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DIABETIC NEPHROPATHY PATIENTS REFERRED TO A TERTIARY NEPHROLOGY CLINIC: THE NEED FOR IMPROVED CARE PATHWAYS

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Introduction

The prevalence of diabetes in Albania has increased rapidly in recent years (1) and is likely to continue to increase in the future, with important implications for health policy. According to the International Diabetes Federation (2), in 2012 there were about 65,000 cases of diabetes in Albania (approximately 2.3% of the population). In local and limited studies, the prevalence was found to be significantly higher than this (6.3% in Tirana and 4.2% in southwest Albania) (3). The difference in prevalence observed between rural and urban areas may reflect differences in lifestyle and nutrition.

The studies have shown that on average, 20–40% of patients with diabetes will develop renal dysfunction (4). Our local data revealed that 7.5% of patients undergoing dialysis in Albania have diabetic nephropathy as a cause of renal failure. The expanding numbers of diabetic patients on renal replacement therapy it is associated with increase in health care expenditure and reinforces the need to better treat diabetic patients in order to prevent or delay the progression of kidney disease. Diabetic nephropathy is also a significant complication that primarily accounts for the increase in morbidity and mortality seen in patients with diabetes (5,6). A number of clinical trials have demonstrated that the intensified glucose control and the use of ACE inhibitors or angiotensin receptor blockers to treat hypertension may reduce progression of renal disease (7,8). Although, despite well management of diabetes, a large number of diabetic patients will develop advanced chronic kidney disease.

Actually, there are no reliable data on renal impairment in diabetics in Albania. Unfortunately, most of diabetic patients are still very late referred to the nephrologists. Patients with moderate established diabetic nephropathy often should often attend hospital clinics for both diabetic and renal care, which increase an unnecessary burden on patients with co-morbidities. It is alarming though that a survey of eight units providing renal replacement therapy in Albania indicates that there is an increase of the diabetic patients on haemodialysis treatment.

In this regard, the primary aim of the present study was to assess the prevalence and stages of nephropathy in diabetic patients referred to the nephrology clinic in UHC Tirana based on the values of proteinuria and glomerular filtration rate. In addition, we wanted to determine if patients are receiving treatment to prevent diabetic kidney disease according to international guidelines. This could enable us to establish a better solution for diabetic patients focusing on new care pathways to achieve therapeutic targets and to ensure a smooth referral to nephrologists of diabetic patients.

Methods

This is a single center study of patients with diabetic kidney disease attending nephrology clinic from September 2011 to December 2012. We excluded diabetic patients with acute infections, hematuria, pronounced hyperglycemia, heart failure and pregnant women. Information obtained from medical records included data on their gender, age, height and weight to calculate body mass index, duration of diabetes, history of hypertension and drugs used, history of smoking, and laboratory data. Patients were defined as hypertensive if they were undergoing treatment with antihypertensive drugs or if their untreated systolic blood pressure was >130 mm Hg and/or diastolic blood pressure >85 mm Hg. Antihypertensive drugs were recorded for each patient. Normal waist circumference was defined as <102 cm for males or <88 cm for females. Glycemic control was considered as good in patients with HbA1c< 7 and poor in patients with HbA1c e" 7.1. Patients were classified as normoprotenuric if they had negative proteinuria over the entire 24 hours, microproteinuric if their protein concentration

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was found in the range of 150–499 mg/day in the presence of diabetic retinopathy. Patients with proteinuria >500 mg/day were classified as macroproteinuric or with overt nephropathy. MDRD formula was used to estimate the glomerular filtration rate (GFR) and then the stage of chronic kidney disease (CKD) was estimated according to NKF-KDOQI classification system. Data analysis was conducted using the Statistical Package for Social Sciences (SPSS) for Windows version 19. The chi-square test was used for categorical variables and Student T test was used to analyze continuous variables.

Results

A total of 98 diabetic patients (57.2% males and 42.8% females) were included in this study. Their mean age was 60.4 ± 15.8 years. The mean duration of diabetes was 8.2 ± 6.9 years. The baseline characteristics of patients are shown in table1. Of the 98 subjects, 11 (11.2%) were found to have diabetes at their first visit to their health care provider and 5 of them had proteinuria at the time of diagnosis. Among study subject, 92 (90.7%) had type 2 diabetes. We found that only a few patients, 24.3% had a blood pressure of <130/80 mmHg. The number of antihypertensive drugs required to control blood pressure are shown in figure 1. Patients with advanced CKD received more drugs. Hence, the CKD stage 2 and 3 patients received at least two anti-hypertensive drugs, compared to CKD patient of stage 4 and 5. We noted that in our group of diabetics, 15 patients (15.3%) on stage 4 of CKD were not taking either an ACE inhibitor or angiotensin receptor blocker. Mean body mass index (BMI) in type 2 patients was 26.45±0.17kg/m2 (male: 25.14±0.8 kg/m^2 and female: 28.29±0.35 kg/m^2). At the time of presentation in the clinic, glycated hemoglobin (HbA1c) was 8.1±1.9% and fasting blood glucose of 190.5±38.6 mg/dl. We found that HbA1c concentrations and fasting plasma glucose levels were significantly higher in diabetics with macroproteinuria than in normoproteinuric patients ($p < 0.001$). The prevalence of macroproteinuria, microproteinuria and normoproteinuria were 56.4%, 33.8% and 9.8 %, respectively. The prevalence of macroproteinuria was 40.5% in males and 41.1% in females. There was no significant difference between males and females in the prevalence of macroproteinuria or microproteinuria (p>0.005). The serum creatinine concentration was used to evaluate the renal function. MDRD formula was then calculated and the patients were grouped into CKD stages. As presented in figure 2, we found that 3.3% had CKD stage 1, 5.2% had CKD stage 2, 22.7% had CKD stage3, 26.3% and 42.5% had CKD stage 4 and 5 respectively. The duration of diabetes was higher in both macroproteinuria and microproteinuria groups compared with the groups with no proteinuria. We found that serum cholesterol levels were significantly higher in the patients with macroproteinuria compared with normoproteinuric group. Serum triglycerides levels were not significantly different in the three groups of proteinuria.

The prevalence of proteinuria increased with the duration of diabetes. Taking d"5 years as the reference value, odds ratios (ORs) for durations of 6–10, 11–15, 16–20 and >20 years were calculated. The OR for microproteinuria became statistically significantly increased 16 years after the diagnosis of type 2 diabetes, by which time 48.2% of patients had microproteinuria.

Discussion

Recent figures released by the International Diabetes Federation confirm the enormity of the diabetes epidemic and indicate that the number of patients with renal failure due to diabetes will continue to increase dramatically. As in other developing countries, the prevalence of diabetes in Albania has increased rapidly (1). The prevalence of type 2 diabetes in south-western rural areas of Albania was found to be 4.17% (3). The difference in prevalence observed between rural and urban areas may reflect differences in lifestyle and nutrition. Although many clinical practice guidelines are avai-lable and intend to enhance the standards of medical dare in diabetes (9, 10), yet DN patients are frequently referred late in our clinics.

The Diabetes Control and Complications Trial Research Group (11) and UK Prospective Diabetes Group (12) studies have shown the impact of blood glucose control on reducing risk of retinopathy and nephropathy. In the present study we found that at the time of presentation in the clinic, glycated hemoglobin (HbA1c) was 8.1±1.9%, hence the majority of patients had uncontrolled diabetes. This emphasises the need for good control of diabetes in our study population in order to prevent diabetic nephropathy.

A lot of studies have demonstrated a strong association between microalbuminuria and risk factors for cardiovascular diseases (13,14). A meta-analysis of 11 longitudinal studies has shown a significant increase in cardiovascular and total

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mortality in subjects with type 2 diabetes who had microalbuminuria (15). Renal involvement in diabetes has been identified as a step wise process and microalbuminuria as an early indicator of diabetic nephropathy. Four methods exist for screening microalbuminuria: measurement of albumin to creatinine ratio in random spot collection or timed collection (four hour or overnight), protein in 24 hour urine collection and measurement of microalbuminuria by using dip stick. As standard assays to measure the microalbuminuria are not generally available in biochemical laboratories in Albania, we used 24 hour urine collection for protein. We found that 90.2% of diabetic patients had proteinuria. This could be explained by the fact that the study was limited to inpatients which undoubtedly may introduce a bias because more severely ill patients presented in the clinic were included in the study.

Middleton showed that the sensitivity of abnormal serum creatinine levels in identifying eGFR <60 ml/ min/1.73 m^2 was 45.3%, of albuminuria was 51.2% and either of an abnormal serum creatinine or albuminuria was 82.4% (16). Therefore the use of creatinine alone will miss a significant number of patients with early nephropathy. According to CKD classification we found that 3.3% of patients had CKD stage 1, 5.2% had CKD stage 2, 22.7% had CKD stage3, 26.3% and 42.5% had CKD stage 4 and 5 respectively. Clearly, the most common stage of DN as per eGFR was stage 4 and 5 reflecting the fact that most critically ill patients were hospitalized and in some cases reflected the late referral to the specialist.

Patients with diabetic nephropathy are at increased risk for cardiovascular diseases. Therefore, the attention to cardiac risk factor is an important part of their medical care. In this study, we found that only a limited part of patients, 24.3% met the recommended value for blood pressure. drugs was necessary for patients in advanced stages. This study highlights the need for better blood pressure control in this high risk group of patients. This can control and delay the progression of renal disease. We noted that except for patients CKD stage 5, they all received an ACE inhibitor or ARB. KDOQI Clinical Practice Guideline for Diabetes and CKD did not recommend the use of a combination of ACE inhibitors and ARBs as a dual blockade of the RAS (17). Clinical trials have shown an increase in adverse events, particularly impaired kidney function and hyperkalemia compared to the use of other agents (18,19).

Given the high cardiovascular risk, diabetic patients with established kidney disease should require further monitoring and management. We noted that these patients were not routinely attending a nephrologist and as a result they did not have annual measurement of calcium, phosphor, vitamin D levels or an annual renal ultrasound scan. Also, we found that the percentage of patients with either type of proteinuria was higher in our patients and this may reflect increased prevalence of diabetic nephropathy as a result of the absence of regular screening methods for early diabetic nephropathy. As noted before in this study, the test for microalbuminuria is not used in every day clinical practice and this may underestimate the complications of diabetes in relation to the renal system in our population.

This study is affected by some limitations. The inpatients are not truly representative of the general population, the small number of the studied patients, and the need for confirmation of albuminuria according to the guidelines are the main limiting factors in this study.

Conclusions

Diabetic kidney disease, especially related to type 2 diabetes, has become the most important cause of ESRD worldwide. Duration of diabetes, poor control of glycemia and hypertension, have been associated with progression of CKD. Therefore, early screening for incipient diabetic nephropathy and aggressive management of risk factors can prevent the kidney disease progression in patients with diabetes mellitus. In this context, it is important to understand the epidemiological aspects of diabetic nephropathy in our population in order to increase the opportunities for early interventions with effective treatments. The results of this study emphasis the fact that early diagnoses of diabetic nephropathy is missed due to the lack of screening methods which further enhances the burden on the health care system.

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Table 1. Characteristics of the study patients

	Mean ± SD
Total number	98
Gender (M:F)	56 : 42
Age (years)	60.4 ± 15.8
HbA1c* (%)	8.1 ± 1.9
BMI (male)	25.14 ± 0.8
Cholesterol (mg/dl)	260 ± 21.3
Triglyceride (mg/dl)	175 ± 15.9
Fasting plasma glucose	190.5 ± 38.6
Duration of diabetes (years)	8.2 ± 6.9
Blood pressure < 130/70 mmHg (%)	24.3

*HbA1c, glycosylated hemoglobin.

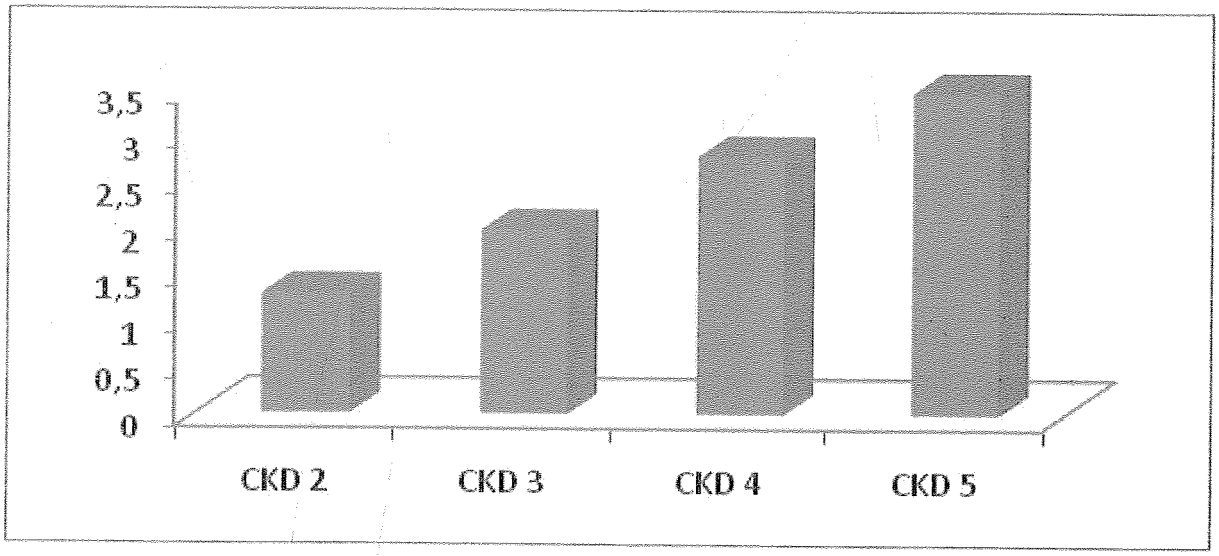

Figure nr. 1. The use of antihypertensive drugs in the study patients according to CKD stages

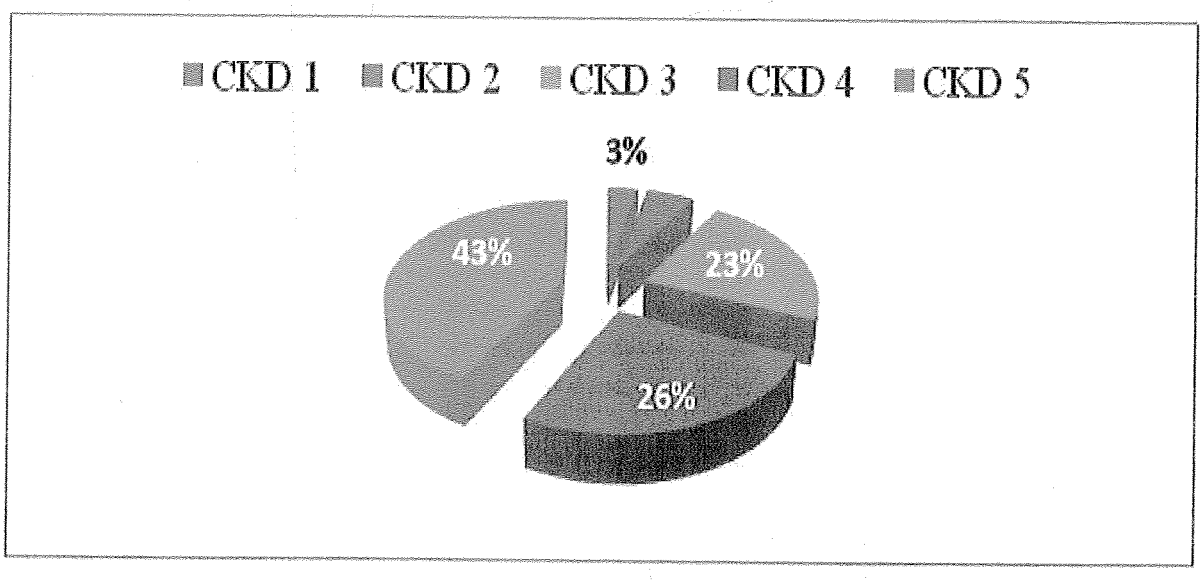

Figure nr. 2. Distribution of the diabetic patients according to CKD stages