genetics Study Report 2. Ophthalmology 2009;116(2):311-318.
[15] Juutilainen A, Lehto S, Rönnemaa T, et al. Retinopathy predicts cardiovascular mortality in type 2 diabetic men and women. Diabetes Care 2007;30(2):292-299.
[16] Zhang J, Wang Y, Li L, et al. Diabetic retinopathy may predict the renal outcomes of patients with diabetic nephropathy. Ren Fail 2018;40(1):243-251.
[17] Stehouwer CDA, Gall MA, Twisk JWR, et al. Increased urinary albumin excretion, endothelial dysfunction, and chronic low-grade inflammation in type 2 diabetes: progressive, interrelated, and independently associated with risk of death. Diabetes 2002;51(4):1157-1165.
[18] Fioretto P, Mauer M. Histopathology of diabetic nephropathy. Semin Nephrol 2007;27(2):195-207.
[19] Cao Z, Cooper ME. Pathogenesis of diabetic nephropathy. J Diabetes Investig 2011;2(4)243-247.
[20] Colhoun HM, Betteridge DJ, Durrington PN, et al. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): Multicentre randomised placebo-controlled trial. Lancet 2004;364(9435):685-696.