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The Role of Hyperglycemia and Coexisting Hypertension in The Development of Diabetic Nephropathy in Type II Diabetes Mellitus

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Abstract

Background: diabetic nephropathy (D.N) is an important cause of morbidity and mortality and now the most common cause of end stage renal failure ESRF worldwide but especially in developed countries.

Objectives: the aim of the study is to know the role of hyperglycemia and co-existing hypertension HTN in the development of D.N. among patients with type II Diabetes Mellitus(DM).

Patients and Method: one hundred and twenty one diabetic patients were enrolled in a prospective observational study. Sixty six patients were females and fifty five were males. Besides full history and physical examination data were collected according to a format. At the end, these data were collected and analyzed statistically.

Results: the average age was (54± 2.1) year , female to male ratio 66 to 55 (1.2:1) the number of patients with hyperglycemia was 90. Average random blood sugar R.B.S was 259± 1.6 mg/dL. number of patients with hypertension was 71, the average of systolic blood pressure BP was 158± 6.1mmHg and diastolic was 10.2±1.1, the average duration of D.M. was (10.5± 4.2) year, the average of glycosylated hemoglobin HbA1c was 9.8± 2.1. the number of patients with D.N was 77.

Conclusion: the data showed that hyperglycemia and co-existing of hypertension were major risk factors in the development of D.N. among patient with type II D.M.

Keywords: *Diabetic Nephropathy, Type II Diabetes Mellitus, Hyperglycemia, Co-Existing Hypertension.*

Introduction

Diabetes Mellitus D.M is defined as fasting blood sugar (F.B.S) at or more than 126 mg/dL or a random blood sugar (R.B.S) at or more than 200 mg/dL. Plus signs and symptoms of DM plus glycosuria and recently by estimation of glycosylated hemoglobin (HbA1c) [1]. Diabetes Mellitus is a heterogeneous disorder or syndrome because overtime it results in damage or dysfunction of multiple organ-system including the kidney causing diabetic nephropathy [2].

Diabetic nephropathy DN is pathologically defined as changes occurring in the kidney as result of DM [3,4] with thickening of basement membrane of glomeruli, widening of the slit membrane of the podocytes, an increased number of mesangial cells, and matrix which invade the glomerular capillaries and eventually produces nodular deposits called kimmelstiel-wilson nodules [5,6].

Chemically high blood sugar leads to formation of advanced glycation end products and cytokines which are implicated in the mechanism of development of D.N [7,8]

Clinically D.N. is characterized by excretion of abnormal amount of albumin in the urine, Plus at the end stage renal failure other signs and symptoms like; tiredness, edema, frequency of urination, pallor, puffiness of the eyes and ankles, anorexia, nausea, and vomiting etc…

Diabetic nephropathy can be monitored by testing urine regularly for urinary albumin, urinary creatinine and serum creatinine (S.Cr). the amount of the protein in the urine reflecs the degree of damage to the any still functioning glomeruli. The value of S.cr can be used to estimate the glomerular filtration rate(GFR).

The most common cause of (ESRF) specially in the developed countries is D.N., that affect approximately one quarter of adults with D.M in united states **(9,10)** and also associated with an increased risk of death in general population particularly from cardiovascular disease**(9,10,11).**

Diabetes Mellitus with co-existing hypertension HTN induce pathophysiological change in the kidney including inappropriate activation of the renin-angiotension-aldosterone system, inflammation, increased sympathetic nervous system activation, increased oxidation stress and other mechanisms which eventually share in the damage of the kidney **12.**

Women with D.M have a higher incidence of HTN than men **(12,13,14).** The earliest evidence of D.N is a microalbuminurea which means the presence of small quantities of albumin in the urine (30-300)mg per 24hours, this stage is called incepient nephropathy beause the patient looks clinically healthy and biochemially the kidney function expressed by glomerular filtration rate GFR is preserved. The disease then progressed with increased excretion of albumin to more than 300mg/24h (macroalbuminemia) , and ultimately progressed to renal impairment and failure. this stage is called overt nephropathy, in which the patient feels ill and unwell,looks pale with puffiness of the face and ankles, dry, itchy skin and frequency of urination.

Regular examination of albumin is a good monitoring test to discover the disease progress. The use of dipsticks is a useful but insensitive way for quantitative albumin measurement, the efficient way is by radioimmunoassay method **(15-16-17).**

The progress of D.N can be delayed, stopped, or even reversed if early discovered by; strict glycemic control , aggressive blood pressure control (below 130/80 mmHg) with the use of angiotension converting enzyme inhibitors (ACEI) or angiotension receptor blockers (ARBs), quit smoking, life style modification, control of obesity, the use of statins and aspirin etc···· **(18,19).**

Patients and Method

The study involved 121 patients (66females and 55males) who were proved to have type II D.M in the diabetic clinic of Al-Hussein medical city Teaching hospital – kerbala holly city from first October 2017 to first April 2019. 5mL of Blood and urine samples were collected from patients during their visit to the diabetic clinic. Data were collected according to the forma which included; Age, Sex, duration of D.M, RBS HTN, HbA1c, S. creatinine, B. urea, urine albumin and creatinie, ACR (albumin creatinine ratio). urinary albumin in mg/dL measured by turbidmetric end point method by I-chroma instrument. Urinary creatinine measured by spectrophotometer in mg/dL. ACR is the ratio of urine albumin in mg/dL to urine creatinine in gms.

HbA1c was measured by clover A1c system, any values more than 6.5% was considered high, any value of RBS equal or more than 200mg/dL was considered high i.e diabetic range.

Values of ACR 0-29 mg/g were considered normal. values of 30-300mg/g were considered as microalbuminurea,and values above 300mg/gm were considered as macroalbuminuria. At the end data results were entered in to SPSS statistical software, p-values less than 0.05 was considered significant and less than 0.01 was highly significant.

Results

The total no. of patient was 121 (66females and 55 males) and the ratio of female to male was 1.2:1, the age ranged between 30-80 years with an average of 54±2.1. age and sex distribution was shown in table1.

The no. of patients with hyperglycemia i.e. R.B.S at or more than 200mg/dL of the both sexes was 86. The no. of patients with microalbumiburea ACR 30-300 mg/g in the total samples was 41, the no. of patients with macroalbuminurea ACR more than 300mg/g in both sexes was 36. This means that the total no. of D.N patients was 77 (63.63% of the total sample) which is the prevalence of D.N in the total sample. Details seen in table 2, The no. of females with D.N was 41,for male it was 36, both sexes were distributed according to age groups, details seen in table 3.

Persistent hyperglycemia represented by raised HbA1c the relation between ACR and HbA1c was seen in table 4. The relation of pre-existing HTN and its effect onACR was shown in table 5, the relation

between chronicity of D.M and the development of D.N is shown in table 6 this table shows that in the first five years after diagnoses of D.M one patient would have D.N microalbuminurea but when more than 20 years has passed since diagnoses of D.M 19 patints would have D.N out of 20 (95%).

Discussion

Women are more liable to develop D.M and HTN than men this is probably due to the increase in their waist circumference and body mass index (BMI) compared with men [13,20]. In addition the no. of patients with D.M increases with age(see table1) which shows the female to male preponderance 1.2:1 . Although not classically: in this study hyperglycemia plays a great role in the development of D.N because it induces pathophysiological changes in the glomeruli e.g by inducing activation protein-kinase C and other product mentioned earlier which induce mesangial expansion and glomerular basement membrane thickening etc….

The usual story is that patients with DM usually startred as normoalbuminuric whether controlled or uncontruoled. By the passage of time(chronicity) especially if remained uncontrolled, some of them will pass to the stage of microalbuminuria.If action would not be taken to control ,stop or reverse the risk factors ,they would pass to the stage of macroalbuminuria and finally,to the end stage renal disease(ESRD)…Table 2). Practically at the time of diagnosis about 1 in 8 (12.5%) of people have microalbuminurea and 1 in 50 (2%) have macroalbuminurea [22] , while in this study for comparison only one patient out of [21] had microalbuminuria at the time of diagnosis(table6),and after 10 years of having DM ,8 patients out of 26(30.7%) had microalbuminuria and 6 out of 26(23.1) had macroalbuminuria. Sixteen to twenty years after diagnosis,10 patients out of30(33%) had microalbuminuria and 18 out of 30(60%) had macroalbuminuria, table 6.

If DM is poorly controlled for a long period of time,this would be reflected by increased HbAIC,and this would be a risk factor to develop DN .There is good correlation between the level of HbAIC and DN represented byACR, table 4.

Hypertension(HTN) is also an important risk factor if it co-exists with DM…..table...(5). The association of HTN and DM increases the pathophyeiological changes in the kidney which eventually share in the damage of the kidney tissue[22-23-24].

In 2008(67%)of American adults aged 20years&over with DM had BP greater than 140/90mmhg and hence type 2 DM and high BP incease the risk of developing diabetes related diseases such as kidney disease(or DN)..

In short female sex increasing age, increasing duration of D.M (chronicity) with persistent hyperglycemia and co-existing HTN are the major risk. Factors which play a great role in the deterioration and damage resulting into ERSD. In addition we have not to forget the role of other factors which contribute or assist in the damage of the kidney such as smoking, obesity, hyperlipidemia, genetic factors and race [26- 27-28-29-30-31].

Table 1: Age and Sex distribution of the study sample n= 121

Age group in years	Sex		Total	Percentage
	Female	Male		
30-39	5	4	9	7.4
40-49	21	16	37	90.1
50-59	17	18	35	
60-69	21	16	37	
70-80	2	1	3	2.5
Total	66	55	121	100%

Table 2: The relation between hyperglycemia (according to elevated R.B.S) and ACR in mg/gm p-value>0.01

Value of ACR		No.of normglycemics	No.of hyperglycemics	Total	
0-29		4	40	44	
D.N	30-300	1	38	39	77=63.63%
	More than 300	0	38	38	
Total		5	116	121	

Table 3: Age and Sex distribution in patients with D.N represented by ACR (30 mg\gm and over).

Age group in years	Sex		Total
	Female	Male	
30-39	2	1	3
40-49	10	8	18
50-59	11	12	23
60-69	16	14	30
70-80	2	1	3
Total	41	36	77

Table 4: The relation between persistent hyperglycemia represented by HbA1C and ACR in mg\gm. p-value>0.001

ACR	Average HbA1C
0-29	7.28
30-300	8.88
More than 300	11.38

Table 5: The relation between pre – existing HTN and ACR in mg\gm. p-value>0.01.

Value of ACR	No. of patients with pre – existing HTN	Percentage of PTS with HTN to the total no. of the sample
0-29	18	14.87
30-300	25	20.66
More than 300	28	23.14
Total	71	58.67

Table 6: The relation between chronicity of D.M (duration in years) and ACR in mg\gm. No. of patients with DN 77 (27+50). p-value>0.005.

Duration of DM.	ACR			Total
	0-29	30-300 Microalbuminuria	Above 300 Macro albuminuria	
0-5	20	1	0	21
6-10	12	8	6	26
11-15	9	5	10	24
16-20	2	10	18	30
More than 20	1	3	16	20
Total	44	27	50	121

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Conflict of Interest: None to declare.

Ethical Clearance: All experimental protocols were approved under the Alsafwa University College, Karbala, Iraq and all experiments were carried out in accordance with approved guidelines.

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