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Research Article

Incidence of Renal Nephropathy after Kidney Transplantation in Patients with or without Pre-Transplant Type II Diabetes

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Abstract

Objectives: A remarkable improvement of impaired patient's kidney function is often observed after renal transplantation. long-term renal allograft survival is ensured on preserving improved kidney function. However, there are different risk factors; one of the major risk factor is diabetic nephropathy (DN). Therefore, the goal of the present study was to predict incidence of diabetic nephropathy after kidney transplantation within the first 8 months.

Methods: To investigate the incidence of diabetic nephropathy after renal transplantation in patients with or without type 2 diabetes, a retrospective analyzed study was performed on fifty-two renal transplant patients, 33 with type 2 diabetes pre-transplant and 19 non-diabetic, they underwent kidney transplantation in 2009 to 2019 in King Abdulaziz Medical City- National Guard and were evaluated consecutively for 8-month before incidence of nephropathy and up to 8 months' post-nephropathy. Time course of changes in kidney functions as, measurements of serum creatinine (Scr), blood urea nitrogen (BUN), microalbuminuria, were recorded before and after incidence of different nephropathy. Estimated glomerular filtration rate (eGFR) was also reported. In addition, age, anthropometric factors and causes of DN were analyzed.

Results: There were no significant difference in all investigated parameters 8 months before and 8 months after incidence of different types of nephropathy as (IgA, Diabetic, Glomerular and others) based on monthly assessment. However, the incidence of nephropathy in post-transplanted non-diabetic patients are associated with a remarkable higher level of serum creatinine, BUN and microalbuminuria and reduction in eGFR starting from first month as compared with non-diabetic without nephropathy. While a profound elevation of serum creatinine and BUN in month 2 and 5 respectively and significant lowering in GFR in month 6 were associated with the incidence of nephropathy in diabetic post-transplant kidney as compared with diabetic non-nephropathy post-transplant patients. Comparing incidence of nephropathy in post-transplant diabetic and non-diabetic patients, serum creatinine started to increase significantly from month 5 while others parameters were kept elevated but non-significant. However, all tested parameters were kept in normal ranges between post-transplant diabetic and non-diabetic patients without nephropathy.

Conclusion: In non-diabetic patients, a consistent significant elevation of serum creatinine, BUN and microalbuminuria and reduction in eGFR starting from first month were associated with incidence of nephropathy in post-transplanted kidney. While in diabetic patients a significant elevation of serum creatinine was noticed in month 2. The clinical use of eGFR and serum creatinine may aid in predicting incidence of early diabetic nephropathy.

Keywords: *Incidence of Renal Nephropathy; Kidney Transplantation; Pre-Transplant Type II Diabetes*

Introduction

Diabetes Mellitus is the main cause behind end stage renal disease [ESRD]. It has been reported that there were 120000 new cases of ESRD diagnosed in united State in 2016, diabetic nephropathy (DN) constitute about 44% of all new cases [1]. One of the main cause of graft loss is DN if it occurs after transplantation [2]. Patients with type II diabetes mellitus (DM) undergoing renal transplantation are at risk of diabetic nephropathy (DN) in the transplanted kidney.

The treatment of choice in end-stage renal disease (ESRD) patients is kidney transplantation (KT) [3]. After renal transplantation, the outcome has improved due to well-functioning transplanted kidney and the effective immunosuppressive agents [4,5]. Therefore, the outcome of renal transplant, an improvement on quality of life and survival for patients with ESRD due to diabetic nephropathy [6,7]. However, long-term survival post renal transplantation in diabetic patients is greatly lower than that in nondiabetics due to progression of atherosclerotic cardiovascular disease [7-9]. One of the major reasons for graft loss is recurrent diabetic nephropathy in a diabetic recipient [10]. It has reported that; recurrent diabetic nephropathy occurs most commonly in the second decade after transplantation [10]. Confirmed by the early changes in glomerular basement membranes because of protein trapping and widening the mesangial matrix, occur as early as 2 years after transplantation [11,12].

Microalbuminuria is clinically considered as a major index to judge the progression of DN [13]. However, it is still difficult to evaluate the severity of the DN disease or its prognosis based on proteinuria. As it is not as accurate as expected and not all diabetic patients who develop DN have elevated level of microalbuminuria [14]. For example, microalbuminuria may have occurred after 2 to 5 years of diagnosis of Type 1 diabetes who develops into DN within 10 to 15 years after diagnosis. While patients with type 2 diabetes without DN and already have microalbuminuria at the time of diagnosis. Therefore, the significance of pathological changes associated with DN should be more investigated in the clinical practice.

Thus, renal biopsy and morphological changes may offer important insights into the understanding of the complex course of diabetes and help to classify, diagnose, prognoses, and management of the disease. However, most of diabetic patients with kidney diseases are not biopsied. As most of diabetic glomerular changes in the early stage of diabetes are nonspecific. Moreover, the risk of bleeding during renal biopsy should be carefully considered in hypertensive, anemic patients [15].

Still there is a lack of information to guide us for understanding DN after kidney transplantation [16], in contrast to other diseases as focal segmental glomerular sclerosis (FSGS) and lupus nephritis [17,18]. Recent publication regarding DN in post-transplant patients are with paucity data, indicating that still, the true risk of developing post-transplantation DN is unknown, and post-transplantation DN is poorly characterized in the literature [19]. Therefore, it is of critical importance for improving post-transplant graft survivals, is to enhance understanding diabetic nephropathy in post-transplantation as an important area of investigation. We also interested to know the prevalence and incidence of DN in post-renal transplant Saudi patients with or without diabetes in pre-transplantation to provide valuable data for clinical decision-making. In this article, we demonstrated our experience about incidence of diabetic nephropathy in renal allografts with clinical and pathological correlations.

Methods

In our present retrospective study, we have included 52 Saudi patients transplant recipients in King Abdul-Aziz Medical City (KAMC), National Guard, aged 20 - 72 years. 33 patients had diabetes mellitus, 8 of them developed diabetic nephropathy (2 males and 6 females), while 25 patients did not develop diabetic nephropathy (14 males and 11 females). However, 19 non-diabetic patients, 7 of them developed nephropathy while the rest without diabetic nephropathy. This study was carried out by reviewing patients' medical record sheet of post renal transplant patients. The inclusion criteria were to be recipients of a single organ, with the graft functioning 12 months after

transplantation. The demographic data concerned recipients were age, gender, height, weight and body mass index and other variables follow-up for 8 months. We have collected the clinical and biochemical variables like serum glucose, glycosylated HB, BUN, Serum Creatinine and Albumin, furthermore, data of eGFR was also collected at every month for 8 months before incidence of nephropathy and 8-month post-incidence of nephropathy. While patients without nephropathy we have collected data of all variables 8 month before transplantation and 8 months after transplantation.

Medical record review was performed according to clinical data confidentiality protection. A blinded number (ID) was assigned to each patients in order to take into consideration confidentiality. The clinical data of the patients' BUN, Serum Creatinine, Albumin, and eGFR were collected from the patients' medical record for this study.

Statistical analysis

In the present study, we have analysed demographic and clinical factors, relevant to nephropathy and non-nephropathy.

In descriptive statistics

The continuous variables were listed mean and standard deviation, and dechotomous variables were presented numbers and pencentages.

In bi-variate analysis

To find association between Nephropathy and Non-Nephropathy were found by using Chi-Square test, the mean comparison between continuous variables and groups using independent samples t-test and those variables were under non-parametric were analyzed using Mann Whitney U test. All data were collected, managed and complied by MS Office 360 [Microsoft Ins Ltd., USA]. Data were analysed by SPSS 21.0 version [IBM SPSS Ltd., Chicago, IL, USA]. The statistical significance was fixed as p-value < 0.05.

Results

Of the 52 patients included in the study, 33 (63%) had diabetes before transplantation. All diabetic patients had type II diabetes. The characteristics of the diabetic patients are described in table 1.

Variables	DM with Nephropathy n (%)	DM with Non-Nephropathy n (%)	p-value
	8 (24.2%)	25 (75.8%)	**0.037**
Female	6 (75.0)	11 (44.0)	0.225^
Male	2 (25.0)	14 (56.0)	
Age (in years)	45.75 ± 21.62	57.88 ± 9.74	**0.037**
Body Weight (in Kgs.)	68.25 ± 18.67	75.00 ± 16.34	0.361

Table 1: *Demographic and clinical characteristics of diabetic renal transplant recipients developed nephropathy and non-developed nephropathy.*

Bolded p-value Significant p<0.05; ^Fisher's Exact test p – value (>0.05) Not Significant.

Within the diabetes group, 8 patients (24%) developed nephropathy after renal transplantation 6 patients are female and 2 are male, while 25 patients without nephropathy, 14 patients are male and 11 are female. Patients with pre-transplant diabetes and did not develop nephropathy were significantly older, received older donor kidneys, and had a higher body weight.

Monthly assessment of post-transplant diabetic with nephropathy as compared with diabetic patients without nephropathy demonstrated that there were a higher level of serum creatinine and urea reach significant differences only in month 2 and 5 respectively. While level of eGFR were lower in diabetic associated with nephropathy reach significant in month 6. In contrast and in unexpected manner a significantly increased level of proteinuria, in diabetic non-nephropathy patients in month 1 while higher level of proteinuria was reported in post-transplant diabetes associated with nephropathy and did not reach significant level (Figure 1 to 4).

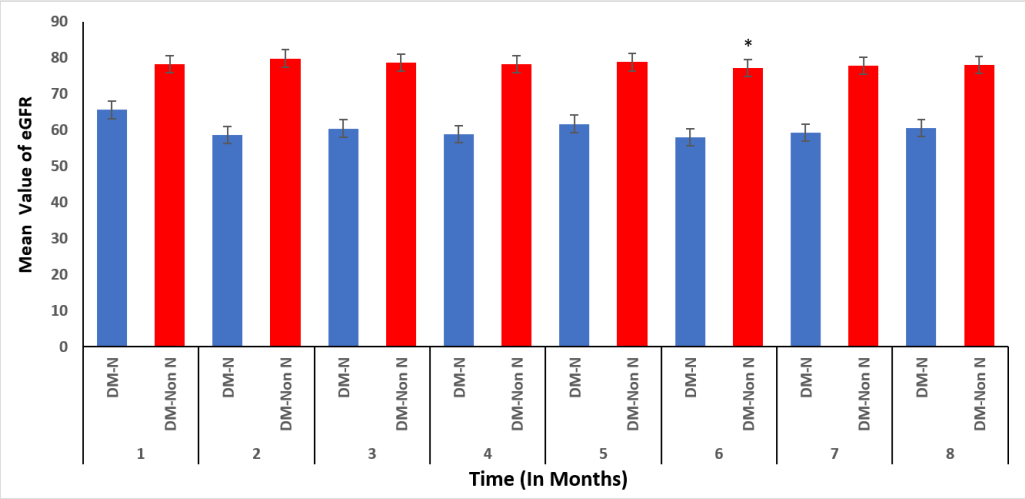


Figure 1: *Monthly assessment of post-transplant eGFR in diabetic renal transplant recipients developed nephropathy and non-developed nephropathy (n = 33).*

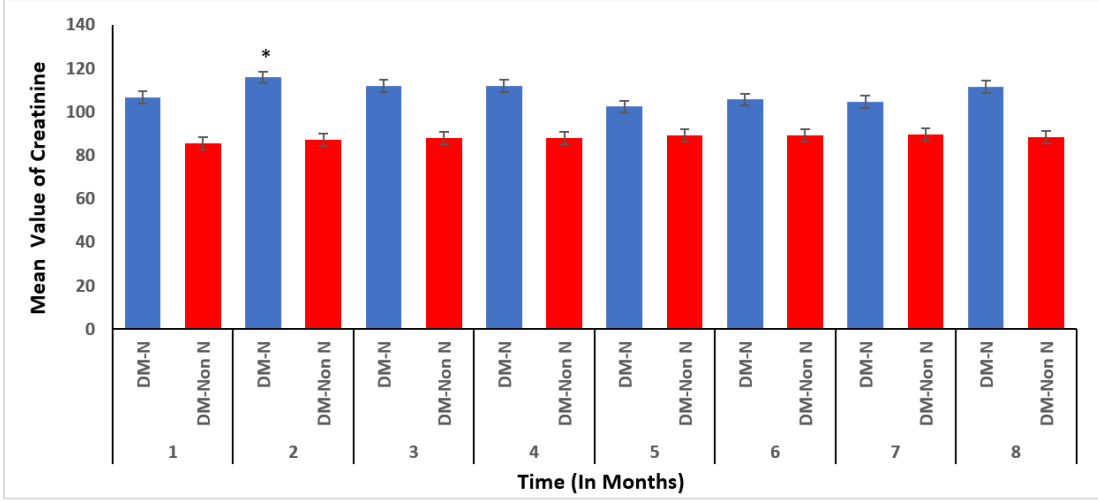


Figure 2: *Monthly assessment of post-transplant serum creatinine in diabetic renal transplant recipients developed nephropathy and non-developed nephropathy.*

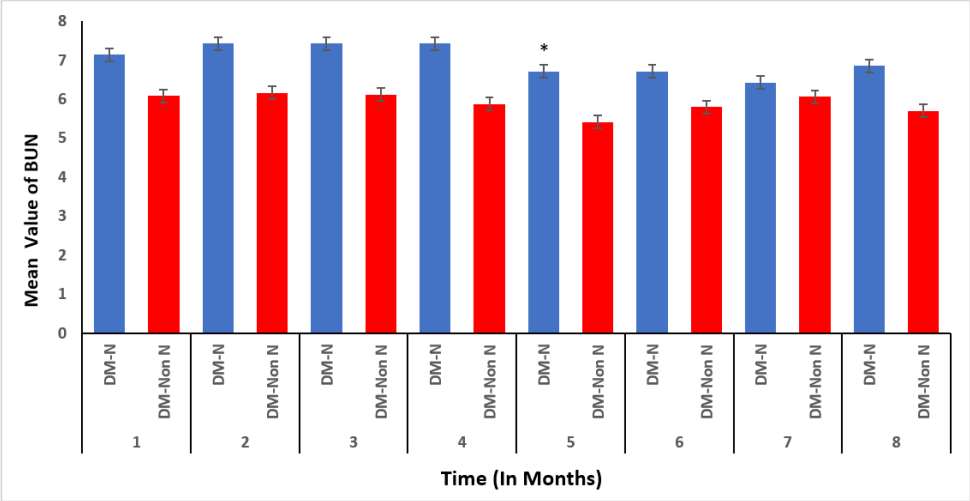


Figure 3: *Monthly assessment of post-transplant BUN in diabetic renal transplant recipients developed nephropathy and non-developed nephropathy.*

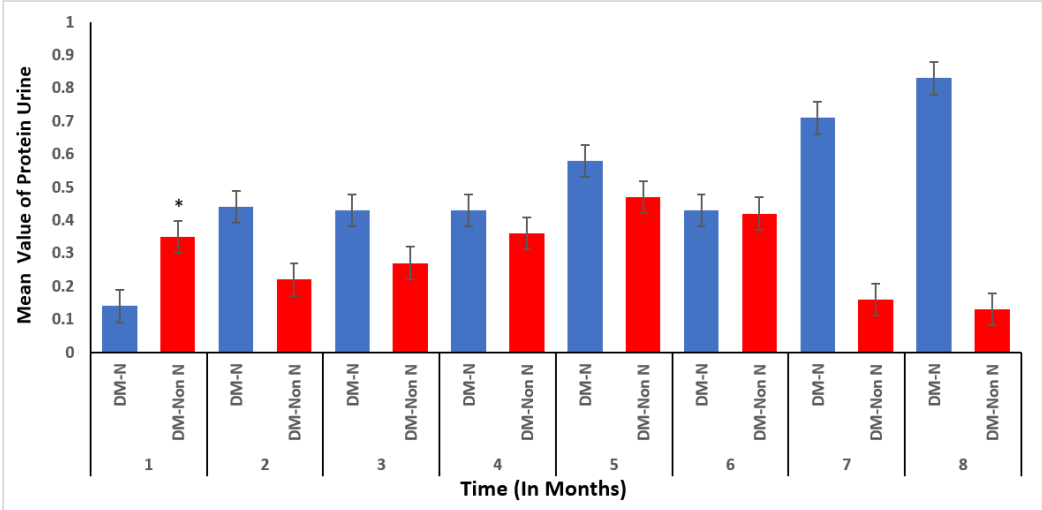


Figure 4: *Monthly assessment of post-transplant albuminuria in diabetic renal transplant recipients developed nephropathy and non-developed nephropathy.*

There are 19 non-diabetic patients, the characteristics of the non-diabetic patients are described in table 2. 7 patients (36.8%) developed nephropathy after renal transplantation 3 patients are female and 4 are male, while 12 patients without nephropathy, 9 patients are male and 3 are female.

Variables	Non-Developed Nephropathy n (%)	Developed Nephropathy n (%)	p-value
Non-DM	12 (63.2)	7 (36.8)	0.279
Female	3 (25.0)	3 (42.9)	0.617^
Male	9 (75.0)	4 (57.1)	
Age (in years)	37.68 ± 13.67 (20 - 71)		0.176*
Body Weight (in Kgs.)	76.58 ± 18.93 (50 - 120)		0.800*

Table 2: *Demographic and clinical characteristics of non-diabetic renal transplant recipients developed nephropathy and non-developed nephropathy.*

*^Fisher's Exact test p - value (> 0.05) Not Significant; *Mann Whitney U test p-value.*

Monthly assessment of kidney functions in post-transplant non-diabetic with nephropathy as compared with non-diabetic patients without nephropathy demonstrated that there were a significant higher level of serum creatinine and urea in all investigated 8 months. Moreover, level of eGFR were significantly lower in non-diabetic associated with nephropathy. In contrast a higher level of proteinuria was reported in post-transplant non-diabetic associated with nephropathy but did not reach significant level (Figure 5 to 8).

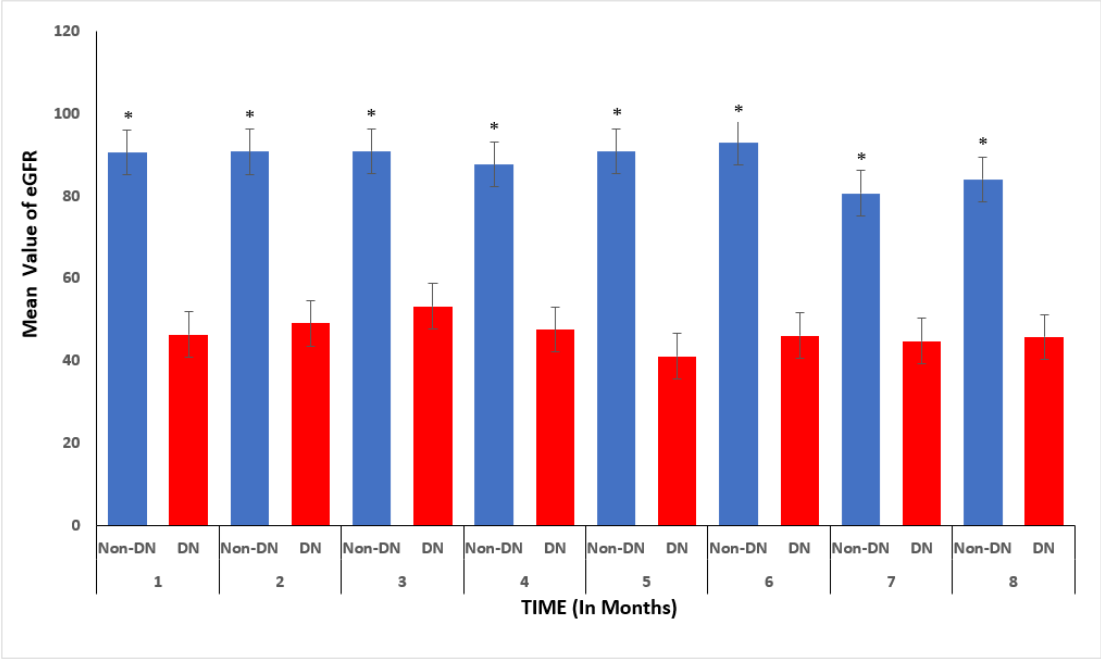


Figure 5: *Monthly assessment of post-transplant eGFR in non-diabetic renal transplant recipients developed nephropathy and non-developed nephropathy (N=19).*

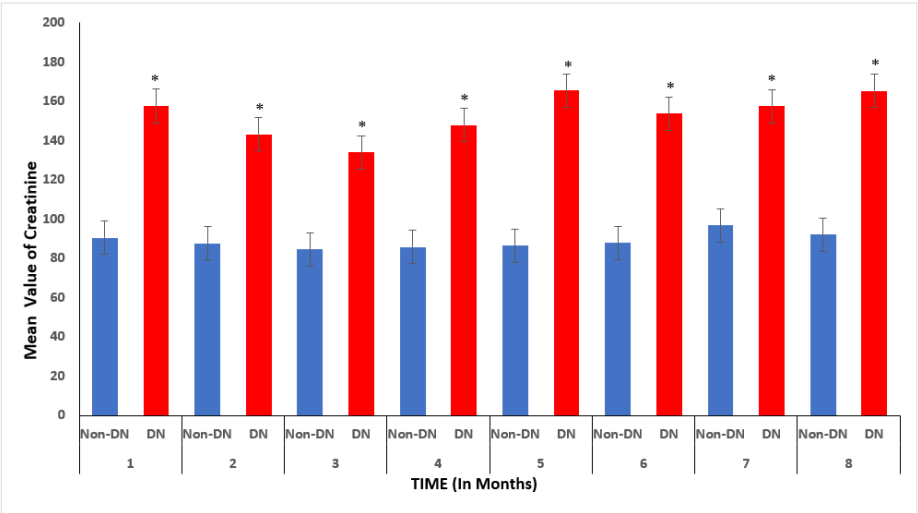


Figure 6: *Monthly assessment of post-transplant serum creatinine in non-diabetic renal transplant recipients developed nephropathy and non-developed nephropathy (N=19).*

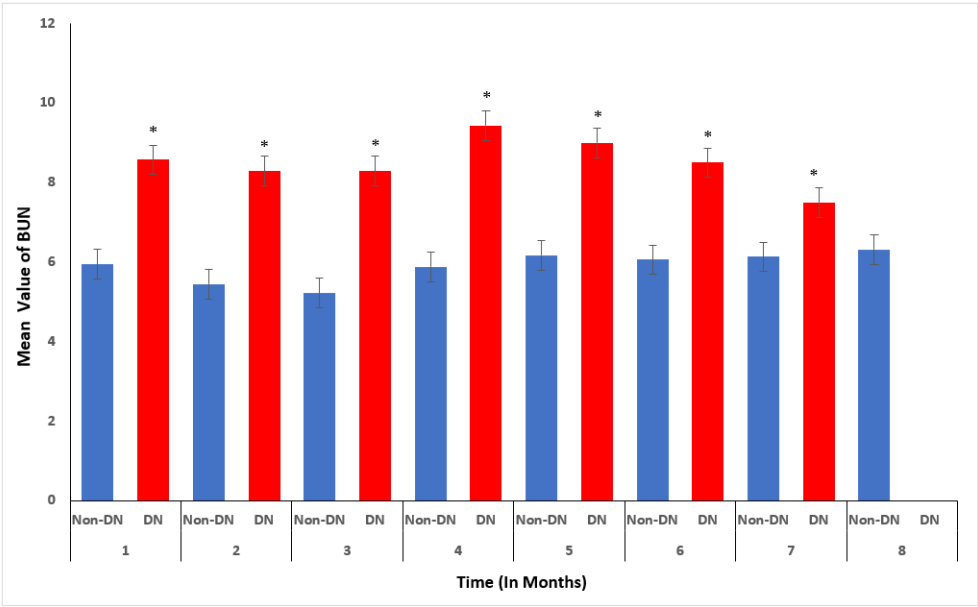


Figure 7: *Monthly assessment of post-transplant BUN in non- diabetic renal transplant recipients developed nephropathy and non-developed nephropathy (N=19).*

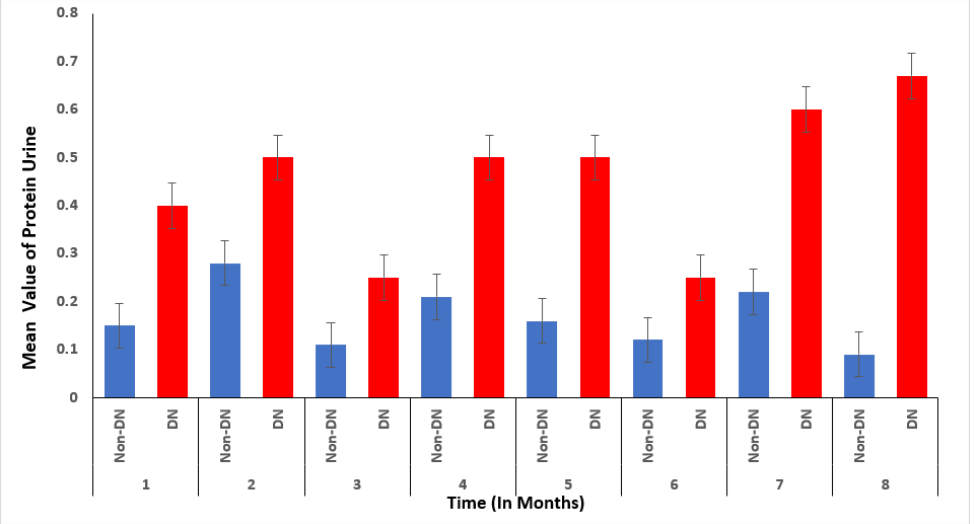
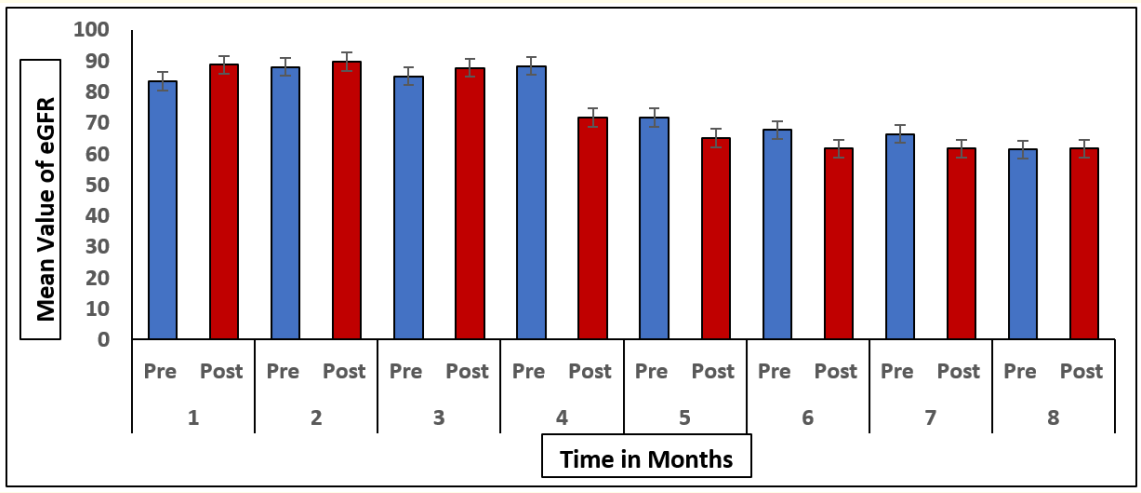


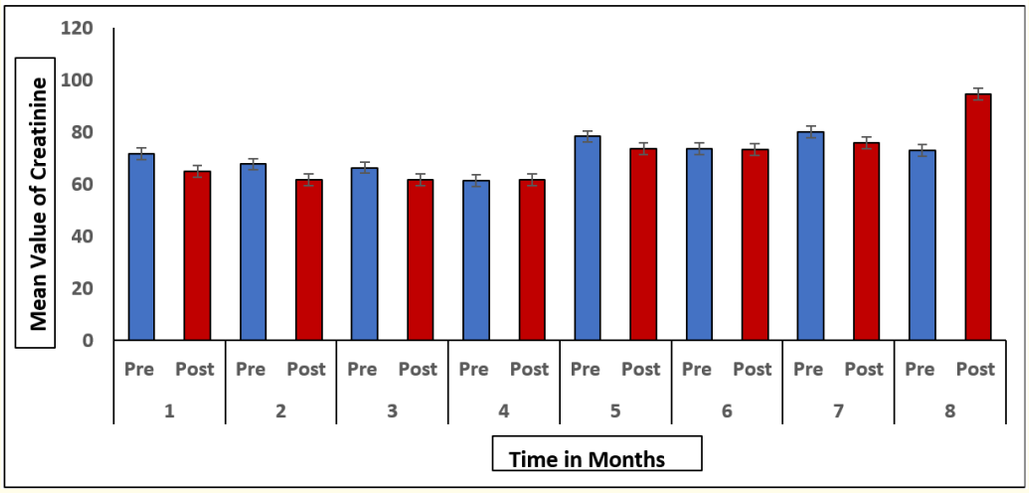
Figure 8: *Monthly assessment of post-transplant albuminuria in non-diabetic renal transplant recipients developed nephropathy and non-developed nephropathy (N=19).*

In an attempt to further, elaborate the effect of incidence of nephropathy on all investigated parameters. The comparison between mean values 8 month before and 8 months after nephropathy were studied. There are no significant difference between mean values of all investigated parameters before and after nephropathy (Figure 9: A,B,C,D,E).

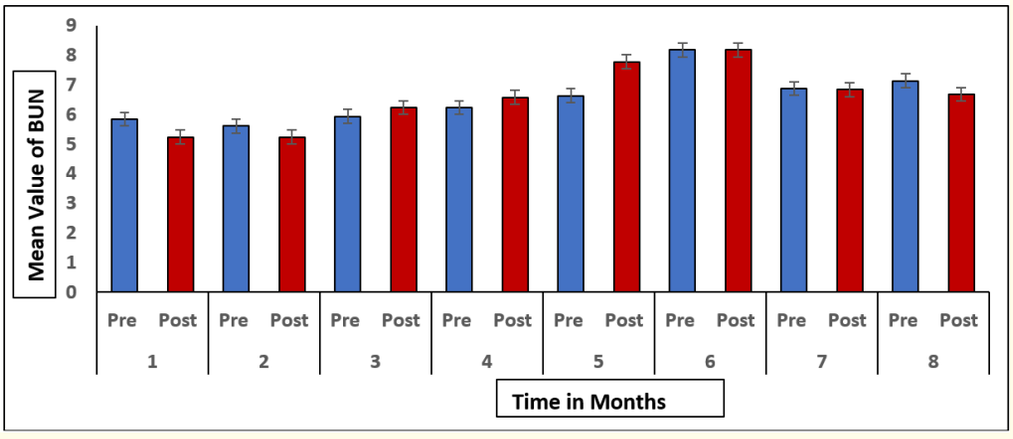
A



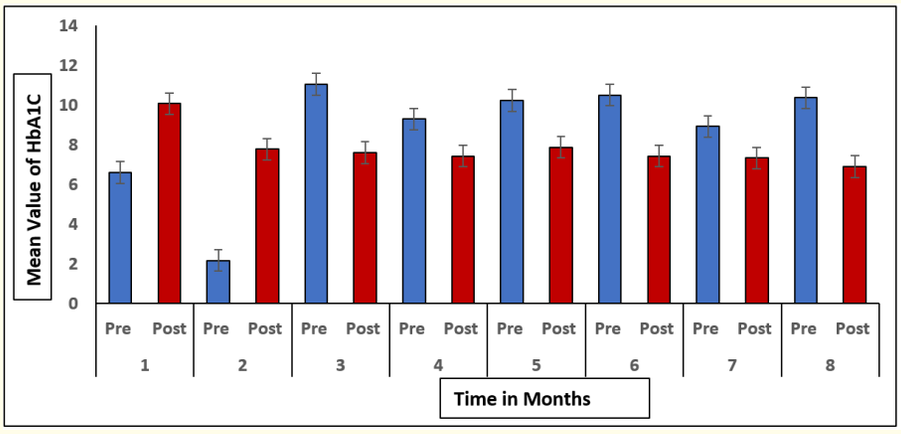
B


Mean Value of Creatinine
120
100
80
60
40
20
0
Pre Post Pre Post Pre Post Pre Post Pre Post Pre Post Pre Post Pre Post
1 2 3 4 5 6 7 8
Time in Months

C


Mean Value of BUN
9
8
7
6
5
4
3
2
1
0
Pre Post Pre Post Pre Post Pre Post Pre Post Pre Post Pre Post Pre Post
1 2 3 4 5 6 7 8
Time in Months

D


Mean Value of HbA1C
14
12
10
8
6
4
2
0
Pre Post Pre Post Pre Post Pre Post Pre Post Pre Post Pre Post Pre Post
1 2 3 4 5 6 7 8
Time in Months

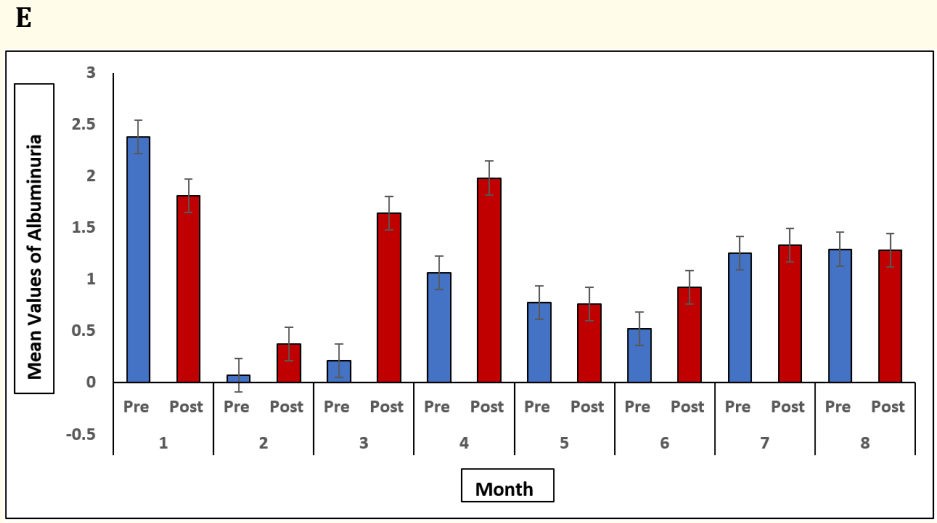


Figure 9: *Evolution of estimated GFR (eGFR), Creatinine, BUN, glycated hemoglobin and albuminuria over time before and after incidence of nephropathy after transplantation.*

Discussion

It has been reported that the prevalence of diabetes worldwide is expected to affect more than 350 million people by the year 2035 and has extended epidemic magnitudes. After 15 years of diabetic disease duration approximately one-third of diabetic patients showed microalbuminuria and less than half suffering from real nephropathy. So about 20% to 30% of all diabetics will develop evident nephropathy. However, a greater percentage of type 1 patients progress to ESKD.

The first choice treatment for patients of kidney failure is kidney transplantation [20,21]. The incidence of diabetic nephropathy has been reported in renal allografts in both patients with pre-transplant diabetes and in patients with new-onset diabetes after transplantation [22-27]. Majority of the studies were performed in patients with type 1 diabetes or were based on biopsies performed at the time of graft dysfunction in a selected group of patients, which obviates assessing the natural evolution of diabetic nephropathy.

Diabetic nephropathy is the main cause behind chronic kidney disease [28]. It is characterized by several functional changes such as structural changes as thickening of the glomerular basement membrane, mesangial matrix expansion, glomerular hyper-filtration, proteinuria and, glomerulosclerosis [29-31]. Because the few histological studies that were performed in native kidneys, still the kinetics of the structural changes associated with diabetic nephropathy in native kidneys are not well documented especially in patients with a variable duration of diabetes [23,33].

Until now the incidence of different nephropathy in post-transplant patients is unclear and not understood. In addition, the evidence is lacking about whether prevention of all risk factors pre-disposing to nephropathy especially intensive glycemic control can inhibit the risk of severe clinical renal outcomes, such as elevation of the serum creatinine level or end-stage kidney disease [34]. It has been reported that improved glycemic control has been shown to attenuate the occurrence of early diabetic nephropathy. However, since the risk factors of diabetic nephropathy after kidney transplantation remain unclear. Therefore, the present study investigated the post-transplant occurrence of diabetic nephropathy and the contribution of post-transplant glycemic control.

In our analysis study, 52 patients were undergoing kidney transplantation, 33 diabetic patients and 19 non diabetic patients. There were 8 diabetic patients and 7 non diabetic patients were developed nephropathy. This effect was noted already by 2 years after transplantation.

Sequential assessment of kidney function for 8 months before and after incidence of different types of nephropathy indicated that there was no significant difference between all investigated measured parameters before and after nephropathy in different types of nephropathy (data not shown). Our results confirm previous results showed that diabetic nephropathy developed despite good glycemic control [35]. In previous studies, it has been showed that diabetic nephropathy was observed within the first 2 years after transplantation [22,25, 36-38], but this phenomenon was associated with less-intensive glycemic control than was achieved in the current study. Glycated hemoglobin levels were kept unchanged after transplantation in our study in both types of patients with pre-transplant diabetes and in patients without diabetes, although the universal use of Calcineurin inhibitors and steroids and the occurrence of new-onset diabetes after transplantation. This results are in contrast with the data reported previously as there were immediately increased in glycated hemoglobin after transplantation [39]. Post-transplant glycated hemoglobin levels, however, did not predict the occurrence of elevation of microalbuminuria as reflected by mesangial matrix expansion in our study, whereas pre-transplant diabetes status remained associated, even after adjustment for other demographic factors like BMI, age, and sex. This is in contrast with an older study where better glycemic control was associated with a lower risk of mesangial matrix expansion in renal allografts [24].

The results of the present study do not necessarily correspond to current clinical practice which implicate the use of advent of novel glucose-lowering agents and new insulin analogs. Our cohort showed average post-transplant glycated hemoglobin levels of 7% (53 mmol/mol) in patients with pre-transplant diabetes compared with 12% (108 mmol/mol) in the previous study [24]. The better glycemic control in our patients thus might partially explain why no cumulative effect of glycated hemoglobin levels after transplantation was found. In addition, most patients included in our study had type 2 diabetes, which is an important difference with the earlier study that was restricted to patients with type 1 diabetes.

The finding that diabetic nephropathy occurs independently of glycated hemoglobin levels could be explained by effects of diabetes on mesangial matrix expansion induced by contribution of various changes associated with oxidative stress, hemodynamics, inflammation, advanced glycation end product formation [40-42]. This is explained by experimental studies using glucose-sodium transporter blockade with SGLT2 inhibitors prevented incidence of diabetic nephropathy [43,44], also independently of its glucose-lowering effect [45,46]. Whether more systematic use of drugs like SGLT2 inhibitors in the post-transplant setting would be able to lower the risk of rapid-onset diabetic nephropathy needs further study. In addition, clinical trials of GLP-1 agonists, a novel therapeutics targeting both podocyte histone modification and apoptosis in preclinical trials have shown promising nephron-protective effects in diabetic kidney disease [47].

Furthermore, the investigation of the effect of different types of nephropathy on kidney functions parameters, we evaluated the effect of nephropathy on graft function and proteinuria in diabetic nephropathy patients and compared the investigated parameters with diabetic non nephropathy patients. The early effect of diabetic nephropathy detected during follow-up time is the elevation of both serum creatinine and BUN reaching significant level at month 2 and 5 respectively. While GFR is decline reaching significant level at month 6. However, level of proteinuria was significantly elevated only in first month, in an unexpected manner. However, it was elevated but did not reach significant level during all follow up time. It remains difficult to explain clinically the elevation of proteinuria during first month only in diabetic nephropathy patients. The only explanation is that the follow up time in our study may be too short to detect these functional changes. In addition, other factors such as drugs as Calcineurin inhibitors, and ACE inhibitors and angiotensin receptor blockers used might abort changes in transplant recipients. Therefore, the association between pre-transplant diabetes and proteinuria was significant early after transplantation but disappeared over time. Although our data cannot prove causality, this time dependency of the association suggest that proteinuria is not the reflection of progressive diabetic nephropathy in the transplanted kidney. This finding

could be explained by early proteinuria originating from the native kidneys in patients with pre-transplant diabetes may be indicator of loss of residual native kidney function over time after transplantation.

Our results are in agreement with previous studies showed that diabetic nephropathy were occurred by hemodynamic factors, especially glomerular hyper-filtration as a results of elevated intra-glomerular pressure resulting in glomerular injury, followed by progressive decline of GFR and microalbuminuria [48-54].

In terms of renal function in non-diabetic patients with or without nephropathy, our present study demonstrated that the follow-up of serum creatinine, and BUN were significantly higher in non-diabetic patients with nephropathy while GFR was significantly lower. Since the impact of nephropathy on renal outcomes in non- diabetic patients has not been well established. In a study [55] that compared the rate of renal decline in diabetic and nondiabetic patients with chronic kidney disease (GFR, 50 ml/min), when controlling for albuminuria, the mean slope of renal decline was similar in patients with and without diabetes. Higher albuminuria was a predictor of poorer renal outcome, regardless of diabetes condition. The renal outcome in patients with DM varied, and may depended on the specific type of normal renal lesion.

The limited information or the small number of each subtype in the present studies did not permit further subgroup analyses. Moreover, most of patients in this study were treated with immunosuppressive agents, which likely had a positive effect on the renal outcomes. Thus, more prospective studies focusing on the renal outcome in patients with DN are needed.

Conclusion

In non-diabetic patients, a consistent significant elevation of serum creatinine, BUN and microalbuminuria and reduction in eGFR starting from first month were associated with incidence of nephropathy in post-transplanted kidney. While in diabetic patients a significant elevation of serum creatinine was noticed in month 2.

Declaration of Conflicting Interest

The authors declare that there are no conflicts of interest.

Funding

This research received no specific grant from any funding agency in the public, commercial or not for- profit sectors.

Data Availability

The data that support the findings of this study are available from the King Abdul-Aziz Medical City (KAMC), National Guard, but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Medical record review was performed according to clinical data confidentiality protection. A blinded number (ID) was assigned to each patients in order to take into consideration confidentiality. Data are however available for the authors upon reasonable request and with permission.

Consent

Written informed consent was obtained from all patient for publication. Medical record review was performed according to clinical data confidentiality protection. A blinded number (ID) was assigned to each patients in order to take into consideration confidentiality.

Ethical Approval

As per international standard or university standard written ethical approval has been collected and preserved by the author(s).

Competing Interests

Authors have declared that no competing interests exist.

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