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ORIGINAL ARTICLE

Association of NF-κB1 Gene Polymorphism with Diabetic Kidney Disease Risk in Type 2 Diabetics

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ABSTRACT

Background: Diabetic kidney disease (DKD) is the most common cause of end-stage renal failure and a significant contributor to cardiovascular mortality in diabetics. The development of diabetic complications is actively triggered by oxidative stress and low-grade inflammation produced by NF-κB. This study a ims to investigate the relationship between Nuclear factor kappa B subunit 1(NF-κB1 (gene polymorphism) and DKD in type 2 diabetic patients attending Zagazig University Hospitals.

Methods: We included three groups: 1st group was a control group and consisted of 33 apparently healthy individuals, the 2nd group was T2DM without nephropathy, and the 3rd group was T2DM with nephropathy, each of them had the same number of patients (33). NF-κB1 gene polymorphism (*rs28362491*) was analyzed by restriction fragment length polymorphism reaction.

Results: We found that Ins/Ins genotype of NF-κB1 prevalence was significantly higher among T2DM with nephropathy patients than the other two groups. In addition, in T2DM with the nephropathy group, Ins/Ins genotype had significantly lower albumin and total protein concentration compared to the other 2 genotypes.

Conclusions: There was a significant relation between NF-κB1 gene polymorphism and DKD risk in T2DM.

Keywords: Type 2 diabetes mellitus; Diabetic kidney disease; NF-κB1 gene; Polymorphisms; genotypes; nephropathy.

INTRODUCTION

Diabetes mellitus (DM) is a chronic metabolic disorder marked by persistent hyperglycemia, disturbing influences of sugar, abnormalities in the metabolism of lipids and proteins, connected with absolute or relative inadequacy in insulin discharge and/or insulin activity with environmental and genetic factors. It is one of the hardest health issues of the twenty-first century [1].

In 2019, there were over 500 million diabetics globally (9.3 percent of adults aged 20–79 years). In Egypt, diabetes is a rapidly growing public health issue; there were 9.8 million diabetics in 2019; by 2030, that number is expected to rise to 11.9 million; and by 2045, it will reach 16.9 million [2]. Around 15.6% of the Egyptian population, ages 20 to 79, have T2DM [3].

Diabetic kidney disease (DKD) is a major microvascular consequence of DM. DKD is the main cause of end-stage renal disease (ESRD) and renal failure because it affects 40% of DM patients [4.5].

Numerous studies have shown that DKD has a genetic predisposition, and family aggregation further suggests that genetic factors are significant in the etiology of the disease.Identifying genes that are involved in DN could lead to novel forms of treatment and maybe even prevention of this life-threatening condition [6].

Nuclear factor-κB (NF-κB) is a group of widely distributed transcription factors. The NF-κB family consists of five members: NF-κB1, RelA, c-Rel, RelB, and NFκB2. NF-κB is involved in the majority of biological processes as a key transcription regulator [7]. We predicted that there might be a

relation between the NF-κB1 gene polymorphism and type 2 diabetes, both with and without nephropathy, because this polymorphism has been linked to a variety of inflammatory diseases.

To our knowledge, No studies have been performed on the relation between NF-κB1 polymorphism and DKD risk in Egyptian T2DM patients. So we aimed to investigate the association between them.

METHODS

Patients and Methods:

This was a case-control study performed on 99 participants (33 participants in three groups) recruited from the Zagazig University Hospitals. All cases were Egyptians. Written informed consent was obtained from all participants, the study was approved by the research ethical committee of the Faculty of Medicine, Zagazig University. The study was done according to The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Group I (control group): This group included 33 normal apparently healthy volunteers not suffering from any diseases that might interfere with the present study. No medications were received for the past four weeks. Group II (T2DM without nephropathy): This group included 33 patients having T2DM without nephropathy. Group III (T2DM with nephropathy): This group included 33 patients having T2DM with nephropathy.

Patients suffering from T1DM, other metabolic disorders except for T2DM, drug intoxication, urinary tract infection, ureteral calculi, tumors, severe cardiac, liver function failure, and inflammatory disorders for 1 month were excluded from the study.

Biochemical Measurements

Eight milliliters of 8 hours' fasting venous blood and one milliliter of 2 hours' postprandial blood were drawn from all participants after their skin had been sterilized with ethyl alcohol swabs. Three ml were taken on Ethylene-diamine tetra-acetic acid having tubes for DNA extraction and glycated hemoglobin (HbA1c) estimation. four ml were left and centrifuged for fifteen minutes at 3000 rpm, and Serum samples were collected and refrigerated at -20 °C until analysis. The final 1 mL was placed in sodium fluoride-coated tubes, and after centrifugation, the plasma was separated to estimate blood glucose levels.

Urea, creatinine, albumin, total protein, aspartate aminotransferase(AST), alanine aminotransferase (ALT), fasting blood sugar (FBS), 2hour postprandial blood sugar (2-hPPBS), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C) and triglycerides (TG) levels were measured by spectrophotometer SUNDSTIK (SBA-733 PLUS), while low-density lipoprotein cholesterol (LDL-C) was calculated according to the Friedewald formula [8].

Using Biosystems (Barcelona, Spain), we assessed the colorimetric levels of HbA1c. The CKD-EPI equation was used to calculate the estimated glomerular filtration rate(eGFR) [9].

First-morning urine samples were collected under complete aseptic conditions for measurement of albumin creatinine ratio that was calculated by dividing urine microalbumin concentration in milligrams by the creatinine concentration in grams [10].

Isolation of DNA

DNA was extracted from whole blood by using the commercially available

gSYNC TM DNA Extraction Kit (Geneaid Biotech Ltd, Taiwan).

Amplification of -94 ins/del ATTG polymorphism in NF-κB1 :

The cases were genotyped for NF-κB1 gene polymorphism (*rs28362491*) by polymerase chain reaction–restriction fragment length polymorphism (PCR-RFLP). The polymorphism region was amplified with the following Forward primers (*5-TGG GCA CAA GTC GTT TAT GA-3*) and Reverse primer (*5-CTG GAG CCG GTA GGG AAG-3*). PCR was performed at 95°C for 1 min followed by 35 cycles at 95°C for 30s, 61°C for 30s, 72°C for 1 min, and finally 72°C for 5 min. Digestion of 285 bp amplified products with Pflm restriction endonuclease yielded 285 bp for the deletion allele and 240 and 45 bp fragments for the insertion allele.

Statistical Analysis

Microsoft Excel software was used to enter data on history, clinical examination, laboratory investigations, and outcome measures. Data then were analyzed into Statistical Package for the Social Sciences (SPSS version 25.0) software.

Qualitative data were expressed as numbers and percentages, but quantitative variables were expressed by mean ± SD. The difference in significance of qualitative variables was tested by the Chi-square test (X2). Also, ANOVA (F) was used to assess the difference of significance in Quantitative independent groups. post-hoc analysis was performed in significant ANOVA tests to elucidate the specific significant differences between groups. $p \leq 0.05$ was considered statistically significant (S) and $p > 0.05$ was non-statistically significant (NS).

RESULTS

Regarding the demographic data, The three groups were age, gender, and BMI -matched with no statistically significant difference (P>0.05). But as regards SBP and DBP, they were significantly higher in the group of T2DM with nephropathy compared to other groups, Regarding Duration of disease, It was

significantly higher in T2DM with nephropathy compared to T2DM without nephropathy group, as shown in (table 1).

There was a statistically significant difference in Serum urea, and creatinine levels in T2DM with nephropathy compared to other groups(p-value 0.001) but regarding estimated GFR, serum albumin, and total protein, they were significantly lower in T2DM with nephropathy group compared to T2DM without nephropathy which was significantly lower compared to controls (p-value 0.001). Also, There was a significant difference in the Albumin/creatinine ratio between the investigated groups with the highest levels of T2DM with nephropathy (p-value 0.001). Regarding AST, it was significantly higher in T2DM with and without nephropathy groups compared to controls, as shown in (table 2).

TC, LDL-c, HbA1c, FBG, and PPBG were statistically significantly higher among T2DM with and without nephropathy groups than the control group (p-value 0.001) but HDL levels were significantly lower in T2DM with and without nephropathy compared to controls(p-value 0.001). Regarding Serum TAG levels, they were significantly higher in T2DM with nephropathy compared to T2DM without nephropathy group which was significantly higher compared to the control group (p-value 0.001), as shown in (table 3).

Genetic analysis of NF-κB1 gene polymorphism revealed that NF-κB1 ins/ins genotyping was higher among T2DM with nephropathy than T2DM without nephropathy than the control group (70% and 49% > 24%) respectively. Regarding NF-κB1 alleles, the (Deletion) allele was higher among the control group than T2DM with and without nephropathy and the (Insertion) allele had the opposite pattern among the studied groups, as shown in (table 4)and (figure1&2). We found significant lower levels of serum albumin and total protein in T2DM with the nephropathy group having the Ins/Ins genotype of NF-κB1 polymorphism as compared to the other 2 genotypes, as shown in table (5).

Table 1: Demographic data and general clinical characteristics in studied groups:

Variables		Studied groups			P value	Post-hoc analysis
Gender	**Male**	18 (54.5%)	18 (54.5%)	15 (45.5%)	0.695# (NS)	-
	Female	15 (45.5%)	15 (45.5%)	18 (54.5%)		
Age (years)	**Mean ± SD**	54.7±5.2	54.7±5.7	56.6±3.8	0.617* (NS)	-
	Range	47-62	47-62	50-62		
BMI (kg/m2)	**Mean ± SD**	22±2.1	22.6±1.8	22.8±1.5	0.586* (NS)	-
	Range	19-25	20-25	20-25		
SBP (mmHg)	**Mean ± SD**	120±3.5	120.8±3.7	124±4.3	0.001* (S)	(1)0.481 (2)0.001 (3)0.001
	Range	114-126	114-126	118-130		
DBP (mmHg)	**Mean ± SD**	74.4±3.8	76.8±4.7	82.7±2.2	0.001* (S)	(1)0.009 (2)0.001 (3)0.001
	Range	70-80	70-85	80-85		
Duration of disease (years)	**Mean ± SD**	-	8.18±3.1	9.89±3.5	0.039+ (S)	-
	Range		6-10	6-15		

#Using Chi-square test, *Using One-Way ANOVA test, +Using Independent T-test, p-value ≤0.05 is significant, NS: non-significant, S: significant, BMI: body mass index, SBP: systolic blood pressure, DBP: diastolic blood pressure. (1) DM vs control, (2) DN vs control, (3) DM vs DN

Table 2: Assessment of kidney and liver functions in studied groups:

Variables	Studied groups			P value	Post-hoc analysis

S. urea (mg/dL)	**Mean ± SD**	26.3±5.3	27.9±8.9	105.8±15.2	0.001 (S)	(1)0.552 (2)0.001 (3)0.001
	Range	19-38	20-42	73-140		
S. creatinine (mg/dL)	**Mean ± SD**	0.77±0.1	0.83±0.1	4.05±0.6	0.001 (S)	(1)0.499 (2)0.001 (3)0.001
	Range	0.5-1.01	0.67-1.09	3.09-5.4		
eGFR (mL/min/1.73m^2)	**Mean ± SD**	103.7±7	93±9.8	14.6±2.8	0.001 (S)	(1)0.001 (2)0.001 (3)0.001
	Range	84-121	75-113	11-22		
Albumin/creatinine ratio (mg/g)	**Mean ± SD**	7.7±4.2	10±3.5	502±278	0.001 (S)	(1)0.013 (2)0.001 (3)0.001
	Range	1.8-18.4	4.6-22.3	120-982		
S. albumin (g/dL)	**Mean ± SD**	4.16±0.3	3.95±0.4	3.05±0.3	0.001 (S)	(1)0.013 (2)0.001 (3)0.001
	Range	3.6-4.9	3.5-4.9	2.4-3.6		
Total protein (g/dL)	**Mean ± SD**	7.95±0.4	7.39±0.5	6.13±0.48	0.001 (S)	(1)0.001 (2)0.001 (3)0.001
	Range	7.1-8.5	6.5-8.5	5.07-7.1		
AST (IU/L)	**Mean ± SD**	21.4±6.2	25.1±4.8	26.5±4.7	0.001 (S)	(1)0.006 (2)0.001 (3)0.269
	Range	12-33	17-33	19-33		
ALT (IU/L)	**Mean ± SD**	24±7.4	23.5±8.7	23.4±8.4	0.732 (NS)	-
	Range	11-40	10-41	10-42		

Using One-Way ANOVA test, p value ≤0.05 is significant, eGFR: Estimated Glomerular filtration rate, AST: aspartate aminotransferase, ALT: alanine aminotransferase. (1) DM vs control, (2) DN vs control, (3) DM vs DN

Table 3: Assessment of lipid profile in studied groups.

Variables		Studied groups			P value	Post-hoc analysis
		Controls (n=33)	**T2DM without nephropathy (n=33)**	**T2DM with nephropathy (n=33)**		
TC (mg/dL)	**Mean ± SD**	**130.7±10**	**170±24.5**	**176±25.7**	**0.001 (S)**	**(1)0.001 (2)0.001**
	Range	**110-152**	**126-200**	**133-220**		**(3)0.227**
HDL-C (mg/dL)	**Mean ± SD**	**63.2±7.5**	**48.3±8.2**	**51.8±9.4**	**0.001 (S)**	**(1)0.001 (2)0.001**
	Range	**50-75**	**35-61**	**31-71**		**(3)0.098**
LDL-C (mg/dL)	**Mean ± SD**	**44.3±15**	**90.4±27**	**91.4±28**	**0.001 (S)**	**(1)0.001 (2)0.001**
	Range	**14-75**	**45-128**	**41.5-154**		**(3)0.098**
TG (mg/dL)	**Mean ± SD**	**116±13.6**	**154±15.7**	**164±12.7**	**0.001 (S)**	**(1)0.001 (2)0.001**
	Range	**94-139**	**130-178**	**143-188**		**(3)0.005**
FBS (mg/dL)	**Mean ± SD**	**102±5**	**171±36**	**186±45**	**0.001 (S)**	**(1)0.001 (2)0.001**
	Range	85-109	115-246	127-285		**(3)0.066**
2-hPPBS (mg/dL)	**Mean ± SD**	123±6.9	282±45	290±38	**0.001 (S)**	**(1)0.001 (2)0.001**

Variables		Studied groups			P value	Post-hoc analysis
		Controls (n=33)	**T2DM without nephropathy (n=33)**	**T2DM with nephropathy (n=33)**		
	Range	110-134	187-351	110-356		(3)0.386
HbA1c (%)	**Mean ± SD**	4.89±0.3	8.2±1.2	7.93±0.85	**0.001 (S)**	**(1)0.001 (2)0.001**
	Range	4.3-5.6	6.5-11.4	6.5-9.5		(3)0.211

Using the One-Way ANOVA test, p-value ≤0.05 is significant, TC: total cholesterol, HDL-C: high-density lipoprotein cholesterol, LDL-C: low-density lipoprotein cholesterol, TG: Triacylglycerol. (1) DM vs control, (2) DN vs control, (3) DM vs DN

Table 4: Genetic analysis of NF-κB1 gene polymorphism in studied groups.

		Studied groups			P value (three-sided)	Two-sided analysis
		Controls (n=33)	**T2DM without nephropathy (n=33)**	**T2DM with nephropathy (n=33))**		
NF-kβ1 genotype	**Insertion/Insertion**	8 (24%)	16 (49%)	23 (70%)	**0.001 (S)**	**(1)0.002 (2)0.001** (3)0.114
	Deletion/Deletion	25 (76%)	12 (38%)	9 (27%)		
	Insertion/Deletion	0	5 (13%)	1 (3%)		
Insertion allele		16	37	47	**0.001 (S)**	-
Deletion allele		50	29	19		

Using the Chi-square test, p-value ≤0.05 is significant, (1) Insertion/Insertion genotype, (2) Deletion/Deletion genotype, (3) Insertion/Deletion genotype

Table 5: Comparison of liver and kidney functions in regards to NF-κB1 genotypes in studied patients.

Variables		T2DM without nephropathy			T2DM with nephropathy		
		Ins/Ins	**Del/Del**	**Ins/Del**	**Ins/Ins**	**Del/Del**	**Ins/Del**
S. albumin (g/dL)	**Mean ± SD**	3.89 ± 0.25	3.85 ± 0.41	4.36 ± 0.46	2.96 ± 0.29	3.23 ± 0.22	3.4
P value		0.075 (NS)			0.032 (S)		
Total protein (g/dL)	**Mean ± SD**	7.31 ± 0.41	7.29 ± 0.63	7.9 ± 0.54	5.98 ± 0.43	6.49 ± 0.48	6.39
P value		0.023 (S) (1)0.778 (2)0.012 (3)0.778			0.022 (NS) -		
AST (IU/L)	**Mean ± SD**	24.31 ± 4.8	25.75 ± 5.2	26 ± 4.9	27.48 ± 4.66	24.33 ± 4.5	25
P value		0.682 (NS)			0.228 (NS)		
S. urea (mg/dL)	Mean ± SD	28.12 ± 10.3	29 ± 7.3	24.6 ± 8.4	105.2 ± 14.2	108.7 ± 18.4	93.5
P value		0.659 (NS)			0.614 (NS)		
S. creatinine (mg/dL)	**Mean ± SD**	0.78 ± 0.1	0.88 ± 0.1	0.83 ± 0.12	3.9 ± 0.56	4.4 ± 0.7	4.1
P value		0.066 (NS)			0.109 (NS)		

Variables		T2DM without nephropathy			T2DM with nephropathy		
		Ins/Ins	**Del/Del**	**Ins/Del**	**Ins/Ins**	**Del/Del**	**Ins/Del**
Estimated GFR (mL/min/1.73m^2)	**Mean ± SD**	95.1 ± 11.1	92.5 ± 8.5	87.8 ± 7.7	14.9 ± 2.9	14.1 ± 2.8	13
P value		0.356 (NS)			0.663 (NS)		
Albumin/creatinine ratio (mg/g)	**Mean ± SD**	9.89 ± 2.2	11.1 ± 5	7.8 ± 1.1	513.8 ± 276.4	486.2 ± 310.3	378
P value		0.203 (NS)			0.881 (NS)		

Using One-Way ANOVA test, p value ≤0.05 is significant, S: significant, NS: non-significant, (1) Ins/Ins vs Del/Del, (2) Ins/Ins vs Ins/Del, (3) Del/Del vs Ins/Del

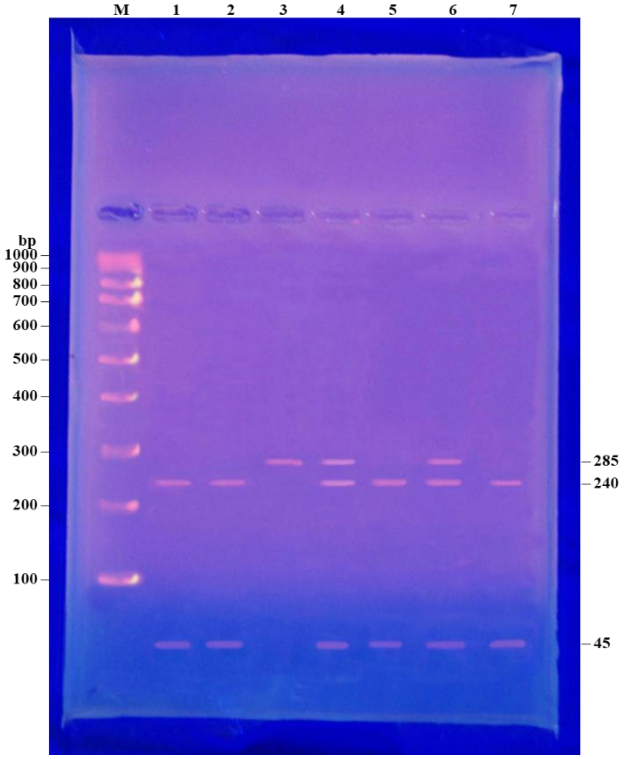

Figure 1: Agarose gel electrophoresis picture stained with ethidium bromide showing the PCR product digested by the restriction enzyme (Pflm) in which there was the analysis of the NF-κB1 (rs28362491) gene polymorphism. DNA size marker (100bp) ladder. Lane (3): del/del genotype showing the presence of one band 285 bp. Lanes (1,2,5,7): ins/ins genotype showing the presence of two bands 240+45 bp. Lanes (4,6): ins/del genotype showing the presence of three bands 285+240+45 bp.

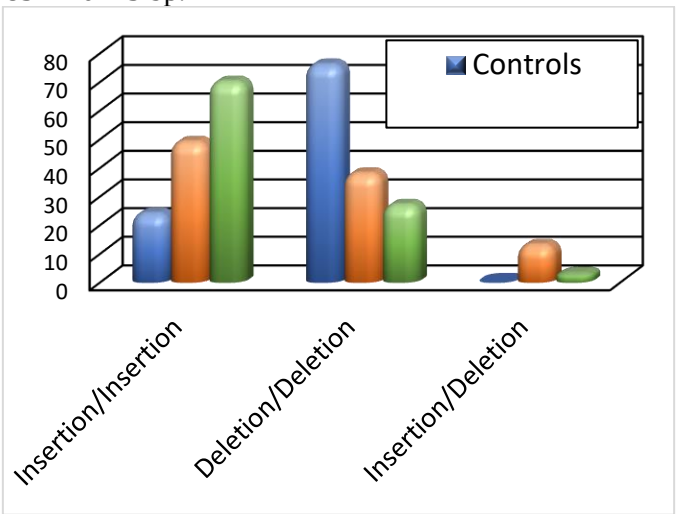

Figure 2: Distribution of NF-κB1 genotypes among studied groups

DISCUSSION

Diabetes mellitus is a metabolic disease characterized by hyperglycemia caused by abnormalities in insulin secretion, action, or both. Nearly 5% of the world's population, or about 366 million people, are predicted to have diabetes mellitus by the year 2030. [11].

Diabetic kidney disease is a typical microvascular consequence for both type 1 and type 2 diabetes that may eventually necessitate dialysis. Although nephropathy does not affect all diabetic individuals, it affects roughly one-third of them over time. Major genes involved in DKD susceptibility are still unknown despite numerous candidate gene association studies and genome-wide scan research [12].

The nuclear factor kappa B (NF-κB) is a transcription factor that controls the expression of many genes, including growth factors and cytokines. Therefore, NF-κB plays a key role in numerous biological processes, and its dysregulation would lead to pathogenic processes. [13].

The NF-κB and its inhibitors may have a significant role in the pathogenesis of T2DM, diabetic nephropathy, diabetic retinopathy, and diabetic cardiomyopathy by controlling the expression of numerous pro-inflammatory genes. [14].

O'Brown et al. [15] found that NF-κB1 (rs12509403) gene polymorphism was connected to lower eGFR on a population level. The NF-κB genotypes may therefore influence the phenotypes of renal aging.

Our study was aiming to predict the development of DKD in patients with T2DM via evaluation of NF-κB1 gene polymorphism in type 2 diabetic patients with or without nephropathy. The three groups were age, gender, and BMI -matched with no statistically significant difference. But as regards SBP and DBP, they were significantly higher in T2DM with nephropathy compared to other groups, Regarding Duration of disease, It was significantly higher in T2DM with nephropathy compared to T2DM without nephropathy group.

Our study agrees in some findings and disagrees in others with the research of Gautam et al. [16], who revealed that regarding sex distribution and BMI, there was no difference within all the three studied groups. The participants in Groups 3 and 2 (T2DM with and without nephropathy) were older than the participants in Group 1 (control); but according to their selection criteria, Group 2 had diabetes for a longer duration of time than Group 3. Raised SBP and DBP in Group 2 and Group 3 participants, compared to Group 1 participants, indicated a considerably increased incidence of hypertension (P 0.001).

The findings of Behera et al. [13] showed that out of 50 people in the control group, 23 were men and 27 were women. 21 men and 29 women made up the group of diabetics without nephropathy. In the group with diabetic nephropathy, there were 23 men and 27 women. No statistical significance in sex, age, and BMI between the groups. The mean blood pressure in diabetic nephropathy patients was greater than in control and diabetic patients without nephropathy.

Our results revealed that there was a statistically significant difference in Serum urea and creatinine levels in T2DM with nephropathy compared to other groups but regarding estimated GFR, it was significantly lower in T2DM with nephropathy group compared to other groups.

These results agreed with Gautam et al. [15] who reported that blood urea, plasma creatinine, and uric acid were significantly higher and eGFR was lower in T2DM with nephropathy as compared to T2DM without nephropathy.

However, in disagreement with our findings; Palazhy, [17] found that regarding blood urea, and serum creatinine there were no significant differences when T2DM with nephropathy patients compared to T2DM without nephropathy subjects, but eGFR was significantly lower among the T2DM with nephropathy patients' group.

Our Data showed that there was a statistically significant difference in Albumin/creatinine ratio among the investigated groups.

Our findings are consistent with those of Behera et al. [14] who revealed that patients with diabetic nephropathy had considerably reduced estimated glomerular filtration rates as well as significantly higher urinary albumin/creatinine ratios.

Our findings in this research have shown that serum albumin and total protein levels were significantly lower and AST was significantly higher in T2DM with nephropathy group compared to other groups.

Furthermore, We found that TC, LDL-C, HbA1c, FBG, and 2-hPPBG levels were statistically significantly higher but HDL-C levels were significantly lower among T2DM with and without nephropathy groups than the control group. Regarding Serum TG levels, they were significantly higher in T2DM with nephropathy compared to T2DM without nephropathy group which was significantly higher compared to the control group.

However, Palazhy, [17] found a significant difference in total cholesterol, LDL-C, and TG in the diabetic nephropathy group compared to T2DM without the nephropathy group with no significant difference in HDL-C among the participants.

Unlike our results, Viverti et al. [18] and Behera et al. [14] showed TG, LDL-C, and HDL-C were not significantly different in between groups.

Gautam et al. [16] observed poor glucose control in

T2DM with nephropathy as compared to T2DM without nephropathy as demonstrated by significantly higher postprandial, fasting, and HbA1c levels.

The outcomes of this study have revealed that the frequency of NF-κB1 del/del genotyping was the most common among the control group than T2DM without nephropathy and T2DM with nephropathy groups (76% > 38% > 27%) respectively, while NF-kβ1 ins/ins genotyping had the opposite pattern where they were higher among T2DM with nephropathy than T2DM without nephropathy than control group (70% and 49% > 24%) respectively.

Regarding NF-κB1 alleles, the (Deletion) allele was higher among the control group than T2DM without nephropathy and T2DM with nephropathy, and the (Insertion) allele had the opposite pattern among the studied groups.

Our findings revealed that the ins/ins genotype prevalence in T2DM patients with nephropathy was significantly higher than the other two groups, hence the rs28362491 ins/ins genotype may be a chronic kidney disease risk factor in T2DM patients among an Egyptian sample. This is agreed with Behera et al. [14] in the East Indian population.

Our study agreed with some findings and disagreed in others with the research of Gautam et al. [16] who found that in control and T2DM people without nephropathy, the frequency distribution of ins/del was the highest, followed by ins/ins, with the least frequency distribution of del/del in the same subjects. But in T2DM with nephropathy, the ins/del genotype was less common than the ins/ins genotype. Also, He revealed that those with T2DM who had the ins/ins genotype had a higher chance of developing nephropathy.

Gupta et al. [20] found that the risk of DKD in people with Type 2 diabetes mellitus is associated with indicators of inflammation and oxidative stress in the North Indian population. They discovered that type 2 DM patients with the ins/ins genotype also had an elevated risk of developing nephropathy. Nephropathy was developed 1.90 times more frequently in patients with diabetes mellitus who had the NF-κB1 ins/del polymorphism.

We also made a comparison of liver functions in regards to NF-κB1 genotypes in both T2DM with and without nephropathy groups and found that in T2DM without nephropathy group, Insertion/Insertion genotype had significantly lower albumin concentration compared to the other 2 genotypes. In addition, in T2DM with nephropathy group Insertion/Insertion genotype had significantly lower albumin and total protein concentration compared to the other 2 genotypes.

The main finding of the study of Coto et al. [13] was the link between T2DM and NF-κB1 variants (−94 indel in the promoter, and rs7667496, intronic) in an elderly cohort. The eGFR < 60 and T2DM groups in their cohort had a greater frequency of the deletion allele, but the genotype frequencies were only statistically related to T2DM in a dominant model.

The functional impact of the NF-κB1 variants and the potential involvement of the NF-κB1 pathway in the development of diabetes may help to explain this association with T2DM. Numerous pro-inflammatory genes are regulated by the NF-κB1 pathway, and several published pieces of evidence suggest that functional NF-κB1 variants and T2DM are related. [21]

It is well recognized that genetic variations significantly influence the risk of DKD. Numerous studies have shown how the insertion allele of the -94 ins/del AGGT polymorphism is related to different inflammatory disorders [16]. Until now, only few studies have attempted to assess the relationship between this polymorphism and the risk of DKD.

Limitations of the study:

The relatively small sample size was the most important limitation of this study. Another important limitation was many associated risk factors that may interfere with the net results of the study and were difficult even impossible to be excluded. Conclusion:

CONCLUSION

In conclusion, We concluded that NF-κB1 gene polymorphisms have a role in the development of DKD in patients with type 2 diabetes mellitus. Finding the genes that increase the risk of DKD and T2DM will eventually make it possible to identify patients who are at risk. Additionally, the genetic investigations of DKD and T2DM will identify heterogeneity among subgroups of diabetic patients, provide different insights into the underlying etiology, and may result in new medications for both treatment and prevention. More investigations having larger cohorts of subjects, and studies in various populations are needed to support these results.

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