



## 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 small 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 Baghdad Teaching Hospital / Medical City from December 2017 until the end of August 2018, the result Table (3-4) shows mean differences of study markers including ( FBS, Blood urea, Serum creatinine and MTHFR) according to study group (macro 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 non diabetic 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:** methylenetetrahydrofolate, Diabetic, nephropathy, major

### 1. 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 "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 small 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).

### 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 .

### Results

In the figure (1-1) shows mean differences of albuminuria (g/dl) according to type (micro albuminuria and macro albuminuria) among patients with diabetic nephropathy. There were significant differences between means of

albuminuria (g/dl) according to study group , Table (3-4) shows mean differences of study markers including ( FBS, Blood urea, Serum creatinine and MTHFR) according to study group (macro albuminuria and control group). There were significant differences between means of all markers according to study group, In this study show that the mean and SD of fasting blood glucose (FBG) ( $9.89 \pm 4.87$ ) in macroalbuminuria show that statistically increase significant ( $P < 0.001$ ) than the mean and SD ( $6.24 \pm 1.15$ ) of control group, in serum urea show that the mean and SD in

macroalbuminuria ( $13.81 \pm 5.29$ ) statistically increase significant ( $p < 0.001$ ) than the control group ( $6.16 \pm 1.98$ ) , in serum creatinine show that the mean and SD in macroalbuminuria ( $3.01 \pm 1.68$ ) statistically increase significant ( $p > 0.001$ ) than the control group ( $0.98 \pm 0.29$ ) ,this study also show that the methylentetrahydrofolat reeducates in macroalbuminuria ( $1490.19 \pm 449.43$ ) statistically increase significant ( $p < 0.001$ ) than the control group ( $809.37 \pm 515.10$ ).

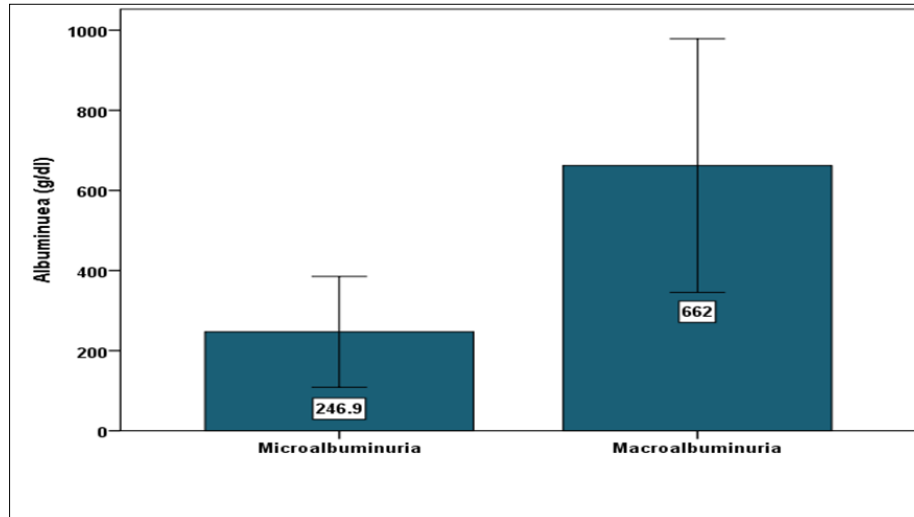


Fig 1.1: The mean differences of albuminuria according to type

Table 1.1: Mean differences of study markers according to study group

Study Markers	Study group	N	Mean	SD	t-test	P-value
FBG (mmol/l)	Macro albuminuria	31	9.89	4.87	4.102	<0.001 *
	Control group	60	6.24	1.15		
Urea (mmol/l)	Macro albuminuria	31	13.81	5.29	7.766	<0.001 *
	Control group	60	6.16	1.98		
Creatinine (mg/dl)	Macro albuminuria	31	3.01	1.68	6.641	<0.001 *
	Control group	60	0.98	0.29		
MTHFR (pg/ml)	Macro albuminuria	31	1490.19	449.43	6.231	<0.001 *
	Control group	60	809.37	515.10		

Micro albuminuria significantly increases the relative risk of development of diabetic nephropathy [9] However, the accuracy of albuminuria in predicting progression to overt diabetic nephropathy and to end-stage kidney disease is unclear. Micro albuminuria, defined as 30–300 mg albumin/day or 30–300 mg albumin/g creatinine (Cr) excreted in the urine, often regresses to normoalbuminuria (<30 mg/gCr) in type 1 diabetes patients [10]. some study showed that baseline albumin creatinine ration( ACR) was associated with an increased incidence of macro albuminuria in type 2 diabetic patients lacking potentially preexisting non-diabetic kidney diseases. Patients with baseline ACR of 150–300 mg/gCr had a significantly higher incidence of macro albuminuria than patients in any of the other ACR categories, regardless of the cause of macro albuminuria. Because elevated ACR in diabetic patients is associated with increased risks of all-cause mortality and cardiovascular events [11], This agreement with other study show that , The prevalence of macro albuminuria and 17.6%, respectively, Macro albuminuria was significantly associated with increased fasting plasma glucose . It was also found that higher plasma glucose and BUN (blood urea nitrogen) were risk factors for macro albuminuria, The

microalbuminuric and macroalbuminuric patients had higher FPG ( $P < 0.05$ ), and longer duration of diabetes ( $P < 0.01$ ) compared to the normoalbuminuric patients. the macroalbuminuric patients ( $P < 0.01$ ), had higher BUN ( $P < 0.001$ ) and serum creatinine ( $P < 0.001$ ) than patients with normal albumin [12].

**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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