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The Impact of Methylenetetrahydrofolate Reductase Gene Polymorphisms on Iraqi Patients with Diabetic Nephropathy

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Abstract--- *Diabetic nephropathy is a major cause of end-stage renal disease. Micro albuminuria is a term to describe a moderate increase in the level of urine albumin. It occurs when the kidney leaks mall amounts of albumin into the urine. The aim of this study was to investigate the influence of the C677T and A1298C polymorphisms of methylene tetrahydrofolate on the progression of chronic kidney disease in diabetic nephropathy of Iraqi patients to delay the deterioration in renal function. A hospital-based case-control study was performed. A total of 60 patients with diabetic nephropathy age (24-87) and 60 controls age(16-68) selected from nephrology center in Bagdad Teaching Hospital /Medical City from December 2017 until the end of August 2018, shows mean differences of study markers including (FBS, Blood urea, Serum creatinine and MTHFR) according to study group (micro albuminuria and control group). There were significant differences between means of all markers according to study group. in result conclusion Urinary biomarkers were significantly elevated in normoalbuminuric type 2 diabetic patients compared with nondiabetic control subjects and could be used as markers of diabetic nephropathy(DN) at a very early stage even before the development of micro albuminuria.*

Keywords--- *reductase, nephropathy, polymorphisms.*

I. INTRODUCTION

Diabetes is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both. The chronic hyperglycemia of diabetes is associated with long-term damage, dysfunction, and failure of different organs, especially the kidneys, nerves and blood vessels (1). Type 1 diabetes mellitus is characterized by loss of the insulin-producing beta cells of the pancreatic islets, leading to insulin deficiency. This type can be further classified as immune-mediated or idiopathic. The majority of type 1 diabetes is of the immune-mediated nature, in which a T cell-mediated autoimmune attack leads to the loss of beta cells and thus insulin. (2),Type 2 DM is characterized by insulin resistance, which may be combined with relatively reduced insulin secretion. (3) Diabetic nephropathy is the leading cause of renal failure, It is defined by proteinuria > 500 mg in 24 hours in the setting of diabetes, but this is preceded by lower degrees of proteinuria, or

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"microalbuminuria." Microalbuminuria is defined as albumin excretion of 30-299 mg/24 hours. Without intervention, diabetic patients with microalbuminuria typically progress to proteinuria and overt diabetic nephropathy, This progression occurs in both type 1 and type 2 diabetes (4) End Stage Renal Disease (ESRD) is a progressive, irreversible deterioration in renal function in which the body`s ability to maintain metabolic and fluid and electrolyte balance falls resulting in uremia or azotemia (5). Urea serves an important role in the metabolism of nitrogen-containing compounds by animals and is the main nitrogen-containing substance in the urine of mammals. It is a colorless, odorless solid, highly soluble in water, and practically non-toxic (LD50 is 15 g/kg for rats) (6) .Serum creatinine is used in the detection and assessment of acute kidney injury and chronic kidney disease (7).Micro albuminuria is a term to describe a moderate increase in the level of urine albumin. It occurs when the kidney leaks mall amounts of albumin into the urine, in other words, when an abnormally high permeability for albumin in the glomerulus of the kidney occurs. Normally, the kidneys filter albumin, so if albumin is found in the urine, then it is a marker of kidney disease (8).

II. SUBJECT AND METHODS

This study was conducted during the period from December 2017 until the end of April 2019. patients with diabetic who will selected from nephrology center in Baghdad Teaching Hospital / Medical City. Sixty (60) patients only (study group) [(29) males and (31) females] aged between (24- 87 years old) followed the schedule of this case control study study in all diabetic nephropathies subjects In addition sixty (60) healthy subjects [(33) males and (27) females] aged between (16-68 years old) were included in this study considered as control group All patients and controls underwent a full physical examination and completed a general questionnaire the demographic, biochemical variables and life style details should be recorded such as: age, gender, body mass index (BMI), family history of hypertension and diabetes, smoking .

III. RESULTS

In the figure(1-1) shows mean differences of MTHFR (pg/ml) according to study group (Patients and Control group). There were significant differences between means of MTHFR (pg/ml) according to study group**,** Table1:The study shows that the table we have no significant relationship between patients and control of C677T the homozygous (AA) genotype have frequency (7.3%) in patients and control (8.9%) ,whereas the heterozygous (AG) (31.7) in patient show no significant with control (46.7%) , but the homozygous (GG) (61.0%) in patient show significant with control (44.4%).

While the other gene is significant ($P<0.006$) relationship between patient and control , in A1298C gene ,the homozygous (AA) is(22.0%) in patient show no significant with control (51.1%) ,but the heterozygous (AC) (63.4%) in patient show significant with control (46.7%) ,in CC show significant in patient (14.6%) than the control (2.2%). In this study The risk of diabetic nephropathy was higher for double hetero-zygotes of A1298C than the C677T genotype. These results suggest that two variants of the MTHFR gene should be assessed as genetic risk factors for diabetic nephropathy in patients with diabetes

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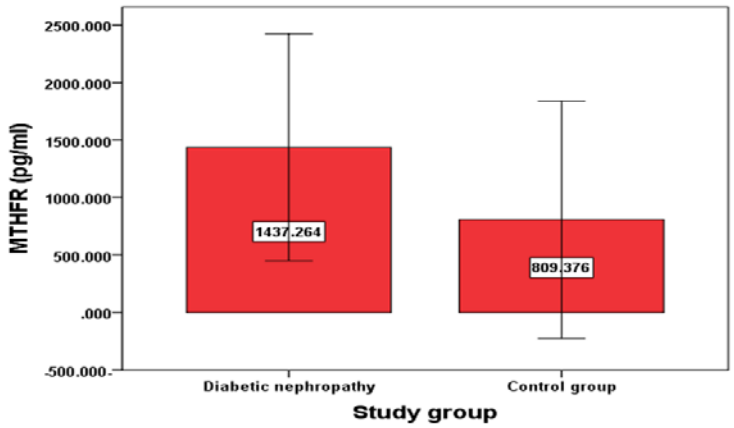

Figure (1-1): The mean differences of MTHFR according to study group

Table (1-1) Association between gene type and study group

Study variables	Study group		P-value	Odds ratio	95% CI
	Patients	Control group			
C677T					
AA	3 (7.3%)	4 (8.9%)			0.233-
AG	13 (31.7%)	21 (46.7%)	0.291	1.212	6.302
GG	25 (61.0%)	20 (44.4%)		0.6	0.120-
Total	41 (100.0%)	45 (100.0%)			2.997
A1298C					
AA	9 (22.0%)	23 (51.1%)			**0.121-**
AC	26 (63.4%)	21 (46.7%)	**0.006***	**0.316**	**0.827**
CC	6 (14.6%)	1 (2.2%)		**0.065**	**0.007-**
Total	41 (100.0%)	45 (100.0%)			**0.621**

IV. DISCUSSION

The microalbuminuria was coined to describe a small increase in the level of albumin of normal urine protein without an associated significant rise in the total urine protein level , This study agreement with other study that show a significantly elevated risk of diabetic nephropathy was associated with all variants of MTHFR C677T when compared with the healthy group (9).The MTHFR gene polymorphism was shown that the significant association between the cases and control. , the MTHFR gene polymorphism was observed that the significant contribution of the progression of CKD in diabetic nephropathy, the present study provides evidence that the MTHFR C677T polymorphism was associated with CKD progression in DN. (10). In this study we genotyped the C677T and A1298C polymorphisms in 60 patients and in 60 healthy persons. The C677T and A1298C genotypes were in agreement with The data analysis of distribution of C677T MTHFR genotypes (Table 1) revealed that in patients with DM, the 677TT genotype was found in 8.84%, the 677CT genotype in 34.90%, and the 677CC

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genotype in 56.74%. In the control group, 9.92% had the 677TT genotype, 46.56% had 677CT, and 43.51% had 677CC. The C677T polymorphism was significantly associated with T2DM in both additive (odds ratio, 1.39; 95% CI,1.07**)** (11).when the C677Tand A1298C genotypes were combined, we found an increasing frequency of the C677T and A1298C double heterozygotes at each stage of diabetic nephropathyin male patients with diabetes nephropathy (12).

V. CONCLUSION

Urinary biomarkers were significantly elevated in normoalbuminuric type 2 diabetic patients compared with nondiabetic control subjects and could be used as markers of DN at a very early stage even before the development of micro albuminuria

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