ASPI | Afarand Scholarly Publishing Institute; Iran
ISSN: 2008-2630 Iranian Journal of War & Public Health 2022;14(2):119-123 DOI: 10.29252/ijwph.14.2.119

Risk Factors for Diabetic Nephropathy in Diabetic Patients

ARTICLE INFO

Article Type
Descriptive study

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How to cite this article
Oleiwi SR, Al-Taie AM, Al-Hilali KA. Risk Factors for Diabetic Nephropathy in Diabetic Patients. Iranian Journal of War & Public Health. 2022;14(2):119-123.

ABSTRACT

Aims Diabetic nephropathy is one of the consequences of type 1 and type 2 diabetes and one of the main causes of End-Stage Renal Disease (ESRD) as well as an important risk factor for cardiovascular morbidity and death. The aim of this study was to identify the risk factors for diabetic nephropathy in diabetic patients.

Instruments & Methods In this cross-sectional descriptive study, 121 patients (66 females and 55 males) with type 2 diabetes in Karbala, Iraq from October 2019 to April 2021were studied. In the first stage, a complete history of the patients was taken and then a physical examination was performed. After that, 5 ml of aspirated blood and 100 ml of urine were collected from each patient and both were sent to the laboratory for biochemical tests and urinalysis. The collected data were statistically analyzed using SPSS 22 software and Chi-square test.

Findings Out of 121 diabetic patients, 77 (63.6%) had diabetic nephropathy. The incidence of diabetic nephropathy was higher in men than women. There was a significant relationship between age, persistent hyperglycemia, obesity, and duration of diabetes with diabetic nephropathy ($p<0.05$).

Conclusion Age, persistent hyperglycemia, obesity and duration of diabetes are involved in the development of diabetic nephropathy in diabetic patients.

Keywords Diabetes Mellitus; Diabetic Nephropathy; End Stage Renal Disease; Risk Factors

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Article History
Received: March 11, 2022
Accepted: April 1, 2022
ePublished: May 30, 2022

CITATION LINKS

[1] Diagnosis and classification of ... [2] Definition, epidemiology and classification ... [3] Definition, epidemiology, risk ... [4] Diabetic nephropathy - complications ... [5] Diabetic nephropathy in Type 1 ... [6] The presence and severity of chronic ... [7] In the absence of renal disease ... [8] Estimated glomerular filtration rate ... [9] Kidney disease and increased ... [10] The burden of chronic kidney disease in Australian ... [11] Renal dysfunction in the presence of normoalbuminuria ... [12] Nephropathy in ... [13] Diabetic nephropathy ... [14] Diabetic ... [15] Pathogenesis, prevention, and ... [16] Diabetic kidney disease ... [17] Genetic associations in diabetic nephropathy ... [18] Diabetic ... [19] Nephropathy in siblings of African Americans with ... [20] Familial predisposition to renal disease ... [21] Racial differences in diabetic ... [22] Genetic associations in diabetic ... [23] Obesity and diabetic kidney ... [24] Obesity, diabetes, and chronic kidney ... [25] Effective antihypertensive treatment postpones ... [26] Angiotensin receptor blockers in diabetic nephropathy ... [27] Diabetic nephropathy: mechanisms of ... [28] Diabetic nephropathy or kidney ... [29] What is the age distribution for diabetic ... [30] Interaction of aging and chronic kidney ... [31] Risk factor, age and sex differences ... [32] Interactions between renin angiotensin system and advanced ... [33] Mechanisms of obesity-associated cardiovascular and renal ... [34] Kidney disease and related findings in the diabetes control and complications trial/ epidemiology of diabetes ...

Introduction

Diabetes Mellitus (DM) a group of metabolic diseases characterized by chronic hyperglycemia resulting from defects in insulin secretion, insulin action, or both. Metabolic abnormalities in carbohydrates, lipids, and proteins result from the importance of insulin as an anabolic hormone. Low levels of insulin to achieve adequate response and/or insulin resistance of target tissues, mainly skeletal muscles, adipose tissue, and to a lesser extent, liver, at the level of insulin receptors, signal transduction system, and/or effector enzymes or genes are responsible for these metabolic abnormalities. The severity of symptoms is due to the type and duration of diabetes [1-3].

Diabetes mellitus prevalence is increasing around the world. It is estimated to affect 8-10% of the global population [4]. By 2035, the number of diabetics is expected to increase to 550 million [5].

Of the long-term complications of diabetes, Chronic Kidney Disease (CKD) imposes the highest burden, both in terms of financial cost and the effects on daily life. The presence and severity of CKD identify individuals who are at increased risk for adverse health outcomes, including frailty, reduced quality of life, End-Stage Renal Disease (ESRD), progressive end-organ damage at other sites and premature mortality. Indeed, excess mortality associated with type 1 diabetes and type 2 diabetes is largely confined to those with CKD [6-9]. Consequently, preventing and managing CKD in patients with diabetes is a key aim of their overall management.

Approximately half of all patients with type 2 diabetes and one-third with type 1 diabetes will develop CKD, which is clinically defined by the presence of impaired renal function or elevated urinary albumin excretion or both [10, 11].

Diabetic Kidney Disease (DKD) or Diabetic Nephropathy (DN) can occur in both forms of DM (1 and 2), although type 2 has a lower rate of progression to End Stage Kidney Disease (ESKD) and End Stage Renal Failure (ESRF), because of higher prevalence of type 2 DM [12]. Not all patients with DM develop kidney disease, which leads to kidney failure, although up to 10-50% of them develop DN, which leads to ESRF and hemodialysis or kidney transplantation [12, 13].

Diabetic kidney disease is a common cause of ESKD in the western world [14]. Diabetic nephropathy (DN) is a clinical disease characterized by a persistent increase in urinary albumin excretion, increased arterial blood pressure, a progressive decline in Glomerular Filtration Rate (GFR), and a significant risk of cardiovascular morbidity and death [15].

In general, well-known risk factors for DKD (or DN) include: age, male sex, hyperglycemia, hypertension, hypovitaminosis D, obesity, chronicity, insulin resistance and some other factors [16].

As previously stated, not all diabetics experience complications. The evolution of DN and those who have it vary according to the influence of risk factors.

DN histopathology starts with a gradual thickening of the glomerular membrane base, which progresses faster or slower depending on the severity of the risk factors for mesangial matrix deposition and podocyte loss, and ends to Kimmelsteil-Wilson nodules and glomerular sclerosis with increased urinary albumin excretion, ending into ESRF or ESKD [15].

DN is now thought to be caused by genetic and environmental factors [17]. Poor glycemic control results in to liberation of glycation products, this with other metabolites and hemodynamic factors have toxic effects on the glomerulus causing their damage.

Diabetic nephropathy is not an uncommon complication of DM among geriatric population [14], and the incidence of DN and ESRD as a result of DM increases with age [4]. Some reports indicate an increase in the incidence of DN in men compared to women [4]. Other reports suggested that type 2 diabetes and DN are more common in women (1 in 4) than men (1 in 5) [18].

Racial, genetics and familial predisposition may play a marked role in the epidemiology of DKD [17, 19-22].

Obesity with type 2 diabetes affects the rate and progression of kidney disease (CKD) and End-Stage Renal Disease (ESRD). However, obesity may increase the risk of renal disease even if type 2 diabetes is not present [23, 24].

Diabetic kidney disease is uncommon in diabetes with a duration shorter than a decade; after which the incidence increases by about 3% to per year [16].

Diabetic nephropathy can be stopped or reduced by continuously monitoring patients, especially in the early stages, detecting risk factors, and treating modifiable factors, such as hyperglycemia, hypertension, obesity, smoking, and hyperlipidemia [25].

Screening should start after five years of diagnosis of type 1 DM and immediately after diagnosis of type 2 DM.

Estimation of urinary albumin and urinary creatinine excretion, as well as albumin creatinine ratio, are all part of routine screening. Other tests may be needed, for example renal function test, GFR and renal biopsy [13].

Angiotensin Converting Enzyme Inhibitors (ACEIs) and angiotensin receptor blockers can help reduce or stop diabetic nephropathy [26].

The aim of this study was to identify the risk factors for diabetic nephropathy in diabetic patients.

Instruments and Methods

In this cross-sectional descriptive research, 121 patients (66 women and 55 men) with T2 DM referred to the Diabetic Clinic of the Medical City of Al-Hussein Teaching Hospital, Karbala Holy City, Iraq, were studied from October 2019 to April 2021.

Initially, written consent was obtained from patients stating their willingness to participate in the study in accordance with human rights guidelines.

In the first stage, a complete history of the patients was taken and then a physical examination was performed. For this purpose, Blood Pressure (BP) was checked twice while sitting. If the blood pressure was above 140/90 mm Hg, high blood pressure was considered.

Then the patient's weight and height were assessed using Physician Balance Beam Scale. Body Mass Index (BMI) was calculated based on the following formula:

$$BMI\ (kg/m^2) = Weight\ in\ kg\ /\ (Height\ in\ meters)^2$$

where BMI = 18-24.9 kg/m^2 is normal, BMI = 25-29.9 kg/m^2 is overweight and BMI ≥30 kg/m^2 is obese.

After that, 5 ml of aspirated blood and 100 ml of urine were collected from each patient and both were sent to the laboratory for biochemical tests and urinalysis. Urine albumin from urine sample was measured in mg/dl turbid metric point method by 1-chroma instrument and urine creatinine was measured by spectrophotometer in g/dl. The Albumin-to-Creatinine Ratio (ACR) was then calculated as follows:

ACR = 0-29 is normal, ACR=30-300 is microalbumiurea, and ACR >300 is macroalbuminurea.

Finally, the collected data were statistically analyzed using SPSS 22 software and Chi-square test.

Findings

A total of 121 patients (66 women and 55 men) participated in the study. The mean age of patients was 54±2.1 years in the range of 30-80 years.

There was a significant relationship between age and DN (p<0.05). The incidence of DN was also higher in men than women (Table 1).

Table 1) Relationship between age and gender with Diabetes Nephropathy (DN)

Variables	Patient with diabetes	Patients with DN
Age group (years)		
30-39	10	3 (30.0%)
40-49	37	18 (48.6%)
50-59	32	23 (71.9%)
60-69	38	30 (78.9%)
70-80	4	3 (75.0%)
Gender		
Male	55	36 (65.4%)
Female	66	41 (62.1%)
Total	121	77 (63.6%)

Persistent hyperglycemia represented by HbA1c and Random Blood Sugar (RBS) showed a significant relationship with DN represented by ACR (p<0.01; Table 2).

The relationship between obesity represented by BMI with ACR was also significant (p<0.05; Table 3).

Table 4 shows the relationship between duration of DM and DN and as you can see, the incidence of diabetic nephropathy increased with the duration of diabetes (p<0.05).

Table 2) Relationship between HbA1c and RBS with ACR

ACR (mg/g)	Total patients	Average HbA1c (%)	Patients with high RBS
0-29	44	7.28	40 (90.9%)
30-300	39	8.88	38 (97.4%)
>300	38	11.38	38 (100%)
Total	121	-	-

ACR: Albumin-to-Creatinine Ratio
High Random Blood Sugar (RBS): ≥200 mg/dl blood sugar

Table 3) Relationship between BMI and ACR

ACR (mg/g)	Total patients	Patients with normal BMI	Patients with increased BMI
0-29	44	18	26 (59.1%)
30-300	39	14	25 (64.1%)
>300	38	12	26 (68.4%)
Total	121	44	77 (63.6%)

ACR: Albumin-to-Creatinine Ratio
Normal BMI: <25 kg/m^2; Increased BM : ≥25 kg/m^2

Table 4) Relationship between chronicity of DM (duration in years) and ACR

Duration of DM in years	ACR (mg/g)	Total patients	Patients with proteinuria
0-5	20	21	1 (4.8%)
6-10	12	26	14 (53.8%)
11-15	9	24	15 (62.5%)
16-20	2	30	28 (93.3%)
>20	1	20	19 (95.0%)
Total	44	121	77 (63.6%)

ACR: Albumin-to-Creatinine Ratio; DM: Diabetes Mellitus

Discussion

In developed and developing countries, diabetes mellitus (DM) is the most common cause of chronic kidney failure (CKF) [27]. In Malaysia, between 2009 and 2011, DM was the predominant cause of ESRD in about 60% of patients, while in Russia, Singapore, South Korea, Hong Kong, Israel, Taiwan, the Philippines, Japan, the United States and New Zealand, 40-50% of patients with DM develop ESRD [15].

Diabetic Nephropathy (DN) is the most common cause of ESRD in the United States [28] and Australia, as well as many other countries [4]. DN affects about one-third of people with type 1 and type 2 diabetes in the United States [16].

The aim of this study was to identify the role of age, sex, glycemic control, obesity and duration of diabetes on diabetic nephropathy (DN).

The aim of this study was to identify the role of age, sex, glycemic control, obesity and duration of diabetes on diabetic nephropathy (DN).

As people get older, they are more likely to develop DN and ESRD as a result of diabetes. It is also more common in the elderly who have had type 2 diabetes for a long time. Although the role of age in the development of DKD is unknown, the average age of patients with ESRD is about 60 years [29].

According to the National Health and Nutrition Examination Survey results from 1999 to 2004, the incidence of chronic kidney disease increases dramatically with age, so that more than a third of people aged 70 and older with moderate or severe CKD are diagnosed, which is defined as the estimated Glomerular Filtration Rate (eGFR) of less than 60 ml/minutes [30].

Our results in Table 1 show an increase in the incidence of DN with increasing age and are consistent with this concept.

In the present study, the incidence of nephropathy was higher in men than women, which is consistent with the results of Lim study [4], but in other reports, the prevalence of DN was higher in women [18]. According to Yu *et al*.'s study, women with diabetes showed a higher prevalence of advanced DKD and common risk factors for DKD than men, and these differences were more pronounced among the elderly [31].

Hyperglycemia is a known risk factor for DN because high blood sugar continuously causes damage to glomeruli through its toxic metabolite or glycation product. In the present study, persistent hyperglycemia represented by HbA1c and Random Blood Sugar (RBS) showed a significant relationship with DN represented by ACR. This finding is consistent with the results of previous studies [16, 18, 27, 32].

Obesity is an important risk factor for diabetes and kidney disease. Obesity may increase the risk of kidney damage even if you do not have type 2 diabetes [33].

This study showed a significant association between obesity as a risk factor and DN. There are studies from various parts of the world that try to link racial, ethical, genetics, and familial profile to DN; for example Mooyaart *et al*. in a meta-analysis found 24 genetic variants associated with diabetic nephropathy [17, 22]. Satko *et al*. [19]. In a study, Pettitt *et al*. investigated the familial predisposition to renal disease in two generations of Pima Indians with type 2 (non-insulin-dependent) diabetes mellitus and conclouded that the asymptomatic elevations in urinary albumin excretion and serum creatinine levels are frequently present in diabetic sibs of African American individuals with overt type 2 DN [20]. In addition, a longitudinal cohort study was conducted by Young *et al*. on veterans with diabetes and racial minority groups were analyzed for baseline differences in prevalence of early diabetic nephropathy, diabetic End-Stage Renal Disease (ESRD), and longitudinal risk of mortality compared with Caucasians [21]. Native Americans, Hispanics, and African Americans have also been shown to be significantly more likely to develop ESRD than non-Hispanic whites with type 2 diabetes. Therefore, these factors may play a marked role in the epidemiology of diabetic kidney disease (DKD) [34].

Finally, our results showed a significant association between the duration of DM and the development of DN. Diabetic nephropathy does not occur early in type 1 diabetes and is uncommon in diabetes with a duration shorter than a decade; after that, the incidence rate increases by about 3% per year [5]. On the other hand, DN may be detected shortly after the diagnosis of type 2 diabetes, especially if it is ignored and not controlled, and especially in the presence of other risk factors.

Conclusion

Age, persistent hyperglycemia, obesity and duration of diabetes are involved in the development of diabetic nephropathy in diabetic patients.

Acknowledgments: None declared.
Ethical Permissions: None declared.
Conflicts of Interests: None declared.
Authors' Contributions: Oleiwi SR (First Author), Introduction Writer/Main Researcher (40%); Al-Taie AM (Second Author), Assistant Researcher /Discussion Writer (30%); Al-Hilali KA (Third Author), Methodologist (30%)
Funding/Support: None declared.

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