Original Article

STUDY OF DIABETIC FOOT DISEASE IN TYPE 2 DIABETIC PATIENTS WITH CHRONIC KIDNEY DISEASE.

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Abstract:

Background: Diabetes mellitus is probably one of the earliest diseases known to man , type 2 DM is the most common which is more vulnerable to microvascular complications such as diabetic neuropathy and diabetic nephropathy causing CKD which is an added risk factor for diabetic foot disease. **Subjects and Methods:** This cross-sectional study included 300 type 2 diabetic patients (aged 30-70 years) with chronic kidney disease classified into 5 groups according to eGFR. Clinical examination and full diabetic foot examination was done to all study subjects. HbA1c, LDL-C, serum creatinine, and urinary albumin creatinine ratio (ACR) were measured for all study subjects. Estimated glomerular filtration rate (eGFR) was calculated using CKD-EPI equation. **Results:** There was statistically significant difference between the five groups as regard DN score ($p<0.001$). The DNS was significantly higher in cases in group 4,5A and 5B CKD as compared with group1 and group2. Regarding ABI, it was significantly low in groups 4,5A and 5B as compared with groups 1 and 2. The mean serum cholesterol, mean TGs level, mean LDL level, mean creatinine level and UACR increased significantly with increasing the stage of CKD while the mean HBA1C and HDL level decreased significantly with increasing the stage of CKD. There was a statistically significant negative correlation between GFR, age, and duration of DM, weight, waist circumference, BMI, DNS, TGs, creatinine and UACR. Also there was statistically significant positive correlation between GFR with ABI, HbA1C and HDL. **Conclusion:** There is a strong association between the degree of renal impairment and DFS. Diabetic patients on dialysis treatment had a high prevalence of DF and most of them had one or more risk factors for developing an ulcer in the future.

Key Words: Diabetic foot, Chronic kidney disease.

Introduction:

Type 2 DM (formerly known as non-insulin dependent DM) is the most common form of DM characterized by hyperglycemia, insulin resistance, and relative insulin deficiency. (1)

People living with type 2 DM are more vulnerable to various forms of both short and long-term complications, which often lead to their premature death. This tendency of increased morbidity and mortality is seen in patients with type 2 DM because of the commonness of this type of DM, its insidious onset and late recognition, especially in resource-poor developing countries like Africa. (2)

CKD can be caused by numerous underlying processes. In general, causes can be grouped into glomerular diseases (such as diabetic nephropathy or lupus nephritis), vascular diseases (such as hypertension), tubulointerstitial diseases (such as obstructive uropathy), and cystic diseases. The most common causes are diabetes mellitus and hypertension, which together account for over two thirds of cases. (3)

Diabetic kidney disease is usually a clinical diagnosis made based on the presence

of albuminuria and/or reduced GFR in the absence of signs or symptoms of other primary causes of kidney damage. The typical presentation of diabetic kidney disease is considered to include a long standing duration of diabetes, retinopathy, albuminuria without haematuria, and gradually progressive loss of e GFR. [4]

Diabetic nephropathy is now the most common cause of chronic kidney disease (CKD). Both types of diabetes can lead to chronic kidney disease and eventually ESRD, but there is much higher prevalence of type 2 diabetes than type 1, often patients with ESRD have type 2 diabetes. The overall incidence 20 years after diagnosis is approximately 4 to 17% and after 30 years is about 16%. [5]

Neuropathies are among the most common long term complications of diabetes, affecting up to 50% of patients. [6]

The neuropathies associated with diabetes mellitus represent insidious and progressive processes for which a disconnection exists between pathological severity and the development of symptoms which are heterogeneous, originating in different parts of the nervous system and resulting in diverse clinical manifestations. By far the most common diabetic neuropathies are chronic sensorimotor distal symmetric polyneuropathy (DPN) and cardiac autonomic neuropathy (CAN). [7]

Risk factors for the development of PN include diabetes duration, degree of hyperglycemia, hyperlipidemia, hypertension, and height. [8] Retinopathy and nephropathy are highly associated with PN, occurring in type 2 diabetic patients by 55% and 32%, respectively. [9]

The definition of the diabetic foot has been described as infection, ulceration and/or destruction of deep tissues associated with neurological abnormalities and various degrees of peripheral vascular disease.[10]

As indicated by this description, one or more of these conditions may coincide, and they often do. Diabetic foot ulcer is the general term to describe a full thickness wound below the ankle in a patient with diabetes, the major adverse outcomes of diabetic foot problems are foot ulcers and amputations, and foot problems account for more hospital admissions than any other long term complications of diabetes, and also result in increasing morbidity and mortality.[11]

Subjects and Methods:

The present study was conducted on 300 patients who were classified into five stages according to estimated glomerular filtration rate (e GFR). Patients of fifth stage (e GFR less than 15) were classified into dialysis group and no dialysis group. [12]

Clinical assessment of the patients included blood pressure, body mass index (BMI), waist circumference (WC) , the severity of peripheral neuropathy by diabetic neuropathy score (DNS) , skin color , hair and nails ,ulcers(size ,depth ,site ,discharge ,margins ,floor, type), checking appropriate foot wear. Also, musculoskeletal assessment of gait, joint flexibility and deformities. [13]

Neurological examination was done by tuning fork, deep tendon reflex of the ankle joints. Vascular examination was done by assessment of ankle brachial pressure index (ABPI) (12), laboratory investigations were done by checking HbA1C, lipid profile, serum creatinine, eGFR (was calculated according to CKD-EPI formula), Urinary albumin creatinine ratio (UACR), complete urine analysis and ultrasound abdomen. [12]

Results:

Regarding demographic data of the study population, the mean age of the cases was 58.2±5.47 years and there were 114 males (38%) and 186 females (62%). The

anthropometric measures of the study population; the mean body weight of the cases is 91.16 ± 9.43 kg, the mean waist circumference is 112.7 ± 27.03 cm and the mean BMI is 27.51 ± 4.87 kg/m2.

Also, there were (18%) current smokers and ex-smokers (19.3%). The median duration of DM among the cases was 12.4 years with range between 3 and 25 years. According to the treatment regimen for DM, insulin was the most commonly used medications alone (38.3%) or in combination with metformin or sulfonylurea. Sulfonylurea is used alone in (29%) and metformin is used alone in (4.7%) while combined regimen (19.3%).

As regarding the past medical history of the cases HTN was present in (72%). CKD (40%), cerebrovascular stroke (12.7%) and coronary artery disease (39.3%). there were (10.7%) with previous hemodialysis, (13.3%) with previous amputation and (6%) with previous foot ulcers. Figure (1)

The cases of study were distributed into 5 groups according to eGFR calculated in ml/min/m2 and demonstrated in the Figure (2).

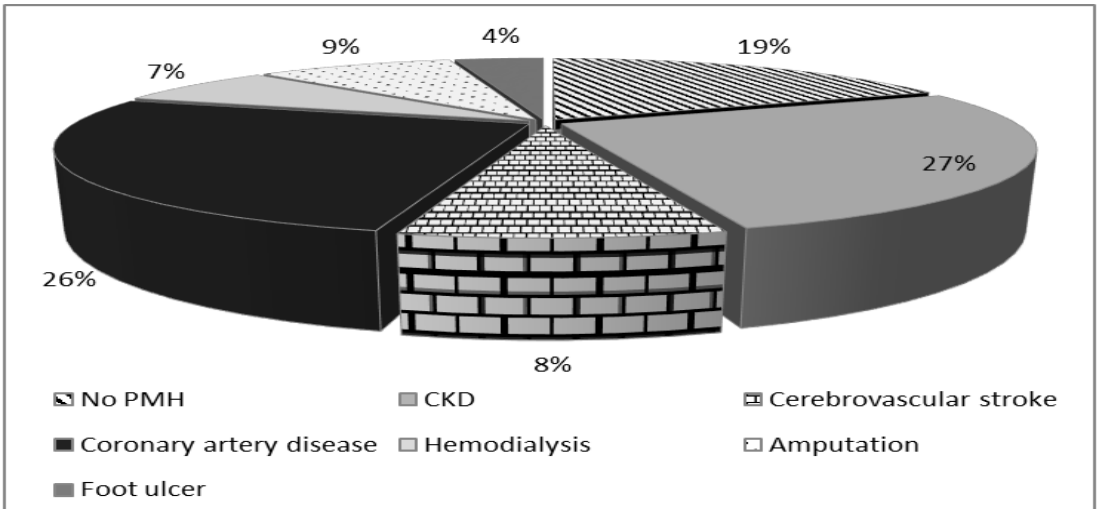

Figure 1: Past medical history

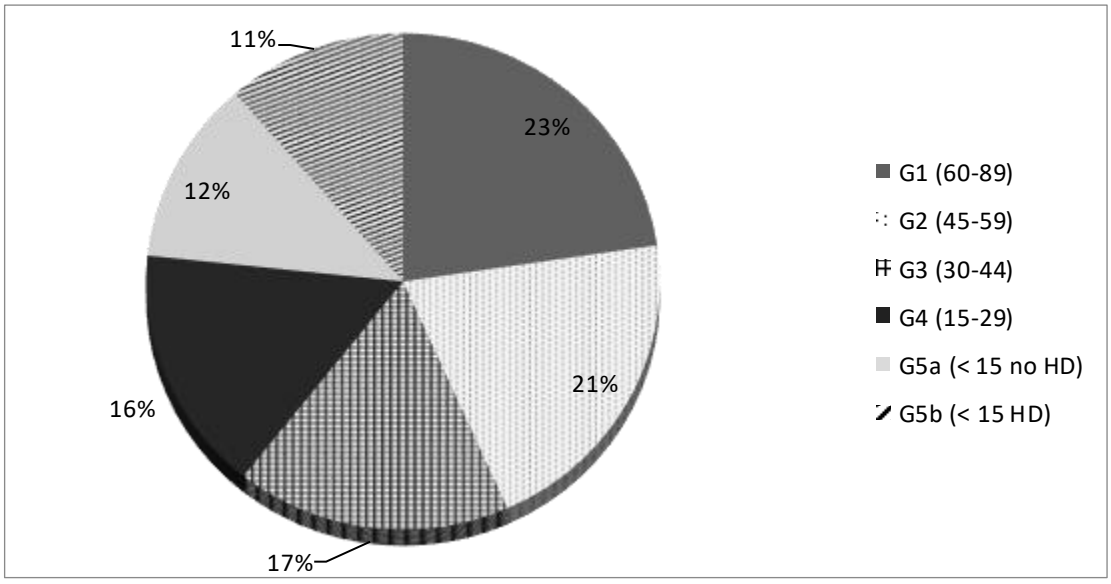

Figure 2: Cases distribution into groups

There was no statistically significant difference in the mean age and sex distribution of the cases within the different subgroups. There was a statistically significant difference between the different subgroups in the mean weight, waist circumference and BMI (p= 0.003, 0.021 and 0.010). There was a significant increase in the weight, waist circumference and BMI with progression of the stage of CKD. There was no statistically significant difference in the prevalence of smoking among the cases in the study (p=0.328).

There was a statistically significant difference in the duration of DM among the cases in the different subgroups (p=0.001). The cases with stage 5B CKD have the longest duration of DM. The cases in the different subgroups have statistically significant longer duration of DM as compared with the cases in group 1.

The prevalence of HTN was high in the cases with stage 5A (94.4%) and stage 5B (94.1%) with statistically significant difference as compared with other groups. Also, the prevalence of HTN was statistically significant higher in cases in stage 3 and 4 CKD as compared with the cases in stage 1 and stage 2 CKD.

Correlating the diabetic neuropathy score (DNS) between the cases within the different groups in the study, there was high statistically significant difference between the different study groups (p<0.001). The DNS was significantly higher in cases in group 4 CKD as compared with G1, in group 5A as compared with group 1 and 2, in group 5B as compared with group 1, 2 and 3. Figure (3)

With comparing the ankle brachial index (ABI) between the cases within the different groups in the study, there was high statistically significant difference between the different study groups (p<0.001). The ABI was significantly lower in cases in group 2 and 3 CKD as compared with G1. The ABI was significantly lower in group 4 as compared with group 1 and 2, in group 5A as compared with group 1, 2 and 3. In group 5B as compared with group 1, 2, 3 and 4. Figure (4)

The nail changes in the form of fungal infection and thick yellow changes were significantly higher with increasing the stage of CKD. The percentage of cases with cold skin temperature and absent skin hair was significantly higher as compared with increasing the stage of CKD.

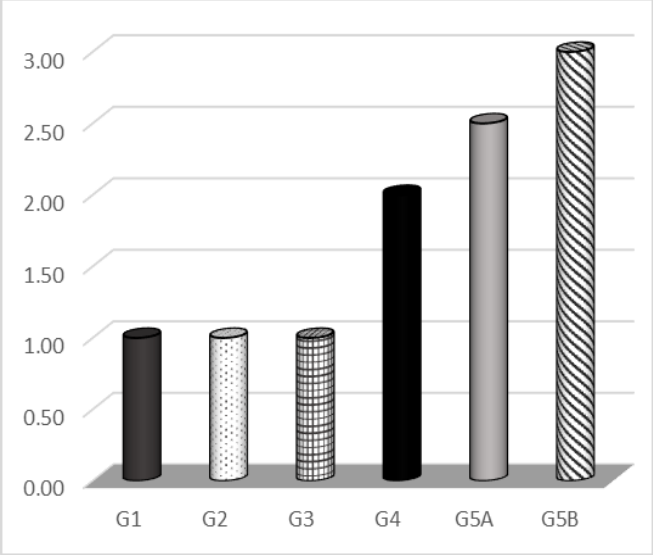

Figure 3: DNS among the cases in the different groups

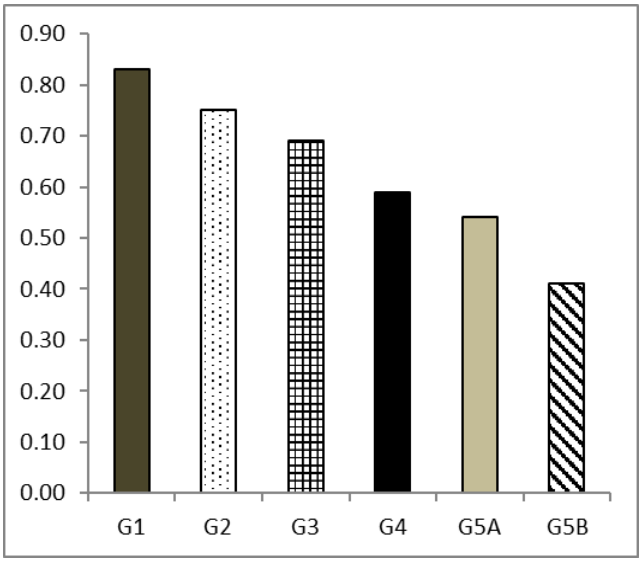

Figure 4: ABI among the cases in the different groups

There was a statistically significant difference in the joint flexibility between the different groups of CKD (P=0.002). There is an increase incidence of limited joint flexibility with increasing the stage of CKD.

The incidence of foot deformities between the different groups of the study (p<0.001) . There is increasing incidence of hallux vulgus and flat foot in group 5A and group 5B. as regards of Charcot joint deformity, 2 cases in group 1 and 4 cases in group 4 CKD had Charcot joint deformity that didn't appear in other groups.

There was a statistically significant difference in the absent tuning fork between the different groups of CKD (p<0.001). There is and increase incidence of abnormal tuning fork with increasing the stage of CKD. Figure (5)

There was a statistically significant difference in the ankle reflex between the different groups of CKD (p<0.001). There is and increase incidence of absent ankle reflex with increasing the stage of CKD. Figure (6)

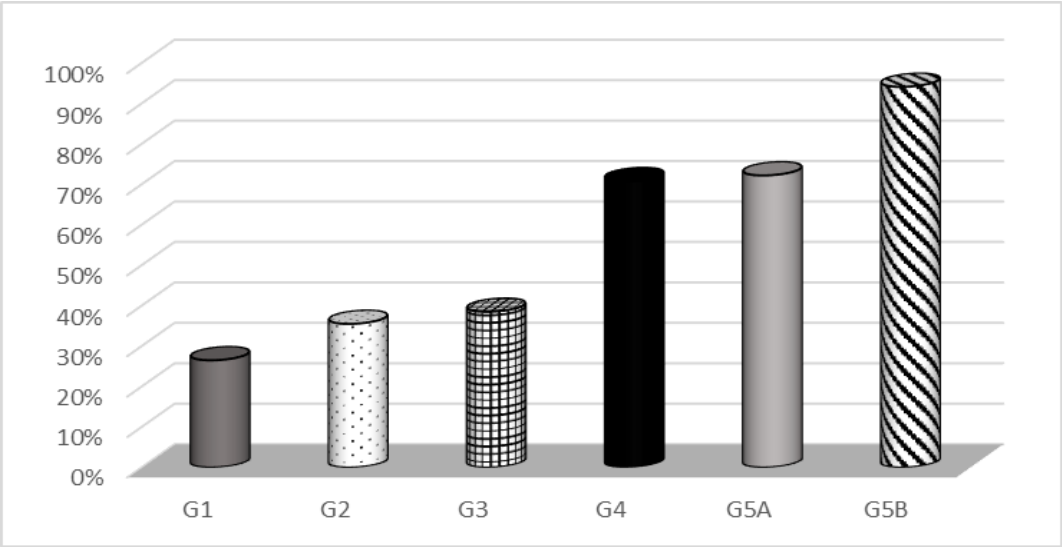

Figure 5: Absent tuning fork test among the cases in the different groups

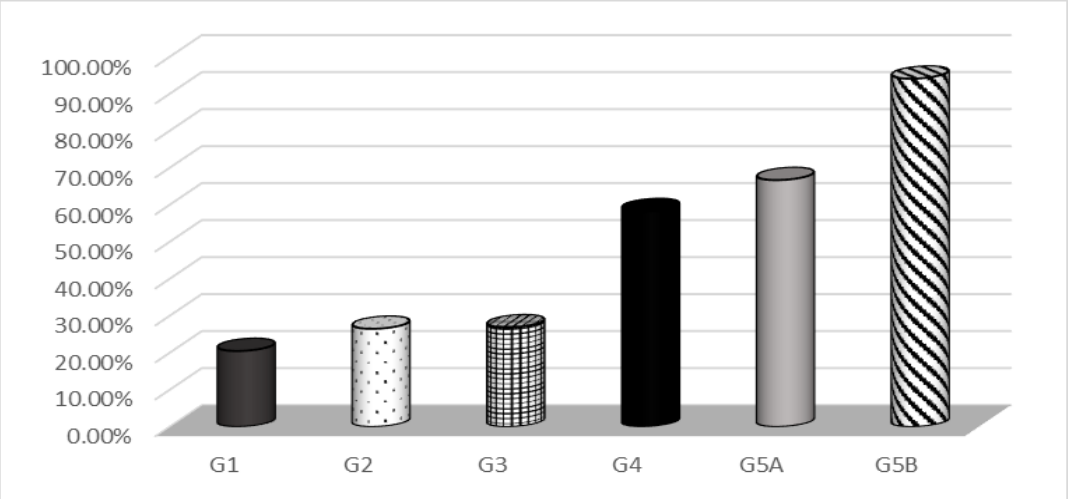

Figure 6: Absent ankle reflex among the cases in the different groups

There was statistically significant difference in the HbA1c, TGs level, HDL, creatinine and UACR between the cases in the within the different study groups. The mean serum cholesterol, mean TGs level, mean LDL level, mean creatinine level and UACR increased with increasing the stage of CKD while the mean HbA1c and HDL level decreased with increasing the stage of CKD.

The ultrasound changes in the kidneys within the cases in the different groups, all cases within group 1 had normal kidneys and (52.9%) of group 5B had grade IV nephropathy. increased cases of grade III nephropathy among group 4,5A,5B.

There is a statistically significant negative correlation between GFR, age, duration of DM, weight, waist circumference, BMI, DNS, TGs, creatinine and UACR. Also, there is statistically significant positive correlation between GFR with ABI, HbA1c and HDL. The multilinear regression analysis, duration of DM and eGFR reveal statistically significant prediction ability with ABI. Table (1)

Table 1: Multinomial regression analysis model for ankle brachial index

	a (constant)	b (regression coefficient)	t	P value
Age	.002	.004	.050	0.960
Duration of DM	.003	-.356	-4.512	<0.001*
Weight	.025	.183	.097	0.923
Height	.014	-.022	-.053	0.958
Waist circumference	.001	-.019	-.111	0.912
Body mass index	.080	-.212	-.119	0.906
HbA1C	.012	-.152	-1.710	0.090
S.Cholesterol	.002	.002	.023	0.982
S.TG	.006	-.064	-.627	0.532
LDL	.001	-.057	-.670	0.504
HDL	.003	.140	1.766	0.080
S.CREATININE	.030	-.001	-.005	0.996
e.GFR ml/min	.001	.342	2.330	0.021*
urinary albumin creatinine ratio (UACR)	.004	-.089	-.597	0.552

$y = a + bx$ where 'y' is the value of the outcome variable, 'x' is the value of the explanatory variable, 'a' is the intercept of the regression line and 'b' is the slope of the regression line

Discussion:

In the present study female were more common than males, In agreement with study of Akbari et al., the present study showed that HTN was present in (72%) of cases. Also, there were 45 current smokers (18%) and 58 ex-smokers (19.3%). [6] The median duration of DM among the cases was 12.4 years. Our results were supported by study of Dòria et al., as they found that the mean diabetes duration was 22.3 years (SD = 12.2 years). 83% of them had HTN. [14]

The current study showed that according to the treatment regimen for DM, insulin was the most commonly used medications alone in 115 cases (38.3%) and as regard the past medical history of the cases, CKD was present in 120 cases (40%), cerebrovascular stroke in 38 cases (12.7%) and coronary artery disease in (39.3%) cases, there were (10.7%) cases with previous hemodialysis, (13.3%) with previous amputation and (6%) with previous foot ulcers.

Our results were supported by He et al., study of More than 90% of patients received insulin therapy to control blood glucose. During the follow up period, (39.3%) of patients suffered from one or more cardiac and (or) cerebrovascular events. Among them, cardiac events occurred in 84 (acute heart failure, 57; acute coronary syndrome, 12; acute coronary syndrome combined with acute heart failure, 9; sudden cardiac death, 6), stroke in 42 and both occurred in 5 patients. Over 50% of the patients with reduced eGFR suffered cardiac events, whereas only less than 30% of patients in the normal eGFR group had cardiac events. [15]

In the study of Wolf et al., forty-six patients (5.1%) of their collective have active or a history of DFS (Diabetic foot syndrome) (defined as acute or previous ulcers or amputation because of DFS). [16]

There was a statistically significant difference in the duration of DM among the cases in the different subgroups (p=0.001). Cases with stage 5B CKD have the longest duration of DM. The prevalence of HTN was high in the cases with stage 5A (94.4%) and stage 5B (94.1%), in cases in stage 3 and 4 CKD.

In the study of Shaheena et al., group 1 included 80 patients with an active foot ulcer, mean age 57.5 ± 7.2 years that was significantly higher than the mean age of group 2, which was 43.2 ± 7.5 years. [17] No significant difference was found between both the groups with respect to BMI. However, Rani et al. found statistical significance were observed in age (P<0.001), gender (P<0.005) duration of diabetes (P<0.001) and duration of hypertension (<0.001) between subgroups. [18]

According to the International Working Group on the Diabetic Foot (IWGDF), DF is defined as the ulceration, infection and/or destruction of deep tissues below ankles in patients with diabetes and/or peripheral arterial disease. Complications affecting the lower limbs are among the most common manifestations of diabetes. It was reported that 15% of T2DM patients will eventually suffer from foot ulceration during their lifetime, and these complications are the frequent cause of hospitalization and disability. [19]

The present study showed that with comparing parameters of DFS as diabetic neuropathy score (DNS), the ankle brachial index (ABI), absent tuning fork, absent ankle reflex, nail changes, cold skin temperature, absent skin hair and limited joint flexibility between the cases within the different groups in the study, there was high statistically significant difference between the different study groups (p<0.001) and increase incidence with increasing the stage of CKD.

Our results were supported by study of Dòria et al., as they reported that the prevalence of foot complications was, from the highest to the lowest, PN (89.1%), moderate or severe PAD (64.2%), foot deformities (54.3%), previous ulcer (19.6%), DF (17.4%), and amputations (16.3%). finally, based on the IWGDF classification, out of 83 patients explored, 87% had some risk grade for suffering DF in the future. [14]

Our results were supported by study of Rani et al. as they demonstrated that neuropathy was higher in group I (34.5 %) followed by group III (33 %) and group II (12 %) respectively (Group I: T2DM with CKD and DFI, Group II: T2DM with CKD, Group III: T2DM with DFI and without CKD and Group IV- T2DM without any complications). [18]

Our results were in contrary with study of Shaheena et al., as they reported that there no statistically significant differences between both the groups with respect to the presence of retinopathy, the presence of ischemic heart disease, mean ankle-brachial index. [17]

The showed current study, the mean serum cholesterol, mean TGs level, mean LDL level, mean creatinine level and UACR increased with increasing the stage of CKD while the mean HBA1C and HDL level decreased with increasing the stage of CKD.

Our results were supported by study of Shaheena et al., as they showed that patients with DFU had a high significant difference with respect to fasting blood glucose, 2 h postprandial blood glucose, HbA1c. [17] Similarly, Wolf et al. concluded that type 2 DM with diabetics' foot syndrome were significantly higher HbA1c and had a longer duration of diabetes compared with type 2 DM without diabetic's foot syndrome. [16]

In the study of Mrozikiewicz-Rakowska et al., the univariate logistic regression analysis showed that CKD risk factors were the following variables: mean creatinine level, mean body weight, mean hips circumference, ischemic heart disease, hypertension and diabetic retinopathy. each mg/dl more in creatinine serum level was increasing the risk of CKD development by 4.5%. The risk of CKD development was increased by 3.7% per each additional kg in body mass. There was also observed an increase in CKD development risk by 6.3% for each additional centimeter in hips circumference. Moreover, CKD risk was increased by the coexistence of ischemic heart disease, hypertension and diabetic retinopathy, over 2.7-fold, 7.3-fold and 4.4-fold, respectively. [20]

As regard the US changes in the kidneys within the cases in the different groups, the present study showed that all cases within group 1 had normal kidney on us examination, grade IV nephropathy was only present in group 5B and increased grade III nephropathy among group 4,5B,5A .

There is a statistically significant negative correlation between GFR with age, duration of DM, weight, waist circumference, BMI, DNS, TGs, creatinine and UACR. Also, there is statistically significant positive correlation between GFR with ABI, HBA1C and HDL. With multi-linear regression analysis, duration of DM and GFR reveal statistically significant prediction ability with ABI. With multi-linear regression analysis, duration of DM and HDL reveal statistically significant prediction ability with DNS.

In the study of Shaheena et al., reported that in a comparison of renal function and urine albumin/creatinine ratio of the study groups. there was a high significant increase in serum creatinine (2.3 ± 0.93 vs. 1.5 ± 0.73) and no significant difference in albumin/creatinine ratio in urine (235.5 ± 274.5 vs. 219.3 ± 112.3) in group 1 versus group 2, and a considerable decrease was seen in

eGFR in group 1 versus group 2 (40.3 ± 24.5 vs. 62.4 ± 23.4) (P < 0.001). [17]

In the study of Ninomiya T, et al., they found that the risk for each outcome increased linearly with lower eGFR levels. Every 10 fold increment in baseline UACR, which corresponds approximately to a change from one clinical stage of albuminuria to the next was associated with a 1.6-fold, two-fold, and 3.3-fold higher, multivariable-adjusted risk of cardiovascular events, cardiovascular death, and renal events, respectively. [21]

In Lepantalo, et al. study it was believed that the essential factor for DFU is a loss of renal function. Disturbance of glucose metabolism and production of glycogen is caused by damaging insulin binding to receptors that cause tissue-insulin resistance, particularly in skeletal muscles. [22]

In the study of Rani, et al. present highlighted that in patients with DFI there is a reduction in eGFR and when the infection subsides the eGFR improved, whereas in patients with preexisting CKD the decrease in eGFR was observed in all the follow-up periods. [18] Among patients with both CKD and DFI, fall in eGFR was similar to that of DFI patients, however the eGFR continues to fall and fails to improve after the DFI subsides.

Wolf, et al., demonstrated that compared to type 2 patients without DFS those with DFS were significantly older (P < 0.005), had a longer duration of diabetes (P < 0.005), higher serum creatinine levels (P < 0.005) and a lower eGFR (P < 0.005). Patients who smoked did not have DFS more frequently than non-smokers. There was a significant negative correlation between the Wagner stages and eGFR (r = −0.104, P < 0.01) as well as Armstrong stages and eGFR (r = −0.125, P < 0.01) in all patients with type 2 diabetes. Non smokers had a similar significant negative correlation between Armstrong and Wagner stages and eGFR. Not surprisingly, Wagner and Armstrong stages showed a highly significant positive correlation in patients with type 2 diabetes (r = 0.698, P = 0.01). Multivariate logistic regression analysis revealed a significant negative association between a 10 ml/min change in eGFR and DFS as well as diastolic blood pressure. [16]

Conclusion:

There was a strong association between the degree of renal impairment and DFS. diabetic patients in dialysis treatment had a high prevalence of DF, and most of them had one or more risk factors for developing an ulcer in the future.

Hypertension is the most common comorbidity of diabetes; insulin is the most common used anti diabetic medication followed by sulphonylurea.

The most common macrovascular complications are coronary artery disease and cerebrovascular stroke. Deterioration of eGFR with the longer duration of diabetes causing Diabetic neuropathy score (DNS) and Ankle brachial pressure index (ABI) to decrease with eGFR decrease.

Fungal infection and foot deformities high risk with increase stages of CKD.

Ultrasound abdomen was normal at early stages of CKD also HbA1c, HDL decrease in delayed stages of CKD.TGs, creatinine and UACR increase in delayed stages of CKD.

Recommendations:

Diabetic patients with CKD should be considered as a high-risk group for the development of DFS and should therefore be regularly screened for DFS during every office visit. Early lesions need consequent management, such as offloading, antibiotic therapy and local wound care.

Ongoing support from a designated podiatrist/chiropodist, an orthotist or shoemaker, and a diabetes or renal physician, depending on available personnel. Routine and systematic assessment for neuropathy, PAD, callus, foot deformity, bed sores, pre ulcerative lesions, ulcers and infection or gangrene in all patients, with the foot rendered completely bare (i.e., no socks or shoes).

Randomized clinical trials and the demonstration of a common mechanism that causes CKD and failure of the skin to heal are required.

References:

1- Baynes H. Classification, pathophysiology, diagnosis and management of diabetes mellitus. J diabetes metab, 2015; 6(5): 1-9.

2- **Surya S, Salam AD, Tomy DV, Carla B, Kumar RA, Sunil C.** Diabetes mellitus and medicinal plants-a review. Asian Pacific Journal of Tropical Disease, 2014; 4(5): 337-347.

3- **Levey AS, Inker LA, Coresh J.** Chronic kidney disease in older people. Jama, 2015; 314(6): 557-558.

4- **Lew SQ, Radhakrishnan J.** Chronic Kidney Disease and Gastrointestinal Disorders. Chronic Renal Disease, 2015; 298-309.

5- **Jha V, Garcia-Garcia G, Iseki K, Li Z, Naicker S, Plattner B, et al.** Chronic kidney disease: global dimension and perspectives. The Lancet, 2013; 382(9888): 260-272.

6- **Tesfaye S, Selvarajah D.** Advances in the epidemiology, pathogenesis and management of diabetic peripheral neuropathy. Diabetes/metabolism research and reviews, 2012;28: 8-14.

7- **Ibrahim A, Owolabi LF, Borodo MM, Ogunniyi A.** Clinical profile of diabetic sensorimotor polyneuropathy in a tertiary hospital in Northwestern Nigeria. Nigerian Journal of Basic and Clinical Sciences, 2015; 12(1): 13.

8- **Smith AG, Singleton JR.** Obesity and hyperlipidemia are risk factors for early diabetic neuropathy. Journal of Diabetes and its Complications. 2013; 27(5): 436-442.

9- **Kohlgruber A, Lynch L.** Adipose tissue inflammation in the pathogenesis of type 2 diabetes. Current diabetes reports. 2015; 15(11): 92.

10- **Bakker K, Apelqvist J, Lipsky B, Van Netten J, Schaper N, International Working Group on the Diabetic Foot (IWGDF).** The 2015 IWGDF guidance documents on prevention and management of foot problems in diabetes: development of an evidence-based global consensus. Diabetes/metabolism research and reviews. 2016;32: 2-6.

11- **Apelqvist J**, Epidemiology of diabetic foot disease and etiology of ulceration, in The diabetic foot. 2014, JP Medical, London. p. 3-9.

12- **Ndip A, Rutter MK, Vileikyte L, Vardhan A, Asari A, Jameel M, Tahir HA, Lavery LA, Boulton AJ.** Dialysis treatment is an independent risk factor for foot ulceration in patients with diabetes and stage 4 or 5 chronic kidney disease. Diabetes Care. 2010; 33(8):1811-1816.

13- **Treece KA, Macfarlane RM, Pound N, Game FL, Jeffcoate WJ.** Validation of a system of foot ulcer classification in diabetes mellitus. Diabet Med. 2004; 21:987–991.

14- **Dòria M, Rosado V, Pacheco LR, Hernández M, Betriu À, Valls J, Mauricio D.** Prevalence of diabetic foot disease in patients with diabetes mellitus under renal replacement therapy in Lleida, Spain. BioMed research international, 2016; 2016:7217586.

15- **He Y, Qian H, Xu L, et al.** Association between estimated glomerular filtration rate and outcomes in patients with diabetic foot ulcers: a 3-year follow-up study. Eur J Endocrinol. 2017;177(1):41-50.

16- **Wolf G, Müller N, Busch M, Eidner G, Kloos C, Hunger-Battefeld W, Müller UA.** Diabetic foot syndrome and renal function in type 1 and 2 diabetes mellitus show close association. Nephrology Dialysis Transplantation. 2009; 24(6): 1896-1901.

17- **Shaheena E, Goda F, Elshazly HM.** Renal function and diabetic foot ulcer. Journal of Medicine in Scientific Research. 2018; 1(3): 180-184.

18- **Rani A, Viswanathanv V.** Diabetic foot infection and worsening kidney function: implication for health care in the developing world. Int J Diabetol Vasc Dis Res, 2017; 5(5): 208-213.

19- **Shahbazian H, Yazdanpanah L, Latifi SM.** Risk assessment of patients with diabetes for foot ulcers according to risk classification consensus of International Working Group on Diabetic Foot (IWGDF). Pak J Med Sci. 2013; 29(3): 730-734.

20- **Mrozikiewicz-Rakowska B, Maroszek, P, Nehring P, Sobczyk-Kopciol A, Krzyzewska M, Kaszuba AM, Ploski R.** Genetic and environmental predictors of chronic kidney disease in patients with type 2 diabetes and diabetic foot ulcer : a pilot study. J Physiol Pharmacol. 2015; 66(5): 751-761.

21- **Ninomiya T, Perkovic V, de Galan BE, et al.** Albuminuria and kidney function independently predict cardiovascular and renal outcomes in diabetes. J Am Soc Nephrol. 2009; 20(8): 1813-1821.

22- **Lepantalo M, Fiengo L, Biancari F.** Peripheral arterial disease in diabetic patients with renal insufficiency: a review. Diabetes Metab Res Rev 2012; 28: 40–45.