Original Article / Orijinal Araştırma

Although Diabetes is Not Obvious, its Complications May Be Obvious, Frequency of Nephropathy in Prediabetic Patients

Diyabet Aşikar Olmasa da Komplikasyonları Aşikar Olabilir, Prediyabet Hastalarında Nefropatinin Sıklığı

İdris Baydar, Ahmet Veli Şanibaş, Doğan Nasır Binici

University of Health Sciences, Erzurum Regional Training and Research Hospital, Department of Internal Medicine, Erzurum, Turkey

Abstract

Aim: Prediabetes is considered a risk factor for diabetes mellitus (DM) and cardiovascular diseases. Complications are also detected during diagnosis in 10-40% of diabetes patients. Diabetic nephropathy is one of the critical microvascular complications of diabetes. Studies have shown that prediabetes is associated with the development of glomerular hyperfiltration and albuminuria, as in the early stages of diabetes. Identifying patients before overt DM occurs is important for early diagnosis and treatment of nephropathy and DM. The aim of our study is to investigate the presence and frequency of nephropathy in prediabetes patients.

Material and Method: Patients who applied to the outpatient internal medicine and endocrinology outpatient clinics and whose random fasting blood sugar was ≥100 mg/dl were evaluated. Oral glucose tolerance test (OGTT) was performed and HbA1C values were measured. 280 patients diagnosed with prediabetes and evaluated for nephropathy were included in the study.

Results: Nephropathy was detected in 81 (28.9%) of the patients. The average HbA1C value of the group with nephropathy was 6.28% (sd: 0.52) and the average HbA1C value of the group without nephropathy was 6.05% (sd: 0.29). The average HbA1C value was found to be significantly higher in the group with nephropathy (p=0.000).

Conclusion: The fact that nephropathy was detected in 28.9% of the patients showed once again the seriousness of prediabetes. Therefore, patients with prediabetes, especially those with higher HbA1C values, need to be evaluated more carefully in terms of nephropathy and CKD.

Keywords: Diabetes, prediabetes, nephropathy

Öz

Amaç: Prediyabet, diabetes mellitus (DM) ve kardiyovasküler hastalıklar için bir risk faktörü kabul edilmektedir. Tip 2 DM tanısı konduğu anda hastaların %10-40'ında komplikasyonlar vardır. Diyabetik nefropati diyabetin önemli mikrovasküler komplikasyonlarından biridir. Yapılan çalışmalar prediyabetin de diyabetin erken dönemlerinde olduğu gibi, glomerüler hiperfiltrasyon ve albüminüri gelişimi ile ilişkili olduğunu göstermiştir. Aşikar DM ortaya çıkmadan önce hastaların tespit edilmesi nefropatinin ve DM'ün erken tanı ve tedavisi için önemlidir. Çalışmamızın amacı prediyabet hastalarında nefropatinin varlığını ve sıklığını araştırmaktır.

Gereç ve Yöntem: Ayaktan İç Hastalıkları ve Endokrinoloji Polikliniğine başvuran, rastgele bakılan açlık kan şekeri ≥100 mg/dl olan hastalar değerlendirmeye alındı. Oral glukoz tolerans testi (OGTT) yapıldı ve HbA1C değerleri ölçüldü. Çalışmaya prediyabet tanısı konulan ve nefropati değerlendirmesi yapılan 280 hasta dahil edildi.

Bulgular: Hastaların 81'sinde (%28,9) nefropati saptandı. Nefropatisi olan grubun ortalama HbA1C değeri %6,28 (ss:0,52) nefropatisi olmayan grubun ortalama HbA1C değeri %6,05 (ss:0,29) düzeyinde saptandı. Nefropatisi olan grupta ortalama HbA1C değerinin anlamlı olarak daha yüksek olduğu görüldü (p=0,000).

Sonuç: Hastaların %28,9'unda nefropati saptanmış olması prediyabetin ciddiyetini bir kez daha göstermiş oldu. Bundan dolayı prediyabeti olan, özellikle de HbA1C değeri yüksek olan hastalarda nefropati ve KBY açısından daha dikkatli olunmalıdır.

Anahtar Kelimeler: Diyabet, prediyabet, nefropati

INTRODUCTION

Diabetes Mellitus (DM) is one of the most common and important diseases all over the world. It constitutes one of the top five causes of death.[1] The number of prediabetic people predicted by the International Diabetes Federation (IDF) in 2035 is 473 million, and the number of patients diagnosed with DM in 2030 is 438 million.[2]

In order to solve Type 2 DM and its complications, extensive research is being carried out all over the world for early diagnosis, treatment and prevention of complications, and different criteria and treatment methods are emerging. It is essential to recognize patients and take early precautions, especially in the prediabetes period before overt Type 2 DM. If precautions are taken in the early period, the emergence of Type 2 DM and its complications can be prevented.

One of the most critical microvascular complications of diabetes is diabetic nephropathy and is the most common cause of end-stage renal failure.[2-4] According to the data of the Turkish Nephrology Association, the most common cause in end-stage renal failure patients receiving dialysis treatment was DM, with a rate of 39%.[5] Microalbuminuria has also been found to be associated with cardiovascular diseases.[1]

Since Type 2 DM often develops silently and insidiously, diabetic nephropathy can be detected at the time of diagnosis. In Type 2 DM, if nephropathy is detected at the time of diagnosis or even during the prediabetes period, the chance of preventing nephropathy will be higher.[3]

Diabetic nephropathy is diagnosed based on the albumin/creatinine ratio measured in the first morning urine.[4] In patients with high albumin/creatinine ratio (>30 mg/g), 2 more repeated measurements are performed at 3-month intervals. As a result of these measurements, if the low glomerular filtration rate (GFR) or the high albumin/creatinine level continues or if albuminuria is detected in 2 out of 3 measurements and if no other reason is found to explain the situation, the patient is considered to have diabetic nephropathy.[3]

Prediabetes is a term used for impaired glucose tolerance (IGT) and impaired fasting glucose (IFG), and both conditions are considered risk factors for DM and cardiovascular diseases.[3] Once type 2 diabetes is diagnosed, 10-40% of patients have complications.[6] Studies have shown that prediabetes is associated with the development of glomerular hyperfiltration and albuminuria, as in the early stages of diabetes.[7] Since patients are generally asymptomatic, it is difficult to catch the disease during prediabetes.

In this study, we aimed to investigate the presence and frequency of nephropathy in patients with prediabetes. Additionally, the relationship of nephropathy with HbA1C value and other variables was analyzed.

MATERIAL AND METHOD

An application was made to the Health Sciences University Erzurum Regional Training and Research Hospital Clinical Research Ethics Committee for the study. As a result of the application, approval was received on 19.03.2018 and with decision number KAEK 2018/06-40.

Patients who were admitted to the Endocrinology and Metabolic Diseases Polyclinic and Internal Medicine Polyclinic at Erzurum Regional Training and Research Hospital as outpatients and whose fasting plasma glucose was found to be between 100-125 mg/dl were included in the study. Afterwards, a 75-g OGTT test was performed. Height, weight, waist circumference, and body mass index (BMI) measurements of the patients were taken. Blood LDL-C (low density cholesterol), HDL-C (high density cholesterol), TG (triglyceride), HbA1C and albumin/creatinine ratio in spot urine were measured. 280 patients diagnosed with prediabetes and evaluated for nephropathy were included in the study.

The diagnosis of prediabetes was made if impaired glucose tolerance (IGT), impaired fasting glucose (IFG) or HbA1C value was detected between 5.7-6.4.[6]

Nephropathy evaluation in patients was made according to the protein, creatinine and total protein/creatinine values requested in the spot urine from the first morning urine. Accordingly, patients with proteinuria of 150 mg/dl and above were considered to have nephropathy. The patients' GFR values were also taken into consideration, and the presence of nephropathy was decided together with GFR and proteinuria. Those with diseases that may cause proteinuria, such as urinary system infection, glomerulonephritis or other active infective pathology, nephrolithiasis, heavy exercise, presence of rheumatic disease, diagnosis of hypertension, steroid use, menstrual bleeding, hemolysis, pregnancy, or heart failure, were not included in the evaluation.

RESULTS

Of the 280 patients included in our study, 36.4% were male (n=102) and 63.6% (n=178) were female. The average age of our patients was 54.15 (sd: 11.6).

The average HbA1C value of the patients was determined as 6.12% (sd: 0.38).

Nephropathy was detected in 81 (28.9%) of the patients. Nephropathy status was compared with other parameters. In the comparison made with HbA1C, the average HbA1C value of the group with nephropathy was found to be 6.28% (sd: 0.52) and the average HbA1C value of the group without nephropathy was 6.05% (sd: 0.29). The average HbA1C value was found to be significantly higher in the group with nephropathy (p=0.000). In addition, the LDL-C value of the group with nephropathy was significantly higher than the group without nephropathy (p=0.006). While the average LDL-C value of the group with nephropathy was 137.5 mg/dl (sd: 28.6), the average LDL-C value of the group without nephropathy was 125.6 mg/dl (sd: 33.9). No significant difference was observed in terms of HDL-C, TG, BMI and waist circumference.

Table 13. Comparative analysis of patients with and without nephropathy			
	With nephropathy	Without nephropathy	p score
Number (n=280)	28.9% (n=81)	71.1% (n=199)	
HbA1C (%)	6.28 (sd:0.52)	6.05 (sd:0.29)	0.000
LDL-C (mg/dl)	137.5 (sd:28.6)	125.6 (sd:33.9)	0.006
HDL-C (mg/dl)	45.4 (sd:10.2)	47.5 (sd:11.3)	0.173
TG (mg/dl)	173.8 (sd:85.0)	153.7 (sd:79.5)	0.062
BMI (kg/cm²)	32.4 (sd:6.5)	31.3 (sd:6.3)	0.175
Waist circumference (cm)	88.4 (sd:8.9)	86.5 (sd:9.2)	0.125

Prediction of nephropathy by HbA1C was analyzed by ROC curve. In the analysis, AUC was found to be 0.642. Based on the HbA1C value of 6.05, it was observed that this value had 65% sensitivity and 50% specificity in predicting nephropathy (p=0.000).
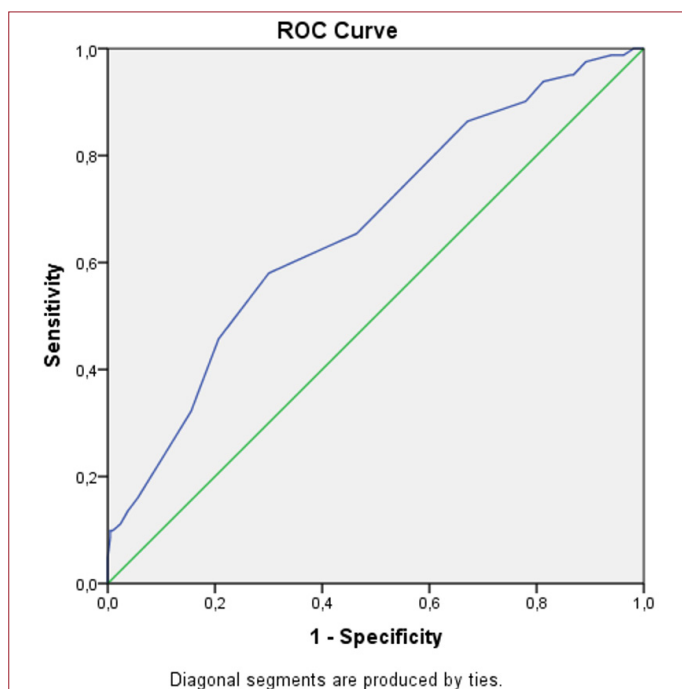

Figure 1. Analysis of HbA1C value predicting the presence of nephropathy with ROC curve

The relationship between OGTT results and nephropathy status was analyzed. It was observed that there was a significant difference between the groups (p=0.001). The highest rate of nephropathy was seen in patients with IFG and IGT together. The lowest rate was detected in the IFG group.

DISCUSSION

Studies show that prediabetes increases risk in many aspects. First of all, 5-10% of prediabetes patients are diagnosed with diabetes every year. Many problems and complications may arise in those who are not diagnosed with diabetes. On the other hand, lifestyle changes in prediabetes patients reduce the risk by 40-70%. This reveals the importance of detection and precautions to be taken at an early stage.[8]

In a study that included 46,911 prediabetes patients in the UK and examined data with a follow-up of 11.1 years, it was shown that the risk of atherosclerotic heart disease increased in those with an HbA1C value of >5.4% compared to those with an HbA1C value of <5%. It was also found that the risk of heart failure and chronic kidney disease increased in those with >6.2%. These results show that there is an increase in risk at HbA1C values below the Type 2 DM diagnostic limit.[9]

In our study, we obtained a result similar to this study. While the average HbA1C value of the patients with nephropathy was 6.28%, the average HbA1C value was 6.05% in the group without nephropathy. This result suggests that an HbA1C value of around 6.2% may be a threshold value in this regard.

In a large-scale review study, the risk of prediabetes in terms of all-cause mortality and complications of diabetes was examined. In this study, it was observed that prediabetes increased the risk of all-cause mortality, coronary heart diseases, stroke, heart failure, atrial fibrillation and chronic renal failure, ranging from 6% to 101%. At the same time, prediabetes has been found to be associated with hepatocellular cancer, breast cancer and dementia. The increased risk of all-cause mortality was found to be higher in those with impaired fasting glucose. As a result, it has been stated that prediabetes poses a significant increase in risk and that these data should be supported by detailed studies (for example, investigating the relationship between nephropathy and prediabetes).[10]

Based on the data of the 4C (China Cardiometabolic Disease and Cancer Cohort) study, which included 55,777 prediabetes patients in China, prediabetes patients were analyzed by dividing them into 6 groups. It has been observed that different risk increases and diseases occur in different clusters. This indicates that prediabetes patients should be examined in detail. For example, it was observed that the risk of cardiovascular disease was highest in the group with more common obesity and insulin resistance. The highest risk of chronic kidney disease was observed in clusters 4 and 6. While obesity and insulin resistance are common in cluster 4, high glycemic levels in multiple parameters are present in cluster 6. According to these data, we can say that if prediabetes is accompanied by obesity and there is a high glycemic level in more than one parameter, the risk of chronic kidney disease increases significantly.[11]

Cross-sectional studies show that prediabetes is associated with CKD. In a study, 1261 patients without diabetes were followed for 5.6 years, and it was shown that prediabetes was associated with the development of glomerular hyperfiltration and albuminuria, as in the early stages of diabetes.[7] Studies have shown that albuminuria increases significantly from normoglycemia to IFG, IGT, IFG+IGT and Type 2 DM, and that this occurs before the development of diabetes.[12-14]

Considering these studies, it is seen that prediabetes is a risk factor for nephropathy, and there is an increased albuminuria

and hyperfiltration state in prediabetes compared to the normal population, which predisposes to nephropathy and CKD.

In our study, 81 (28.9%) of 280 patients evaluated for nephropathy were found to have nephropathy. In the comparison made with HbA1C, the average HbA1C value of the group with nephropathy was 6.28% (sd: 0.52) and the average HbA1C value of the group without nephropathy was 6.05% (sd: 0.29). The mean HbA1C value was significantly higher in the group with nephropathy (p=0.000). Prediction of nephropathy by HbA1C was analyzed by ROC curve. In the analysis, AUC was found to be 0.642. Based on the HbA1C value of 6.05, it was observed that this value had 65% sensitivity and 50% specificity in predicting nephropathy (p=0.000).

As a result of these findings, we can say that there is a significant relationship between HbA1C and nephropathy. However, it does not seem possible to predict nephropathy status with HbA1C. It should be kept in mind that nephropathy may occur in patients with high HbA1C, even if it is at the prediabetes level. Patients should definitely be examined in this respect.

According to our study results, the highest risk of nephropathy was detected in the IFG+IGT, IGT and IFG groups, respectively. While there are data compatible with these results in the literature, there are also studies with different results.[11,15] As a result, it should be kept in mind that there is a significant increase in risk in all groups, but there may be differences between groups and this may be affected by side factors.

CONCLUSIONS

It was observed that prediabetes status and HbA1C value revealed a significant relationship with the presence of nephropathy. The fact that nephropathy was detected in 28.9% of the patients showed once again the seriousness of prediabetes. Therefore, early diagnosis and treatment of prediabetes is important in terms of nephropathy and CKD.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Health Sciences University Erzurum Regional Training and Research Hospital Clinical Research Ethics Committee (Date:19.03.2018, Decision No: KAEK 2018/06-40).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

REFERENCES

1. Deshpande AD, Harris-Hayes M, Schootman M. Epidemiology of diabetes and diabetes-related complications. Phys Ther. 2008;88(11):1254-64.
2. Diabetes Atlas | International Diabetes Federation [Internet]. [cited 2018 april 05]. https://diabetesatlas.org/atlas/seventh-edition/
3. Çalışma, TEMD Diabetes Mellitus, and Eğitim Grubu. "TEMD Diabetes Mellitus ve Komplikasyonlarının Tanı, Tedavi ve İzlem Kılavuzu-2019. 12." Baskı. Ağustos (2019).
4. Ruggenenti P, Remuzzi G. Nephropathy of type 1 and type 2 diabetes: diverse pathophysiology, same treatment? Nephrol Dial Transplant. 2000 Dec;15(12):1900-2.
5. Seyahi N, Altiparma MR, Süleymanlar G. Türkiye'de Renal Replasman Tedavilerinin Güncel Durumu: Türk Nefroloji Derneği Kayıt Sistemi 2013 Yılı Özet Raporu Current Status of Renal Replacement Therapy in Turkey: A Summary of Turkish Society of Nephrology 2013 Annual Registry Report. Süleymanlar, Gültekin–Ateş, Kenan–Seyahi, Nurhan. 2015.
6. TURKDİAB Diyabet Tanı ve Tedavi Rehberi Nisan 2019, . Türkiye Diyabet Vakfı. 2019. [Internet]. https://www.turkdiab.org/admin/PICS/files/Diyabet_Tani_ve_Tedavi_Rehberi_2019.pdf
7. Melsom T, Schei J, Stefansson VT, et al. Prediabetes and Risk of Glomerular Hyperfiltration and Albuminuria in the General Nondiabetic Population: A Prospective Cohort Study. Am J Kidney Dis. 2016;67(6):841-50.
8. Tabák AG, Herder C, Rathmann W, Brunner EJ, Kivimäki M. Prediabetes: a high-risk state for diabetes development. Lancet. 2012;379(9833):2279-90.
9. Honigberg MC, Zekavat SM, Pirruccello JP, Natarajan P, Vaduganathan M. Cardiovascular and kidney outcomes across the glycemic spectrum: insights from the UK biobank. J Am Coll Cardiol. 2021;78(5):453-64.
10. Schlesinger S, Neuenschwander M, Barbaresko J, et al. Prediabetes and risk of mortality, diabetes-related complications and comorbidities: umbrella review of meta-analyses of prospective studies. Diabetologia. 2022;65(2):275-85.
11. Zheng R, Xu Y, Li M, et al. China Cardiometabolic Disease and Cancer Cohort (4C) Study Group. Data-driven subgroups of prediabetes and the associations with outcomes in Chinese adults. Cell Rep Med. 2023;4(3):100958.
12. Plantinga LC, Crews DC, Coresh J, et al. CDC CKD Surveillance Team. Prevalence of chronic kidney disease in US adults with undiagnosed diabetes or prediabetes. Clin J Am Soc Nephrol. 2010;5(4):673-82.
13. Tapp RJ, Shaw JE, Zimmet PZ, et al. Albuminuria is evident in the early stages of diabetes onset: results from the Australian Diabetes, Obesity, and Lifestyle Study (AusDiab). Am J Kidney Dis. 2004;44(5):792-8.
14. Wang XL, Lu JM, Pan CY, Tian H, Li CL. A comparison of urinary albumin excretion rate and microalbuminuria in various glucose tolerance subjects. Diabet Med. 2005;22(3):332-5.
15. Echouffo-Tcheugui JB, Narayan KM, Weisman D, Golden SH, Jaar BG. Association between prediabetes and risk of chronic kidney disease: a systematic review and meta-analysis. Diabet Med. 2016;33(12):1615-24.