

Diabetic Nephropathy and Its Risk Factors in a Society with a Type 2 Diabetes Epidemic: A Saudi National Diabetes Registry-Based Study

Khalid Al-Rubeaan^{1*}, Amira M. Youssef², Shazia N. Subhani³, Najlaa A. Ahmad⁴, Ahmad H. Al-Sharqawi⁴, Hind M. Al-Mutlaq⁵, Satish K. David⁶, Dhekra AlNaqeb⁷

1 University Diabetes Center, College of Medicine, King Saud University, Riyadh, Saudi Arabia, **2** Registry Department, University Diabetes Center, King Saud University, Riyadh, Saudi Arabia, **3** Department of Biostatistics, Epidemiology and Scientific Computing, King Faisal Specialist Hospital and Research Centre, Riyadh, Saudi Arabia, **4** Biostatistics Department, University Diabetes Center, King Saud University, Riyadh, Saudi Arabia, **5** Family and Community Medicine Department, Qassim University, Qassim, Saudi Arabia, **6** Information Technology Department, Strategic Center for Diabetes Research, King Saud University, Riyadh, Saudi Arabia, **7** Research Department, University Diabetes Center, King Saud University, Riyadh Saudi Arabia

Abstract

Aims: The prevalence of diabetic nephropathy and its risk factors have not been studied in a society known to have diabetes epidemic like Saudi Arabia. Using a large data base registry will provide a better understanding and accurate assessment of this chronic complication and its related risk factors.

Methodology: A total of 54,670 patients with type 2 diabetes aged ≥ 25 years were selected from the Saudi National Diabetes Registry (SNDR) and analyzed for the presence of diabetic nephropathy. The American Diabetes Association (ADA) criterion was used to identify cases with microalbuminuria, macroalbuminuria and end stage renal disease (ESRD) for prevalence estimation and risk factor assessment.

Results: The overall prevalence of diabetic nephropathy was 10.8%, divided into 1.2% microalbuminuria, 8.1% macroalbuminuria and 1.5% ESRD. Age and diabetes duration as important risk factors have a strong impact on the prevalence of diabetic nephropathy, ranging from 3.7% in patients aged 25–44 years and a duration of >5 years, to 21.8% in patients ≥ 65 years with a diabetes duration of ≥ 15 years. Diabetes duration, retinopathy, neuropathy, hypertension, age >45 years, hyperlipidemia, male gender, smoking, and chronologically, poor glycemic control has a significantly high risk for diabetic nephropathy.

Conclusion: The prevalence of diabetic nephropathy is underestimated as a result of a shortage of screening programs. Risk factors related to diabetic nephropathy in this society are similar to other societies. There is thus an urgent need for screening and prevention programs for diabetic nephropathy among the Saudi population.

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* E-mail: krubeaan@ksu.edu.sa

Introduction

Electronic medical health systems have made chronic diseases like diabetes mellitus easier to monitor and understand through large data base registries. Diabetes Registry is gaining popularity nowadays as a result of its advantages in collecting and characterizing data about the disease for clinical and scientific studies. The prevalence of diabetes is increasing globally as a result of urbanization, human aging and lifestyle changes. Diabetes registries track this disease behavior, and provide a better understanding of its clinical, social, cultural and economic impact. Disease registries not only improve perception of the disease, but help in the health planning and assessment of health care quality. They are considered to be a reliable source of epidemiology data that serve to highlight both morbidity and mortality from such

diseases [1]. Many countries have adopted renal registries, such as Finland, Hong Kong and the United Kingdom, and this shows that diabetic renal disease remain the single most common cause of renal failure, amounting to 24.8% [2]. Health care stakeholders are currently more interested than before in data provided by registries, and this may explain the large increase in the number of registries at a global level [3].

Diabetes prevalence in the Middle Eastern region is considered to be the highest, averaging 10.9%. In 2011, six Middle Eastern countries were listed among the top ten countries with a high prevalence of diabetes for ages 20–79 years, with Saudi Arabia ranking seventh [4]. Abnormal glucose metabolism has reached an epidemic stage in the Kingdom, with diabetes and impaired fasting

glucose crude prevalence being 23.7% and 14.1% respectively, accounting for 37.8% of Saudis aged between 30 to 70 years [5].

Evidence based medicine shows that diabetes morbidity and mortality are attributed to its chronic complications. According to ADA (2012), Diabetic nephropathy (DN) is a microvascular complication known to be the leading cause of ESRD worldwide, and is associated with increased cardiovascular risk. Epidemiology studies of type 2 diabetic patients show that DN prevalence ranges from 7.6% to 55% [6], while in different international registries it varies between 11.5% in United Kingdom and 42.9% in Thailand [7,8]. This large variation in DN prevalence reported by registries may be related to registry size, screening and management practice, and can be improved with larger registries, and by implementing standardized practice, especially a longer follow up period.

Saudi Arabia, known as a society with high type 2 diabetes prevalence, has limited data concerning diabetic nephropathy can be used for better understanding of this chronic complication. A study in 2008 unexpectedly considered DN to be the most prevalent chronic complication among Saudi type 2 diabetic patients, accounting for 32.1%, which could be attributed to the sample selection methodology used [9]. Hypertension, longer diabetes duration, poor glycemic control, dyslipidemia, smoking, obesity, male gender and presence of retinopathy are well known risk factors for DN in type 1 diabetes [10]. These risk factors were not tested on a large number of diabetic patients in a high diabetes prevalent society so as to validate the importance of such risk factors. Hazard ratio tested for the progression of diabetic nephropathy among Saudis showed significant values for presence of retinopathy, male gender, diabetes duration >10 years and presence of hypertension [11].

Methodology

SNDR, hosting more than 100.000 Saudi diabetic patients, can be the best environment to study DN and its risk factors. It is a specially designed electronic web-based data system which incorporates demographic data, diabetic and social history with clinical and biochemical parameters. This registry includes the presence of chronic complications, namely neuropathy, retinopathy, nephropathy, and vasculopathy, as well as associated diseases like hypertension, hyperlipidemia and thyroid disease. The design and development of a web-based SNDR has already been explained in a previously published paper, available at <http://www.jmir.org/2013/9/e202>, and the registry website can be accessed from <http://www.diabetes.org.sa>. This diabetes national registry is one of the Saudi strategic research projects approved and funded by King Abdulaziz city for science and Technology (KACST), which is the official largest funding body in the kingdom.

This is a cross-sectional, randomized observational study, where 67,075 Saudi diabetic patients (51.2% males and 48.8% females) were selected from SNDR to assess the presence of diabetic nephropathy after been de-identified. ADA criteria were used to identify diabetes types and DN diagnostic criteria. The selected sample was categorized according to DN classification into microalbuminuria, macroalbuminuria, and ESRD. Nephropathy was excluded if a patient had no proteinuria or albumin excretion <30 µg/mg creatinine and normal glomerular filtration rate (GFR) ≥90 ml/min per 1.73 m² body surface area. Microalbuminuria is diagnosed when albumin is between 30–299 µg/mg creatinine, and macroalbuminuria when albumin excretion ≥ 300 µg/mg creatinine. Patients were identified with ESRD if they had GFR <30 ml/min per 1.73 m² body surface area, or had been diagnosed by their treating physician [8]. Patients on dialysis

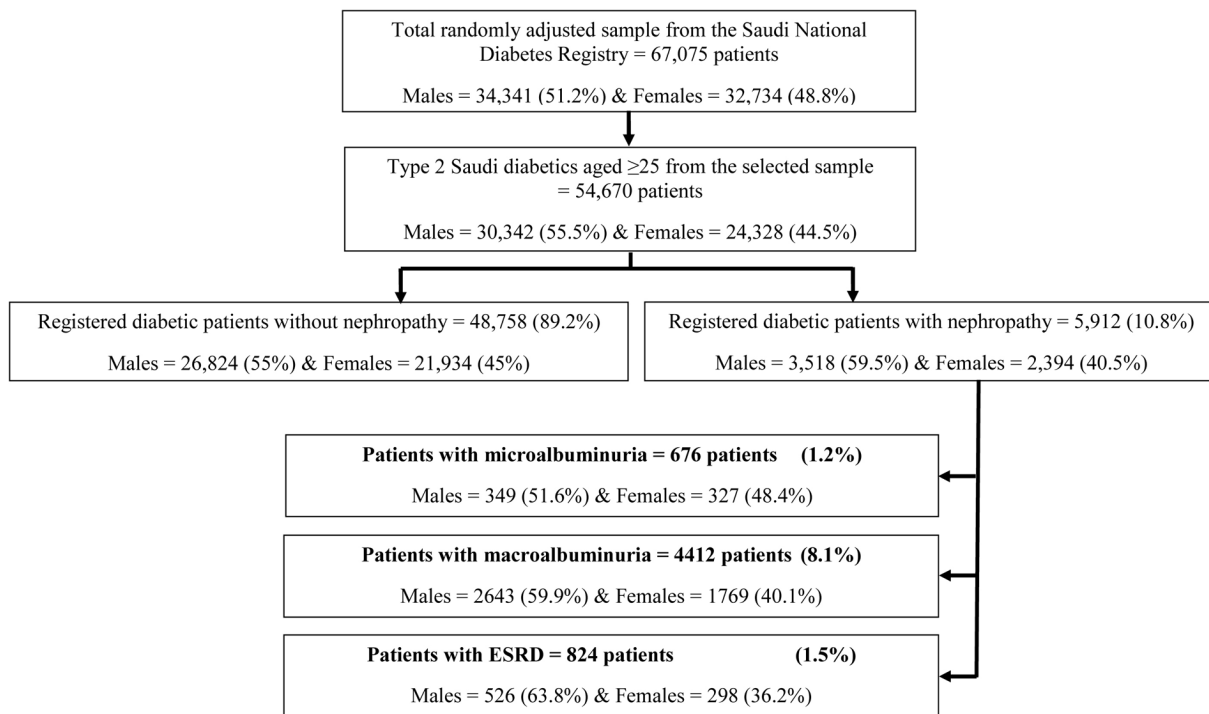


Figure 1. Sampling methodology for patients with diabetic nephropathy and its different types, among type 2 diabetes patients aged ≥25 years from the Saudi National Diabetes registry.
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at the time of the registry, or who had received kidney transplant, were considered to have ESRD.

Figure 1 shows the selection of type 2 Saudi diabetic patients aged ≥ 25 years totaling at 54,670 patients, of which 30,342 (55.5%) were males and 24,328 (44.5%) females. Diabetic nephropathy was found in 5,912 (10.8%), of which 59.5% were males and 40.5% females. Microalbuminuria was found in 676 (1.2%) patients, of which 51.6% were males and 48.4% were females. Macroalbuminuria prevalence was 8.1%, of which 59.9% were males and 40.1% were females. ESRD affected 1.5% of the total sample, with 63.8% being males and 36.2% being females.

Statistical Analysis

All data were entered into the centralized database via the web application SADR, and was analyzed using SPSS program version 17.0. Descriptive analyses and frequency tables were performed using this program for all variables. Chi square test (χ^2) was used for categorical variables such as gender and smoking status, while t-test was used for continuous variables such as age, duration of diabetes and body measurements, including height, weight, Body Mass Index (BMI), and HbA1c. Odds ratio (with 95% confidence interval) and p-value of 0.05 or less were used as a level of significance for assessing the risk factors of diabetic nephropathy. The risk factors of DN were plotted using Graph Pad software.

Results

A total of 5,912 patients fulfilled the diabetic nephropathy criteria from the selected sample, accounting for 10.8% of the 54,670 Saudi type 2 diabetic aged ≥ 25 years patients, divided into Microalbuminuria, macroalbuminuria and ESRD, representing 11%, 75% and 14% of the total nephropathic patients respectively.

Table 1 shows the descriptive analysis of the selected sample and nephropathy cases. The total sample mean age was 59.91 (± 12.72) years, and BMI is 30.46 (± 6.30) kg/m² with mean weight and height being 78.55 (± 16.50) kg and 160.24 (± 9.74) cm respectively. Mean diabetes duration was 13.55 (± 8.14) years.

When comparing patients with and without nephropathy, nephropathic patients were significantly older (63.99 vs 59.41 years) and had longer diabetes duration (18.81 vs. 12.85 years), ($p < 0.0001$). Non-nephropathic patients had significantly higher weight, height and BMI than total nephropathic, ($p < 0.0001$, 0.02, < 0.001) respectively and macroalbuminuria patients, ($p = 0.006$). Microalbuminuria patients had a significantly higher weight than non-nephropathic. Patients with ESRD were significantly lower in weight and BMI when compared with non nephropathic. Mean age was significantly higher in microalbuminuria, macroalbuminuria and ESRD patients, representing 57.83 (± 11.58), 64.34 (± 11.87) and 64.29 (± 11.12) years, ($p = 0.014$, < 0.0001 , < 0.0001) respectively. Diabetes duration was significantly longer in patients with macroalbuminuria and ESRD, but not for patients with microalbuminuria, at 19.40, 19.59 and 13.47 years respectively, ($p < 0.0001$, < 0.0001 , 0.128).

Table 2 shows the descriptive analysis of the selected sample and nephropathy cases.

The highest frequency was seen among the 45 to 64 age group in the total sample (52.2%), among non-nephropathic (53.3%) and microalbuminuria (59.9%) patients, but among age group ≥ 65 years, in total nephropathic (51.2%), macroalbuminuria (53.2%) and ESRD (52.3%) patients.

Males had higher frequency in the total sample or nephropathic patients, regardless of the nephropathy types, but the highest in macroalbuminuria and ESRD, with a percentage of 60.2% and 64.3% respectively. When comparing the marital status of nephropathic patients with their non nephropathic counterparts, there was a significantly lower percentage of singles, but a higher percentage of widows among nephropathic patients (2.1% vs 1.5% and 5.2% vs 6.5%), ($p = 0.001$, < 0.0001). The presence of diabetes family history was significantly higher among nephropathic and patients with microalbuminuria and macroalbuminuria, ($p < 0.0001$), but not with ESRD patients, ($p = 0.866$), represented by 43.9%, 49.4%, 45.1%, 36.5% respectively. Smoking was significantly more prevalent among nephropathy patients in general, at 10.9%, and at 13.9% for ESRD patients, ($p = 0.001$, 0.029) respectively, but not in patients with microalbuminuria or macroalbuminuria.

Table 1. Descriptive analysis of the selected cohort according to the Nephropathy type.

| Variables | Selected sample | No Nephropathy | Diabetic Nephropathy | | | | | | | |
|-------------------------------|-----------------------|-----------------------|---|------------------------|-----------------------|-------------------------|-----------------------|------------|------------------------|----------|
| | | | Classification according to diabetic nephropathy status | | | | | | | |
| | Total (54670) | Total (48758) | Total (5912) | Microalbuminuria (676) | | Macroalbuminuria (4412) | | ESRD (824) | | |
| | Mean (SD) | Mean (SD) | Mean (SD) | P value* | Mean (SD) | P value* | Mean (SD) | P value* | Mean (SD) | P value* |
| Age (years) | 59.91 (± 12.72) | 59.41 (± 12.71) | 63.99 (± 12.06) | <0.0001 | 57.83 (± 11.58) | 0.014 | 64.34 (± 11.87) | <0.0001 | 64.29 (± 11.12) | <0.0001 |
| Weight (kg) | 78.55 (± 16.50) | 78.73 (± 16.52) | 77.20 (± 16.27) | <0.0001 | 80.31 (± 14.81) | 0.044 | 76.96 (± 16.57) | <0.0001 | 71.82 (± 15.70) | <0.0001 |
| Height (cm) | 160.24 (± 9.74) | 160.29 (± 9.73) | 159.93 (± 9.77) | 0.02 | 160.66 (± 9.74) | 0.485 | 159.71 (± 9.20) | 0.006 | 160.86 (± 10.62) | 0.381 |
| BMI (kg/m²) | 30.46 (± 6.30) | 30.52 (± 6.29) | 30.07 (± 6.38) | <0.0001 | 31.06 (± 6.11) | 0.11 | 30.11 (± 6.44) | 0.004 | 27.70 (± 6.54) | <0.0001 |
| DM duration (years) | 13.55 (± 8.14) | 12.85 (± 7.81) | 18.81 (± 8.61) | <0.0001 | 13.47 (± 7.77) | 0.128 | 19.40 (± 8.32) | <0.0001 | 19.59 (± 8.26) | <0.0001 |

*P value is the difference between non-nephropathic patients and microalbuminuria, macroalbuminuria, and ESRD patients. Frequency analysis was adjusted according to the data availability.

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Table 2. Frequency analysis of the selected cohort according to the Nephropathy type.

| Variables | Selected sample | | No Nephropathy | | Diabetic Nephropathy | | Classification according to diabetic nephropathy status | | | | | | | | | |
|-----------------------------|-----------------|---------------|----------------|------------|----------------------|------------|---|------------|-------------|-------------------------|------------|----------|------------|------------|----------|--|
| | Total (54670) | Number (%) | Total (48758) | Number (%) | Total (5912) | Number (%) | Microalbuminuria (676) | Number (%) | P value* | Macroalbuminuria (4412) | Number (%) | P value* | ESRD (824) | Number (%) | P value* | |
| Age | | | | | | | | | | | | | | | | |
| 25–44 years | 5765 (10.5%) | 5440 (11.2%) | 325 (5.5%) | <0.0001 | 49 (12.3%) | 0.455 | 123 (4.7%) | <0.0001 | 21 (4.3%) | <0.0001 | | | | | | |
| 45–64 years | 28548 (52.2%) | 25988 (53.3%) | 2560 (43.3%) | <0.0001 | 238 (59.9%) | 0.008 | 1088 (42%) | <0.0001 | 210 (43.4%) | <0.0001 | | | | | | |
| ≥65 years | 20357 (37.2%) | 17330 (35.5%) | 3027 (51.2%) | <0.0001 | 110 (27.7%) | <0.0001 | 1379 (53.2%) | <0.0001 | 253 (52.3%) | 0.001 | | | | | | |
| Gender | | | | | | | | | | | | | | | | |
| Male | 30342 (55.5%) | 26824 (55%) | 3518 (59.5%) | <0.0001 | 206 (51.9%) | 0.213 | 1559 (60.2%) | <0.0001 | 311 (64.3%) | <0.0001 | | | | | | |
| Female | 24328 (44.5%) | 21934 (45%) | 2394 (40.5%) | <0.0001 | 191 (48.1%) | 0.213 | 1031 (39.8%) | <0.0001 | 173 (35.7%) | <0.0001 | | | | | | |
| Marital Status | | | | | | | | | | | | | | | | |
| Single | 1069 (2%) | 985 (2.1%) | 84 (1.5%) | 0.001 | 5 (1.3%) | 0.284 | 30 (1.2%) | 0.002 | 15 (3.2%) | 0.084 | | | | | | |
| Married | 48755 (91.6%) | 43505 (91.6%) | 5250 (90.9%) | 0.053 | 352 (91.2%) | 0.75 | 2289 (89.8%) | 0.001 | 421 (90.5%) | 0.392 | | | | | | |
| Divorced | 600 (1.1%) | 532(1.1%) | 68 (1.2%) | 0.7 | 5 (1.3%) | 0.746 | 38 (1.5%) | 0.086 | 3 (0.6%) | 0.331 | | | | | | |
| Widow | 2825 (5.3%) | 2451 (5.2%) | 374 (6.5%) | <0.0001 | 24 (6.2%) | 0.351 | 191 (7.5%) | <0.0001 | 26 (5.6%) | 0.678 | | | | | | |
| Family history of DM | | | | | | | | | | | | | | | | |
| Yes | 14008 (36.8%) | 11975 (35.8%) | 2033 (43.9%) | <0.0001 | 160 (49.4%) | <0.0001 | 1027 (45.1%) | <0.0001 | 113 (36.5%) | 0.866 | | | | | | |
| No | 4366 (10.6%) | 3796 (10.4%) | 647 (10.9%) | 0.001 | 64 (9.5%) | 0.645 | 468 (10.6%) | 0.734 | 115 (13.9%) | 0.029 | | | | | | |
| Smoking | | | | | | | | | | | | | | | | |
| Yes | 6075 (18%) | 5184 (17.7%) | 891 (20.4%) | <0.0001 | 46 (13.8%) | 0.067 | 441 (20%) | 0.006 | 86 (35.7%) | <0.0001 | | | | | | |
| No | 11399 (33.8%) | 9913 (33.7%) | 1486 (34%) | 0.721 | 106 (31.8%) | 0.457 | 752 (34.1%) | 0.782 | 77 (32%) | 0.552 | | | | | | |
| BMI | | | | | | | | | | | | | | | | |
| ≤25 kg/m ² | 16246 (48.2%) | 14258 (48.6%) | 1988 (45.5%) | <0.0001 | 181 (54.4%) | 0.036 | 1015 (45.9%) | 0.018 | 78 (32.3%) | <0.0001 | | | | | | |
| 25–29.9 kg/m ² | 10387 (19.1%) | 7928 (16.3%) | 2459 (42.4%) | 0.001 | 94 (24%) | <0.0001 | 1244 (48.3%) | <0.0001 | 169 (36.7%) | <0.0001 | | | | | | |
| ≥30 kg/m ² | 9749 (19.4%) | 7011 (15.7%) | 2738 (48.8%) | <0.0001 | 91 (23.8%) | <0.0001 | 1518 (60.1%) | <0.0001 | 188 (41%) | <0.0001 | | | | | | |
| Neuropathy | | | | | | | | | | | | | | | | |
| Yes | 10110 (18.5%) | 7972 (16.4%) | 2138 (36.6%) | <0.0001 | 55 (13.9%) | 0.169 | 756 (29.2%) | <0.0001 | 244 (50.4%) | <0.0001 | | | | | | |
| No | 28026 (51.4%) | 23541 (48.4%) | 4485 (76.2%) | <0.0001 | 275 (69.4%) | <0.0001 | 1821 (70.7%) | <0.0001 | 443 (91.7%) | <0.0001 | | | | | | |
| Retinopathy | | | | | | | | | | | | | | | | |
| Yes | 20789 (38.2%) | 17989 (37.0%) | 2800 (48.0%) | <0.0001 | 264 (66.7%) | <0.0001 | 1077 (42.1%) | <0.0001 | 189 (40.9%) | 0.084 | | | | | | |
| No | 6098 (11.2%) | 4983 (10.2%) | 1115 (18.9%) | <0.0001 | 27 (6.8%) | 0.025 | 504 (19.5%) | <0.0001 | 78 (16.1%) | <0.0001 | | | | | | |
| Vasculopathy | | | | | | | | | | | | | | | | |
| Yes | 2,253 (15.1%) | 1,167(9.3%) | 935 (60.6%) | <0.0001 | 132 (61.1%) | <0.0001 | 284 (59.5%) | <0.0001 | 35 (63.6%) | 0.0001 | | | | | | |

*P value is the difference between non-nephropathic patients and microalbuminuria, and macroalbuminuria, and ESRD patients. Frequency analysis was adjusted according to the data availability. doi:10.1371/journal.pone.0088956.t002

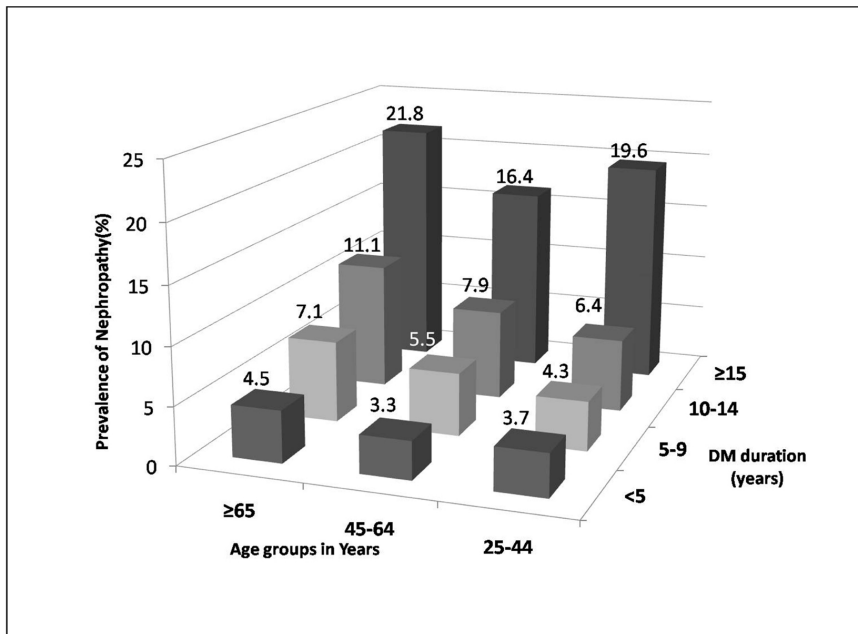


Figure 2. Three dimensional figure for prevalence of diabetic nephropathy according to age and diabetes duration grouping. Nephropathy prevalence calculated per group according to age in relation to the five years duration for the total of 54,670 patients. doi:10.1371/journal.pone.0088956.g002

Extremes of BMI of ≤ 25 and ≥ 30 kg/m² had significant differences in the total nephropathic patients, when compared with non-nephropathic patients. The percentage was higher in patients with microalbuminuria in ≥ 30 kg/m² BMI patients at 54.4%, and was significantly higher in the two extremes of BMI in macroalbuminuria at 20% for BMI ≤ 25 and 45.9% for BMI ≥ 30 . This was the same for ESRD patients, where 35.7% for BMI ≤ 25 and 32.3% for BMI ≥ 30 .

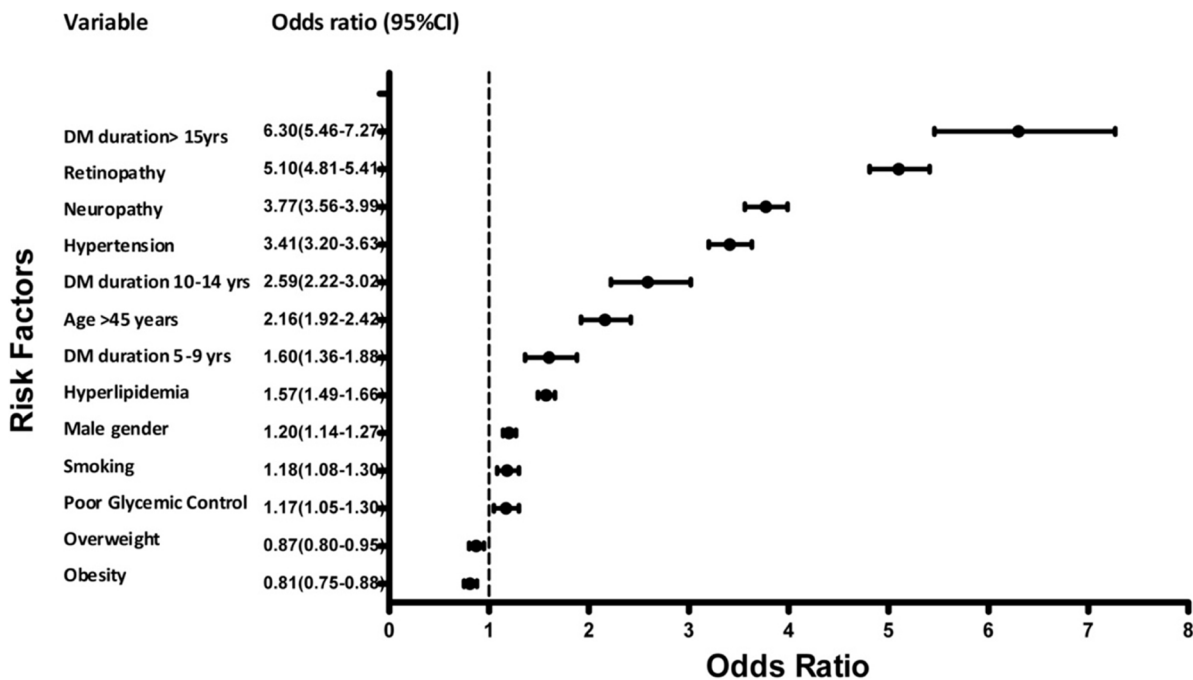
Prevalence of neuropathy was significantly higher in nephropathic patients as a whole, accounting for 42.4% and each type, namely microalbuminuria, macroalbuminuria, and ESRD 24%, 48.3%, and 36.7%, ($p = 0.001$, < 0.0001 , < 0.0001 , < 0.0001) respectively. Retinopathy prevalence was significantly higher among nephropathic patients 48.8% and 23.8%, 60.1% and 41% for microalbuminuria, macroalbuminuria, and ESRD respectively, ($p < 0.0001$).

Vasculopathy as ischemic heart disease, cerebrovascular disease or peripheral vascular disease was found in 36.6% of nephropathic patients, and was significantly higher in macroalbuminuria, ($p < 0.0001$) and ESRD but not in microalbuminuria. Hypertension prevalence was significantly higher among microalbuminuria, macroalbuminuria and ESRD patients, accounting for 69.4%, 70.7% and 91.7%, ($p < 0.0001$) respectively, with an overall prevalence of 76.2%. Hyperlipidemia prevalence was 48.0% in patients with nephropathy, and significantly higher in microalbuminuria and macroalbuminuria patients 66.75 and 42.1%, ($p < 0.0001$) respectively, but not in patients with an ESRD of 40.9%. 18.9% of patients with nephropathy were using insulin, which is significantly higher than non-nephropathic patients, ($p < 0.0001$). This was true for macroalbuminuria, and ESRD 19.5%, and 16.1%, but significantly lower in patients with microalbuminuria 6.8%. Poor glycemic control, represented by the percentage of patients with HbA1c $> 8\%$, showed a significantly higher percentages in nephropathic patients, microalbuminuria, macroalbuminuria and ESRD, representing 60.6%, 61.1%, 59.5% and 63.6% respectively with p value < 0.0001 .

Figure 2 shows the correlation between patients' age groups and diabetes duration in relation to the prevalence of diabetic nephropathy. The prevalence of nephropathy multiplied with increase in age and diabetes duration. The lowest prevalence was in 25–44 and 45–64 years age groups, with diabetes duration < 5 years represented by 3.7% and 3.3% respectively, while the highest was with duration ≥ 15 years in age groups 25–44, 45–64 and ≥ 65 years, amounting to 19.6%, 16.4% and 21.8%.

Figure 3 is the forest plot for odds ratio (OR) and relative (RR) risk for diabetic nephropathy risk factors in the studied sample. Diabetes duration was the most significant risk with OR (95%CI) being 6.30 (5.46–7.27), 2.59 (2.22–3.02) and 1.60 (1.36–1.88) for the duration ≥ 15 , 10–14, and 5–9 years. Retinopathy and neuropathy were the second and third significant risk factors with OR (95%CI) of 5.10 (4.81–5.41) and 3.77 (3.56–3.99) respectively. Patients aged > 45 years had an OR (95%CI) of 2.16 (1.92–2.42) followed by hyperlipidemia, male gender, and smoking, with OR (95%CI) 1.57 (1.49–1.66), 1.20 (1.14–1.27) and 1.18 (1.08–1.30) respectively. Poor glycemic control had the lowest but significant OR (95%CI) of 1.17 (1.05–1.30). Overweight and obesity showed significant protective risk for diabetic nephropathy, with OR (95%CI) 0.87 (0.80–0.95) and 0.81 (0.75–0.88) respectively.

Table 3 demonstrates OR and RR for risk factors related to the different types of diabetic nephropathy. In patients with microalbuminuria OR (95% CI) was the highest, with hyperlipidemia mounting for 3.4 (2.76–4.20) followed by hypertension mounting for 2.42 (2.0–3.0). Retinopathy and neuropathy had OR of 1.67 (1.32–2.11) and 1.62 (1.29–2.05) respectively. Obesity had a significant OR of 1.43 (1.03–1.98), but diabetes duration did not show any significant risk for microalbuminuria, which was also true for age > 45 years, male gender, smoking, poor glycemic control, and overweight. Significant risk factors seen with macroalbuminuria were diabetes duration ≥ 15 years with OR (95% CI) of 8.00 (6.38–10.05) and presence of retinopathy followed by neuropathy with OR (95% CI) of 8.07 (7.43–8.78) and 4.48 (4.42–5.20). Hypertension, age > 45 years, and hyperlipide-



| Risk factors | Odds Ratio | Relative Risk | p-value |
|------------------------|------------------|------------------|---------|
| DM Duration: ≥15 yrs* | 6.30 (5.46-7.27) | 5.28 (4.61-6.05) | <0.0001 |
| Retinopathy | 5.10 (4.81-5.41) | 3.95 (3.77-4.14) | <0.0001 |
| Neuropathy | 3.77 (3.56-3.99) | 3.12 (2.97-3.27) | <0.0001 |
| Hypertension | 3.41 (3.20-3.63) | 3.02 (2.86-3.20) | <0.0001 |
| DM Duration: 10-14yrs* | 2.59 (2.22-3.02) | 2.45 (2.11-2.83) | <0.0001 |
| Age > 45 years | 2.16 (1.92-2.42) | 2.03 (1.82-2.26) | <0.0001 |
| DM Duration: 5-9yrs* | 1.60 (1.36-1.88) | 1.57 (1.34-1.82) | <0.0001 |
| Hyperlipidemia | 1.57 (1.49-1.66) | 1.50 (1.43-1.57) | <0.0001 |
| Male gender | 1.20 (1.14-1.27) | 1.18 (1.12-1.24) | <0.0001 |
| Smoking | 1.18 (1.08-1.30) | 1.16 (1.07-1.26) | 0.001 |
| Poor glycemic control | 1.17 (1.05-1.30) | 1.15 (1.04-1.26) | 0.005 |
| Overweight | 0.87 (0.80-0.95) | 0.89 (0.82-0.96) | 0.003 |
| Obesity | 0.81 (0.75-0.88) | 0.83 (0.78-0.90) | <0.0001 |

*Related to diabetes duration <5 years.

Figure 3. Forest plot for odds ratio & 95% confidence interval for diabetic nephropathy risk. * Related to diabetes duration <5 years. doi:10.1371/journal.pone.0088956.g003

mia had OR (95% CI) of 2.57 (2.36–2.80), 2.52 (2.10–3.03) and 1.24 (1.14–1.34) respectively for macroalbuminuria. While male gender showed a significantly low OR (95% CI) of 0.73 (0.68–0.79). Microalbuminuria and macroalbuminuria had no significant OR or RR for smoking, poor glycemic control and overweight, but this was not the case for obesity, which had an increased OR (95% CI) and RR (95% CI) of 1.43 (1.03–1.98) and 1.43 (1.03–1.97) respectively for microalbuminuria and a decreased OR (95% CI) of 0.84 (0.75–0.94) and RR of 0.85 (0.76–0.94). Both overweight and obesity had significant reduced risk for ESRD, while smoking had a significant increased risk with OR (95% CI) and RR (95% CI) of 1.41 (1.03–1.92) and 1.41 (1.03–1.92), but non-significant increase for poor glycemic control.

In patients with ESRD, diabetes duration of ≥15 years had the highest significant OR (95% CI) of 12.77 (6.32–25.81), followed by the presence of hypertension with OR (95% CI) of 11.81 (8.54–16.32). Retinopathy, neuropathy and age >45 years were significant risk factors with OR (95% CI) of 3.73 (3.09–4.50),

2.97 (2.45–3.60) and 2.77 (1.79–4.29) respectively. Male gender and Smoking were the least risk factors, although still significant, with an OR (95% CI) of 1.47 (1.22–1.77) and 1.41 (1.03–1.92). Poor glycemic control was not a significant risk factor, while both overweight and obesity had significant low risk in ESRD with OR (95% CI) of 0.47 (0.34–0.64) and 0.33 (0.24–0.45) respectively.

Discussion

The study sample used in this study represents the known age and gender distribution seen in Saudi society [5]. The overall prevalence of diabetic nephropathy among type 2 diabetic patients older than 25 years in the SNDR was 10.8%, which is similar to what has been reported by the UK primary care initiative 11.5% [7]. A similar cohort of type 2 diabetic patients reported by Mohan et al. [12] from India in the year 2000 showed a macroalbuminuria prevalence of 6.9%, which is less than reported in this study, and microalbuminuria of 2.5%, which is more than reported here. These findings are less than expected, as proven by different

Table 3. Multiple logistic regression analysis of risk factors for different type of nephropathy.

| Risk factors | Microalbuminuria | | | Macroalbuminuria | | | ESRD | | |
|------------------------------|---------------------|---------------------|---------|----------------------|---------------------|---------|-----------------------|-----------------------|---------|
| | OR (95%CI) | RR (95%CI) | p-value | OR (95%CI) | RR (95%CI) | p-value | OR (95%CI) | RR (95%CI) | p-value |
| Duration ≥15 years* | 1.38 (0.97–1.96) | 1.37 (0.97–1.95) | 0.077 | 8.00 (6.38–10.05) | 7.28 (5.82–9.10) | <0.0001 | 12.77 (6.32–25.81) | 12.56 (6.22–25.34) | <0.0001 |
| Retinopathy | 1.67 (1.32–2.11) | 1.66 (1.31–2.10) | <0.0001 | 8.07 (7.43–8.78) | 6.81 (6.31–7.35) | <0.0001 | 3.73 (3.09–4.50) | 3.65 (3.04–4.39) | <0.0001 |
| Neuropathy | 1.62 (1.29–2.05) | 1.62 (1.28–2.04) | <0.0001 | 4.48 (4.42–5.20) | 4.28 (3.98–4.61) | <0.0001 | 2.97 (2.45–3.60) | 2.93 (2.43–3.54) | <0.0001 |
| Hypertension | 2.42 (2.0–3.0) | 2.4 (1.94–2.98) | <0.0001 | 2.57 (2.36–2.80) | 2.46 (2.26–2.67) | <0.0001 | 11.81 (8.54–16.32) | 11.61 (8.40–16.03) | <0.0001 |
| Duration 10–14 years* | 1.22 (0.84–1.79) | 1.22 (0.84–1.78) | 0.301 | 3.05 (2.40–3.89) | 2.96 (2.34–3.76) | <0.0001 | 4.22 (2.02–8.83) | 4.20 (2.01–8.78) | <0.0001 |
| Age >45 years | 0.89 (0.66–1.20) | 0.89 (0.66–1.20) | 0.455 | 2.52 (2.10–3.03) | 2.44 (2.04–2.91) | <0.0001 | 2.77 (1.79–4.29) | 2.75 (1.78–4.26) | <0.0001 |
| Duration 5–9 years* | 1.27 (0.87–1.84) | 1.26 (0.87–1.84) | 0.216 | 1.51 (1.16–1.95) | 1.50 (1.16–1.93) | 0.002 | 3.06 (1.44–6.48) | 3.05 (1.44–6.45) | 0.002 |
| Hyperlipidemia | 3.4 (2.76–4.20) | 3.37 (2.74–4.15) | <0.0001 | 1.24 (1.14–1.34) | 1.22 (1.13–1.32) | <0.0001 | 1.17 (0.97–1.41) | 1.10 (0.99–1.23) | 0.095 |
| Male gender | 0.88 (0.72–1.08) | 0.88 (0.73–1.07) | 0.213 | 0.73 (0.68–0.79) | 0.75 (0.70–0.80) | <0.0001 | 1.47 (1.22–1.77) | 1.47 (1.22–1.76) | <0.0001 |
| Smoking | 0.91 (0.61–1.36) | 0.91 (0.61–1.35) | 0.645 | 1.02 (0.89–1.18) | 1.02 (0.90–1.17) | 0.734 | 1.41 (1.03–1.92) | 1.41 (1.03–1.91) | 0.029 |
| Poor glycemic control | 1.19 (0.90–1.57) | 1.19 (0.91–1.56) | 0.214 | 1.12 (0.93–1.34) | 1.11 (0.93–1.33) | 0.251 | 1.33 (0.77–2.30) | 1.33 (0.77–2.29) | 0.313 |
| Overweight | 1.21 (0.85–1.71) | 1.20 (0.85–1.70) | 0.292 | 0.89 (0.79–1.01) | 0.90 (0.80–1.01) | 0.066 | 0.47 (0.34–0.64) | 0.47 (0.35–0.64) | <0.0001 |
| Obesity | 1.43 (1.03–1.98) | 1.43 (1.03–1.97) | 0.03 | 0.84 (0.75–0.94) | 0.85 (0.76–0.94) | 0.003 | 0.33 (0.24–0.45) | 0.33 (0.25–0.45) | <0.0001 |

*Related to diabetes duration <5 years.
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studies from the United States and India in the years 1993 and 2004, where microalbuminuria and macroalbuminuria were reported to be (25.9% and 32.1%) and (17.6% and 2.2%) respectively [13,14].

This is true in the Saudi cross sectional hospital based study, where microalbuminuria was reported to be 41.3% in 1994 [15]. The low percentage of microalbuminuria and macroalbuminuria reported by SNDR patients resulted from a lack of screening programs in most health institutions, which is not the case in ESRD cases that do not need screening, but usually discovered because of the acute presentation and clinical symptoms.

Saudi men with type 2 diabetes have a higher prevalence of diabetes nephropathy, as has been observed by similar studies in different communities [16,17]. This may be explained by the fact that the estrogen hormone plays an important role in protection [18].

In this study, men have a higher risk of ESRD, which differs from what has been found by the Denmark and Korean studies. This may be explained by the lower number of male patients [16,19].

The prevalence of ESRD in this cohort is three times that reported by the Thailand Diabetes Registry, where it was 0.47% [8]. This may be explained by the high percentage of poor glycemic control, retinopathy and hypertension, in addition to the longer duration of diabetes among the SNDR cohort. This study reports on the age effects of both microalbuminuria and macroalbuminuria, which are similar to the CURES study in India [14].

In comparing this registry with similar registries, BMI was found to be higher among Saudi diabetic nephropathy patients than has been reported in Danish people [16], due to the high prevalence of obesity and being overweight among the Saudi population [20].

There is a strong correlation between age and diabetes duration, as seen in other published data [14,21]. We report for the first time the accumulative effect of both age and duration on the prevalence of diabetic nephropathy, where it increases by about five times in patients with diabetes duration ≥ 15 years, regardless of the patient's age.

The forest plot shows diabetes duration to be the most important risk factor, especially ≥ 15 years. This was the same finding in different ethnic groups, as shown in Korean, Indian and Taiwanese studies [19,21,6]. In the Saudi population, the hazard ratio for diabetes nephropathy was found to be 2.3 with a duration >10 years [11]. The role of diabetes duration has been proven by the UKPDS, where approximately one quarter of patients, developed microalbuminuria or worsening nephropathy after ten years [22].

Diabetic retinopathy is a known risk factor for diabetic nephropathy in different ethnic populations, as reported in Taiwanese and Danish studies [6,16]. Since diabetic neuropathy has been found by the UKPDS to be a risk factor for renal insufficiency or microalbuminuria and macroalbuminuria [23], this study moves in the same direction, proving that neuropathy has a higher OR and RR. Hypertension presents a significant risk for nephropathy in general, and with each type of diabetic nephropathy, which was also observed by another Saudi study [11]. Age

alone has been found to be an important risk factor, which is the same observation in this study, but not for microalbuminuria patients [16,17].

The RENAAL study showed that dyslipidemia was associated with greater hazards in the development of a renal end point [24], and high cholesterol, LDL and triglyceride has been proven to be a risk for diabetic nephropathy by many studies [17,23]. This is also true in this study, with significantly increased OR and RR when looking at hyperlipidemic patients, but was not significant for ESRD cases. Male gender is a known risk factor in many studies, which is true in this study but not for microalbuminuric subjects, which could be explained by underestimation due to underscreening [16,17]. This study has a lower OR and RR for smoking than reported by other studies [17,19,25] due to low smoking prevalence among Saudi women [26].

The role of strict control on the progression of diabetic nephropathy is not firmly established [27], although poor glycemic control is a recognized cause of diabetic nephropathy [6,27,28]. In agreement with a number of previous studies, we also demonstrate that poor glycemic control is associated with diabetic nephropathy [29].

We have identified being overweight or obesity as a strong and potentially modifiable risk factor for the development of ESRD, which was the same observation as seen in other studies [30].

Our observation shows that Obesity seems to be an important - and potentially preventable- risk factor for ESRD that may be explained by weight loss among case patients, as a consequence of morbidity related to renal failure itself, as also seen by another study [31].

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