

## Early Development of Overt Proteinuria in Extremely Uncontrolled Type 1 Diabetic Patients

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### ABSTRACT

**Introduction:** Overt proteinuria usually occurs in 15 to 40% of patients with type 1 diabetes, with a peak incidence around 15 to 20 years of diabetes. The aim of the study is to know the incidence of overt proteinuria in extremely uncontrolled type 1 diabetes with less than 10 years diabetes duration.

**Methods:** 50 patients (23 female and 27 male) with extremely uncontrolled type 1 diabetes (group A), attending the study with 22 good controlled type 1 diabetic patients (control group or group B) All patients had diagnosis of type 1 diabetes of less than 10 years. The average of the readings of the proteinuria was taken for each patient.

**Results:** 18 patients of group A (36%) had overt proteinuria (biopsy proven). Three of them (6%) with a mean duration of diabetes of 5.2 years and 15 of them (30%) with mean duration of diabetes of 8.1 years.

**Conclusion:** We may find overt proteinuria in extremely

uncontrolled type 1 diabetic patients with less than 10 years duration of diabetes.

**Key Words:** Proteinuria, Diabetes, Diabetic Nephropathy.

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### INTRODUCTION

Diabetic nephropathy is the leading cause of chronic kidney disease in patients starting renal replacement therapy.<sup>1</sup> Diabetic nephropathy is a clinical syndrome characterized by albuminuria (>300 mg/day) confirmed on at least two occasions 3-6 months apart, permanent and irreversible decrease in glomerular filtration rate (GFR) and arterial hypertension.<sup>2</sup> The main potentially modifiable diabetic nephropathy initiation and progression factors in susceptible individuals are sustained hyperglycemia.<sup>3-6</sup>

The natural history of diabetic nephropathy has been extensively studied in type 1 diabetes because it is normally possible to specify the exact time of onset. Without specific intervention, microalbuminuria usually progresses to the next stage of diabetic nephropathy -macroalbuminuria or "overt" nephropathy. Overt proteinuria usually occurs in 15 to 40% of patients with type 1 diabetes, with a peak incidence around 15 to 20 years of diabetes.<sup>7-9</sup>

Diabetic nephropathy is usually associated with hypertension, which also aggravates the injury to the diabetic glomerulus. Hyperglycemia leads to spontaneous non-enzymatic reaction between glucose, lipids and proteins leading to formation of advanced glycosylated end products. Several reactive substances have been postulated to be involved in the genesis of hemodynamic abnormalities. Besides this, various cytokines have been implicated in triggering renal injury such as transforming

growth factor  $\beta$ 1, platelet-derived growth factor and fibroblast growth factor.<sup>10</sup>

Type 1 diabetes is commonly associated with a period of hyperfiltration<sup>11-14</sup> followed, in a subset of patients, by the development of persistent microalbuminuria after as little as 7-10 years of type 1 diabetes.<sup>15-17</sup> Microalbuminuria identifies type 1 diabetic patients who, on average, have more advanced diabetic nephropathy lesions compared with patients remaining normoalbuminuric.<sup>18-20</sup> Moreover, Persistent micro albuminuria is associated with a 400-500% increase in the risk of progression to overt proteinuria and eventual ESRD.<sup>21,22</sup> Early identification of patients at high risk for diabetic nephropathy is important to intensify the treatment and modify associated risk factors.<sup>23</sup> Diabetic nephropathy often develops in patients with poor glycemic control. The degree of glycemic control is an important predictor of terminal kidney failure.<sup>24</sup>

Clinical trials have consistently demonstrated that glycosylated hemoglobin (HbA1c) levels are associated with decreased risk for clinical and structural manifestations of diabetic nephropathy in type 1 and type 2 diabetic patients. In the Diabetes Control and Complications Trial (DCCT), intensive treatment of diabetes reduced the incidence of microalbuminuria by 39%.<sup>25</sup>

Differential diagnosis is usually based on the history, physical examination, laboratory evaluation, and imaging of the kidneys.

Renal biopsy is only recommended in special situations. The diagnosis of diabetic nephropathy is easily established in long-term type 1 diabetic patients (>10 years diabetes duration), especially if retinopathy is also present.<sup>26</sup>

The criteria for renal biopsy are not well established, but in type 1 diabetes the presence of proteinuria in association with short diabetes duration and/or rapid decline of renal function, especially in the absence of diabetic retinopathy, have been used.<sup>27</sup>

#### AIM OF THE STUDY

To know the incidence of overt proteinuria in extremely uncontrolled type 1 diabetic patient with less than 10 years diabetes duration.

#### MATERIALS AND METHODS

Fifty patients (23 female and 27 male) with intensely uncontrolled type 1 diabetes (group A), attending the outpatient clinic in shorsh hospital in sulaimani city/ Kurdistan region / Iraq, All participated in the study with 22 good controlled type 1 diabetic patients (control group or group B). The study was conducted between September 2010 and September 2011. All patients had diagnosis of type 1 diabetes of less than 10 years.

All patients were investigated for fasting blood sugar, general urine examination, 24 hour urine for protein, urine albumin / creatinine ratio, renal function tests, renal sonography and Hb A1c. Renal biopsy was performed to the group A patients who had overt proteinuria to confirm the diagnosis of diabetic nephropathy and to exclude other differential diagnosis.

Medical history was taken and physical examination (including blood pressure measures, and ophthalmoscope examination by an experienced ophthalmologist) was performed. All investigations were done at least 3 times during the study and the mean values

of the readings were taken. All patients had no pre-existing hypertension.

In group A patients, the extremely uncontrolled blood sugar was determent by repeated high figures of fasting blood sugar on the follow up chart, history of uncontrolled diet and high figures of HbA1c more than 10 in patients files and follow up charts. While in group B patients (control group), the fasting blood sugar were in accepted figures and the Hb A1c were less than 7 in more than three times per year.

We exclude all patients that presented with symptoms during urination suggests urinary tract disorders such as obstruction, infection, or stones. Skin rash or arthritis that may indicate systemic lupus erythematosus or cryoglobulinemia. Presence of risk factors for parenteral transmitted disease that may raise the suspicion of kidney disease associated with HIV, hepatitis C, or hepatitis B. History of proteinuria and/or hypertension during childhood or pregnancy may suggest other glomerulonephritis. All these cases we excluded from the study. Patients, who were taking antihypertensive agents at baseline or had other diabetic complications, were also excluded. (The patients refuse to take any medication apart from insulin).

#### Statistical Methods

The data were entered into a Microsoft Access Spreadsheet. After data cleaning, the data were interpreted using SPSS (Statistical Package for the Social Sciences-version).

Descriptive statistics (numbers, percentages, means, and standard deviation, minimum and maximum) were calculated for all variables, and analytical statistics were done to find the relations between variables.

Association between variables was detected by using the appropriate statistical tests like t-test, and analysis of variance (ANOVA). A p-value  $\leq 0.05$  was considered as significant.

**Table 1: The relation between both groups, regarding the age, Weight, height and duration of diabetes.**

Females/ Males	Group A		Group B		P value
	Mean	Std. Deviation	Mean	Std. Deviation	
No.	23	-	10	-	-
	27		12		
Age (years)	22.5	3.8	21.6	3.5	N.S.
	22.2	4.1	22.5	4.6	
Weight (Kg)	47.0	6.4	46.8	7.2	N.S.
	50.2	9.7	50.8	12.9	
Height (cm)	157.7	6.4	157.5	7.5	N.S.
	161.9	8.6	161.2	10.6	
Duration of DM (years)	7.6	3.3	7.7	4.1	N.S.

**Table 2: The differences of the diastolic blood pressure between both groups.**

Female and male patients	Group A		Group B		P value
	Mean	Std. Deviation	Mean	Std. Deviation	
Diastolic BP	80.7	14.6	68	7.6	< 0.0005

**Table 3: The number and percentage of patients with overt proteinuria in group A**

No. of Patients (group A)	% of Patients	Mean duration of diabetes (years)	Std. Deviation	Mean albuminuria (gm/day)	Std. Deviation
3	6	5.2	1.4	0.42	0.1
15	30	8.1	1.8	0.89	0.6
32	64	3.4	1.1	< 0.3	-

## RESULTS

Both groups were matched for age, sex, weight, height and the duration of diabetes. The mean age of the 1<sup>st</sup> group was 22.4 years (range of 15-30 years). All patients had diagnosis of type 1 diabetes of less than 10 years. The average duration of their diabetes since diagnosis was 7.6 years. There were no statistical differences between both groups. (Table 1)

There was a statistical difference between the diastolic blood pressure (BP) in Group A and Group B. As the diastolic BP is more in Group A patients. (Table 2)

All the patients in the control group had no evidence of overt proteinuria, while 18 patients of group A (36%) had it. Three of them (6%) with a mean duration of diabetes of 5.2 years and 15 of them (30%) with mean duration of diabetes of 8.1 years. (Table 3) All patients with overt proteinuria have diabetic retinopathy and renal biopsy changes confirming the diagnosis of diabetic nephropathy.

## DISCUSSION

According to other studies we did not suspect to find overt proteinuria in uncontrolled type 1 diabetic patients with less than 10 years duration of diabetes.<sup>7-9</sup> Other studies shows approximately 25% of type 1 diabetic patients will develop overt diabetic nephropathy<sup>28</sup>, but they didn't mention after how many years we may suspect to find overt proteinuria in the uncontrolled type 1 diabetes. We find high incidence of overt proteinuria (36%) in our patients with intensely uncontrolled type 1 diabetes with less than 10 years duration of diabetes.

This is due to the fact that the poor control of blood sugar is an important factor for the development of diabetic nephropathy in addition to the duration of the disease.

Our study agreed with other study, as they found that overt diabetic nephropathy developed in patient with four years history of uncontrolled diabetes.<sup>29</sup>

Another study shows that the presence of gross proteinuria  $\geq 0.30$  g/L) was determined by means of a reagent strip. The incidence of proteinuria in a 4-year interval was 14.4%. The relative risk of developing proteinuria after 4 years for those with glycosylated hemoglobin levels in the highest quartile compared with those in the lowest quartile was 3.0.<sup>30</sup>

Moreover, intensive glycemic control also reduced the rate of development of micro- and macroalbuminuria.<sup>31</sup> As expected, glycaemic control was also strongly associated with progression to macroalbuminuria, in line with multiple follow-up studies.<sup>32-34</sup>

## CONCLUSION

Not only the duration of type 1 diabetes is important factor in the development of diabetic nephropathy but also the factor of controlling of the blood sugar is important. We may find overt proteinuria in extremely uncontrolled type 1 diabetic patients with less than 10 years duration of diabetes.

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## ETHICAL CONSIDERATIONS

Present study was approved by the Ethical committee, scientific committee and the College Council of Sulaimani Medical School / Sulaimani University.

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