Initial Recognition and Prophecy of Diabetic Nephropathy in Type I Diabetes in a Sample of Iraqi Patients

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Abstract

Back ground: Diabetic nephropathy is rapidly becoming the leading cause of end-stage renal disease (ESRD). The onset and course of DN can be ameliorated to a very significant degree if intervention institutes at a point very early in the course of the development of this complication.

Objective: The aim of this study was to characterize risk factors associated with nephropathy in type I diabetes and construct a module for early prediction of diabetic nephropathy (DN) by analyzing their risk factors.

Methods: Case control design of 400 patients with type I diabetes mellitus (IDDM), aged 19-45 years. The cases were 200 diabetic patients with overt protein urea while the controls were 200 diabetic patients with no protein urea or micro-albumin urea.

Results: concurrent occurrence of retinopathy and nephropathy was the main predictors for nephropathy in type I DM patients. Disease duration more than 10 years, uncontrolled hyperglycemia, age more than 30 years and presence of hypertension were the other predictors respectively. Gender and hypercholestremia showed no predictive value in occurrence of DN.

Key words: diabetic nephropathy, diabetes mellitus, case control

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Introduction

Diabetes mellitus is a global health problem, affecting all age groups. Currently, around 177 million people have diabetes worldwide; however, it has been projected that this number will increase to at least 300 million by 2025 [1].

With an overall prevalence of over 10% among the adult population of Iraq, diabetes mellitus (DM) has become a serious health problem for Iraqis. [2] In the year 2000, death from diabetes-associated complications accounted for approximately 6% of worldwide mortality. [3] Type 1 diabetes accounts for 5% to 10% of all cases of diabetes. Its risk factors include autoimmune, genetic, and environmental factors. To date, there are no known ways to prevent type 1 diabetes [4].

Diabetes mellitus is now approaching epidemic proportions. [5].

Diabetic Nephropathy (DN) is the major life-threatening complication of DM and occurs in 20-40% of the patients. Diabetic nephropathy is the leading cause of end-stage renal disease and kidney disease in patients starting renal replacement therapy. It increases the risk of death, mainly from cardiovascular causes, and is defined by increased urinary albumin excretion (UAE) in the absence of other renal diseases. Diabetic nephropathy is categorized into stages: microalbuminuria (UAE >20 μg/min and ≤199 μg/min) and macroalbuminuria (UAE ≥200 μg/min). Hyperglycemia, increased blood pressure levels, and genetic predisposition are the main risk factors for the development of diabetic nephropathy. [6] Elevated serum lipids, smoking habits, and the amount and origin of dietary protein also seem to play a role as risk factors. Screening for microalbuminuria should be performed yearly, starting 5 years after diagnosis in type 1 diabetes or earlier in the presence of puberty or poor metabolic control. The prevalence of diabetic nephropathy is expected to rise in future as the incidence of diabetes increases and the age of onset declines [7]. Once in the advanced stages of diabetic nephropathy, patients are at high risk of cardiovascular death as well as renal failure [8].

Diabetic nephropathy is defined as persistent proteinuria (more than 500 mg of protein or 300 mg of albumin per 24 hours) in patients without urinary tract infection or other diseases causing the proteinuria. In patients with type 1 diabetes, development of clinical nephropathy is a relatively late event; as the diagnosis of diabetes occurs early in life[9] Thus far, the earliest clinical evidence of diabetic nephropathy is the appearance of low but

abnormal levels of albumin in the urine, referred to incipient nephropathy (albuminuria ⩾30 mg/24 h or ⩾20 μg/min). These levels of microalbuminuria, when sustained, may lead to overt nephropathy and consequently to ESRD. [10]

The incidence of DN increases linearly during the first 20 years after diagnosis of diabetes, but starts to decline thereafter. [11] Suggesting that there may be a subset of diabetic patients at an especially high risk for DN. Not all patients with poor glycemic control develop DN during their lifetimes. The observed incidence patterns suggest that genetic factors linked to a predisposition for DN play an important role in the regulating processes that lead to DN.

The etiology of diabetic nephropathy is poorly understood. Several risk factors are involved, some of which are modifiable and others are not. Metabolic regulation is one of the key modifiable risk factors for development of diabetic nephropathy. Strict metabolic control leads to a significant reduction in the risk of developing microalbinuria and the risk of progression to persistent proteinuria.(12)

The impact of strict metabolic control on prognosis is most pronounced in patients with normal levels of albumin in the urine and patients with microalbuminuria. Increasing blood pressure and hypertension also are associated with an increased risk of progression of diabetic renal disease. (13) However, it is still unclear whether blood pressure at diabetic onset predicts later development of diabetic nephropathy. Other risk factors, including cigarette smoking, obesity, anemia, and genetic factors, also have been suggested. [14]

Snieder et al. [15] have shown in a recent twin study that HbA_{1c} levels are genetically determined; additive genetic effects explained 62% of the population variance of HbA_{1c}, with the remaining effects being influenced by a unique environmental effect and age. Genes associated with HbA_{1c} may play a role in a background of DN predisposition. On the other hand, observations that some patients with relatively good glycemic control may develop DN and some patients with poor glycemic control do not [16], support the hypothesis that additional factors unrelated to glycemia must be operating in the development of DN. [17]

This study aims to predict DN in type 1 DM. we chose type I DM as many of patients with type II diabetes may already have microalbuminuria at the time they are diagnosed with diabetes.

Methods

In this retrospective, observational study, patients with type I diabetes presenting for routine follow-up care were recruited from those attending the Specialized Center for Endocrinology & Diabetes and the National Center for Treatment & Research of Diabetes in Al-Mustanseria College of Medicine-Baghdad during the period from September 2008 to December 2009. Consecutively, with an aim of including 400 subjects (200cases and 200 controls) as below equation.

$$\textbf{Sample size n (each group) was calculated as} = \frac{(p_0q_0 + p_1q_1)\,(z_{1-a/2} + z_{1-b})^2}{(p_1-p_0)^2}$$

p0=Proportion of controls with risk factors = 0.10

p1=Proportion of cases with risk factors = 0.20

q0=1-p0 = 1.0 - 0.10 = 0.90

q1=1-p1 = 1.0 - 0.20 = 0.80

z(1- /2) = 1.96 Value of the standard normal distribution corresponding to a significance level of (0.05, 2 sided)

z(1-) = 0.84 Value of the standard normal distribution corresponding to the desired level of power (80%)

The study was approved by the scientific committee of Al Kindy College of Medicine and the authority of the center. All patients who agreed to participate in the study signed a written informed consent. Exclusion criteria included gestational diabetes, age < 15 years, inability to complete laboratory data and follow-up visits requested over three years. This paper describes and discusses the cross-sectional data at recruitment of this cohort

A convenient sample technique was used to enroll the 200 cases with newly diagnosed DN, overt proteinuria diagnosed by general urine

examination, who met the following inclusion criteria:

1- Patients with age of 15 to 45 years. (Classified as G1=15-29years, G2= 30-45years)

2- The duration of DM should be 5 years or more. .(classified as D1=5-10 D2=>10 years)

3- No past history of renal disease.

Patient considered to have overt proteinuria when urinary albumin rate equal or above 300 mg/24 hr in at least two out of three consecutive samples as recommended. (18)

A General urine examination (GUE) was done for each patient by collecting freshly voided urine sample to test the presence of protein. Proteinuria is the best indicator for DN, detection protein using a dipstick technique (Multistix 10, SG, Bayer, Bridgend, UK), to detect proteinuria (strip result of ³30 mg/dl), UTI, haematuria, and ketonuria.

The study adapted the following exclusion criteria:

1- Presence of Urinary tract infection (UTI).

3- Presence of Haematuria or Ketonuria.

4- Pregnancy in female patients.

5- Acute febrile illness.

Control participants were selected on the same inclusion criteria besides no macro or micro albuminuria(MA) . Micro albuminuria remains the best available marker for DN risk as majority of patient with MA, progress to proteinuria years later .

Micro-albominuria was assessed (and patient excluded from control group) by Micral Test II (Roche diagnostic GmbL, Mannheim, Germany) which is an immunological strip, highly sensitive and specific, gold labeled, optically read test for the immunological, semi-quantitative in vitro determination of urinary albumin from 0 up to concentration of 100 mg/L. Micro-albominuria was considered to be present if urinary albumin excretion rate (AER) in spot (first morning urine sample) was 20-199 mg/l.

Controlled hyperglycemia (HG) assessment was done by HbA_1C % level estimation. HbA_1C % level is used as proxy measure of long term glycemic control in all researches of people with diabetes. Patients with HbA1C % level less than 6.5% were considered have controlled HG (classified as R1) while those with 6.5% or more were considered as uncontrolled (classified as R2) (14).

Patients were considered hypertensive if already diagnosed and receiving antihypertensive medications (classified as HT2).Patients with no such a history were considered not hypertensive(classified as HT1)

Patients with cholesterol ≥ 250 mg/dL were considered as hypercholesterolaemic (classified as (CHOL 2). Normocholestremia was considered in patient with serum cholesterol less than 250 mg/dL (classified as (CHOL 1) (14)

To assess the presence of diabetic microvascular complications, patients with well established complication were denoted for these complications. Neuropathy was assessed by neurologist through history of symptoms provided by the patient and physical examination with evidence of bilateral decreased pressure sensation by monofilament test; (19). Retinopathy was based on a dilated eye examination by a retinal specialist; moderate to severe non proliferative or proliferative retinopathies were included and considered to have this complication(20)

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Patient with no complication C1, Patient have one of the above complication C2

Data were entered and analyzed by MINI TAB software version 14. Chi square test was used to estimate the association between predictors and outcomes. Logistic regression models were conducted in the derivation data set to predict each complication Coefficients for significant predictors were applied to predictor values of the validation data set members. Risk scores for each factor were calculated by summing coefficients across all predictors. Coefficient finds the degree of association of each predictor while keeping other constant

Results

The general characteristics of patients at recruitment to the study are shown on table 1.

Table 1. Characteristics of study subjects with type 1 diabetes (n=400)

Characteristic	Cases	Controls	P value
No. of participants	200	200	-
Age G1/G2 ratio	0.13	0.96	0.000
Female /male ratio	0.94	1.08	0.484
Duration D1/D2 ratio	0.49	2.45	0.000
Dm control R1/R2 ratio	0.34	1.08	0.000
BP Ht1 / Ht2 ratio	1.53	7.00	0.015
Bl cholest chol1/chol2 ratio	1.53	2.45	0.027
Other complication C1/C2 ratio	0.15	5.25	0.000

Logistic regression analysis (tab2) shows that the presence of other complications (retinopathy and neuropathy) has the highest prediction coefficient (5.32, OR=25.81, p=0.000). This means diabetic patient with retinopathy or neuropathy have 25.81 times risk to develop nephropathy than patient without such complications after keeping other factors constant.

Duration of the disease was the second predictor (coeff=3.00, OR= 4.74, p=0.000) which indicates 4.74 times risk for DN as the duration of DM exceeds 10 years while other factors are controlled .

The third predictor was uncontrolled hyperglycemia (coeff=2.40, OR= 3.09, p=0.000). Diabetic patients who had failed to maintain their blood glucose in the near normal level and their HbA1C % was 6.5 or more had 3 times probability to develop DN than those with HbA1C % less than 6.5 after keeping other factors constant.

Age and hypertension were the next predictors with roughly the same effect (coeff=1.88, OR= 2.40, p= 0.000 for age and coeff=1.84, OR= 2.32, p=0.008 for hypertension respectively). This revealed that 30 or more years old DM patients or patient with HT had about 2.40 to 2.32time to develop DN than DM patients less than 30 years old or normotensive patients.

Sex and hypercholestremia showed no significant association with DN development (coeff=-o,58, OR= 0.56, p= 0.152 for sex and coeff=0.49, OR= 0.61, p=0.311 for hypercholestremia respectively).

In prediction of DN, the logistic regression module is: $\ln(P/(1-P)) = b_0+b_1X_1+b_2X_2+. . .$, and to estimate the probability of DN development for any type I DM patient with any of above predictors (risk factors) while controlling the others, the equation would be: ln(P(DN)/(1-P(DN)) = 8.33+5.32*Other complic+ 3*Duration + 2.4*control + 1.88 Age +1.84*HT

Table 2 Logistic Regression Table

					Odds	95% CI	
Predictor	**Coef**	**SE Coef**	**Z**	**P**	**Ratio**	**Lower**	**Upper**
Constant	**8.33**	**1.70**	**5.25**	**0.000**			
Other co	**5.32**	**0.56**	**9.46**	**0.000**	**25.81**	**15.19**	**43.85**
Duration	**3.00**	**0.58**	**5.15**	**0.000**	**4.74**	**3.11**	**7.23**
Control	**2.40**	**0.52**	**4.59**	**0.000**	**3.09**	**1.03**	**10.25**
Age	**1.88**	**0.52**	**3.56**	**0.000**	**2.40**	**0.59**	**9.35**
Hyperten	**1.84**	**0.50**	**3.76**	**0.008**	**2.32**	**0.91**	**6.45**
Hypercho	**0.49**	**0.48**	**1.01**	**0.311**	**0.61**	**0.24**	**1.58**
Sex	**-0.58**	**0.40**	**-1.43**	**0.152**	**0.56**	**0.25**	**1.24**

Discussion

An important health concept is that the best results are obtained when the complications are treated at the very early stages of the disease. It is therefore crucial to develop early markers able to identify patients at high risk of developing any microvascular complication in diabetes. The availability of early markers/predictors would allow high-risk patients to be intensively treated with currently available therapies as well as with new agents.

For a predictor of DN to be optimally useful, it should identify individuals at increased risk for the development of serious diabetic renal disease early enough in the natural history of the disorder that the evolution of the process can be influenced by intervention strategies. (21)The major determinants of progression to incipient or overt diabetic nephropathy were, identified as minimal increase of urinary albumin excretion within the normal range, presence of microvascular complication (retinopathy or neuropathy), poor long term glycaemic control, disease duration more than 10 years, older age, and hypertension. (22) . Although microalbuminuria has a predictive value for the risk of nephropathy, recent investigations suggest that it is not an inexorable process leading to overt proteinuria; only 10–30% of microalbuminuric patients develop macroalbuminuria during a long follow-up (23). The incidence of DN reached a peak around the age of 25–29 years for both sexes. (24).This study try to find other predictors for this important complication as the finding that some MA patients have only mild diabetic renal lesions is consistent with the lower than originally estimated risk of progression from MA to proteinuria and with the notion that some MA patients revert to normoalbuminuria.

In agreement, this study also found a strong association between DN and other chronic microvascular complications, retinopathy and neuropathy, the same result consistently reported in the literature**.** (25) Also, patients with DN frequently have neurological disturbances and, in fact, some investigators have suggested a causal role for autonomic neuropathy in the genesis of renal injury (26) and this is in agreement with our study.

The findings of the current study regarding the association of duration of the disease and development of diabetic nephropathy were also statistically significant. Our results suggest that disease duration was an important predictor of the development of DN especially among younger persons, since the long duration of disease and substantial changes in urinary albumin excretion are required to reduce ultra filtration capacity of the glomeruli. (27) The predictors of control for individual risk factors beyond age and sex were different for each individual factor.

Like other microvascular complications of diabetes, there are strong associations between glucose control (as measured by HbA1c) and the risk of developing diabetic nephropathy which is proportional to both the magnitude and duration of hyperglycemia (28).

In type 1 diabetes hyperglycemia starts in the first decades of life and is usually the only recognized cause of nephropathy among children and adolescents in particular. On the contrary, in type 2 diabetes hyperglycemia starts after the forties, usually when the kidneys have already suffered the long-term consequences of ageing and of other recognized promoters of chronic renal injury such as arterial hypertension, obesity, dyslipidaemia, and smoking, these risk factors may contribute to the specific changes of arteriolosclerotic type which is the typical feature of diabetic glomerulopathy in type 2 diabetes (29).

Individual differences in HbA1C of more than 2% will double the risk of developing microvascular complications (30). An increase in HBA1c over time was well described by Diabetes Control and Complications Trial (DCCT) and the United Kingdom Prospective Diabetes Study (UKPDS) have definitively shown that intensive diabetes therapy espcially glycemic control can significantly reduce the risk of the development of microalbuminuria and overt nephropathy in type 1 diabetes (31).

In the study by John et al glycaemic control did not appear as a risk factor, but only the fasting blood glucose concentration was measured(32) .Several but not all studies in insulin dependent diabetic patients have shown beneficial effects of long term strict glycaemic control on the start and progression of microalbuminuria.(33)

Similarly, increasing blood pressure and proteinuria are to be expected in patients with progressive diabetic nephropathy (34).

Some studies have shown that in type 1 diabetic patients with intermittent or persistent microalbuminuria seemed to have higher diastolic blood pressures (35). Therefore, it would appear that the blood pressure changes preceded the finding of persistent microalbuminuria, and this finding may help to identify type 1 diabetic children prone to nephropathy (36). There is benefit in reducing the progression of microalbuminuria in normotensive patients with type 1 diabetes (34).

The influence of the duration of diabetes on DN development was the strongest predictor, after exclusion of other DM complications. The results of our study, like many other reports, did not show an association between gender and the development of diabetic nephropathy. This contrasts with a previous finding by Holl et al., showing an impact of female gender on the development of insidious nephropathy(37).While other study shown that Male sex has been reported to be a risk factor for development of diabetic nephropathy(38)The factors involved in this sex-specific difference could possibly include lifestyle, diet, kidney and glomerular size, differences in glomerular hemodynamic, and direct effects of sex hormones .The different patterns of risk by sex suggest a role for puberty and sex hormones (39)

In the present study the concentration of serum cholesterol was associated with an increased risk of developing incipient or overt nephropathy. Nelson RG et al., showed that, High serum cholesterol also seems to be a risk factor for GFR loss in macroalbuminuric type 1 diabetic subjects (40).

In type 1 DM patients increased serum triglycerides, total and LDL-cholesterol were associated with micro- and macroalbuminuria(41).

In contrast previous study done in Serbia revealed that there is no association has been found between abnormal lipids and the development of MA in adolescents nor is the influence of increased lipid levels on progression of MA known(42).

As determinants of risk for diabetic nephropathy, including a family history of hypertension. In the study by Rudberg et al, a parental history of hypertension was associated with a four-fold risk for micro- or macroalbuminuria in the offspring. Likewise,Freire .Parents of patients with type 1 diabetes who develop nephropathy have higher arterial blood pressures than do parents of patients who have no nephropathy.(43,44) Moreover, parents of type 1 diabetic patients with nephropathy seem to have an increased incidence of cardiovascular disease as compared with parents of type 1 diabetic patients with normal albumin excretion. (45) Albuminuria, cardiovascular disease, and hypertension might be linked by an inherited predisposition to insulin resistance.

In type 1 diabetes with incipient nephropathy, defined by the presence of microalbuminuria, hypertension is not usually present. (46)

Hypertension was associated with DN as found in other studies (47) and this is in agreement with our study but as previously mentioned a family history was not, particularly in IDDM (48).

It is of interest that a family history of hypertension has been associated both with elevated systemic blood pressure and with increased glomerular filtration in recent-onset type 1 diabetic patients as well as in non-diabetic subjects (49).

Of these abnormalities, glomerular hyperfiltration may be more important in the initiation of renal damage, since hyperfiltration is a more powerful predictor of subsequent microalbuminuria or overt diabetic nephropathy than is the level of systemic blood pressure(50). However, at a later stage, the level of systemic blood pressure is strongly positively correlated with the rate of decline in renal function (51); such findings are consistent with our study which show that blood pressure was significantly higher in those who progressed to diabetic nephropathy.

Regarding the development of retinopathy, some studies revealed that several variables were found to exert significant independent influences on the development of such a complication in type 1DM patients: diabetes duration, long-term glycaemic control, serum triglycerides and age. (52)While in the present study patients who developed abnormally high urinary albumin excretion were significantly more likely to have retinal lesions at baseline than those who remained normoalbuminuric. A close relation

between the presence of diabetic retinopathy and risk of developing an abnormally high urinary albumin excretion rate has also been reported. In contrast, lack of retinopathy in type 2 diabetes does not preclude diabetic nephropathy, which remains the most likely diagnosis.(53).

Conclusion

From this study we concluded that several potentially modifiable risk factors, such as urinary albumin excretion rate, long term poor glycaemic control, high blood pressure and hypercholesterolaemia predict the development of diabetic nephropathy in type 1 diabetes mellitus.

Recommendation:

Patients with type 1 diabetes of > 5 years' duration should have annual screening for microalbuminuria, and all patients with diabetes should have serum creatinine measurement performed annually. With type 1 diabetes should receive a comprehensive eye examination and dilation within 3-5 years after the onset of diabetes.

Blood pressure should be measured routinely; Lipid testing should be performed in patients with diabetes at least annually. All patients with diabetes should be encouraged to limit consumption of saturated fat, Trans fat, and cholesterol.

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