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Study of Serum Milk Fat Globule-epidermal Growth Factor 8 (MFG-E8) in Patients with Type 2 Diabetes Mellitus

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Background: Milk Fat Globule-Epidermal Growth Factor 8 (MFG-E8) has been shown to be involved in various biological functions including the phagocytic clearance of apoptotic cells, neovascularization and epithelial restitution. Recently, emerging studies have reported that MFG-E8 plays a role in inflammatory responses and inflammatory/autoimmune diseases. The aim of the present study was to investigate the role of serum MFG-E8 in early diagnosis of microvascular complications in type 2 diabetic (T2D) patients.
Methods: The study included 80 patients with T2D; they were divided in to 4 groups depending on the value of clinical and laboratory parameters. Group A: included 20 patients free of any vascular complications. Group B: included 20 patients with subclinical atherosclerosis. Group C: included 20 patients with early microvascular complications without subclinical atherosclerosis. Group D: included 20 patients with both subclinical atherosclerosis and early microvascular complications. Serum (MFG-E8) was measured by ELISA technique.
Results: There was a significant decrease in the mean value of serum MFG-E8 concentrations in groups C (T2D with early microvascular complications) and D (T2D with both early microvascular complications and subclinical atherosclerosis) when compared to those in groups A (T2D without any

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vascular complications) and B (T2D with subclinical atherosclerosis only). It negatively correlated with age, fasting and postprandial glucose level, HbA1C, urinary albumin excretion rate, hs-CRP and positively correlated with HDL-C while didn't correlate with body mass index, triglycerides, cholesterol, LDL-C or carotid intima media thickness.

Conclusions: Serum MFG-E8 may be used as an early diagnostic marker of microvascular complications in T2D. MFG-E8 seemed not to be a sensitive biomarker for early diagnosis of subclinical atherosclerosis in T2DM.

Keywords: Serum milk fat globule-epidermal growth factor 8; MFG-E8; type 2 DM.

1. INTRODUCTION

Diabetes Mellitus is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both. As the disease progresses tissue or vascular damage ensues, leading to severe diabetic complications such as nephropathy, neuropathy, retinopathy, cardiovascular complications [1].

Type 2 diabetes (T2D) is associated with a chronic state of low-grade inflammation, which has been implicated in the pathogenesis of both the macrovascular and microvascular complications of diabetes. The World Health Organization (WHO) estimates that 629 million people would have diabetes by the year 2045. Diabetes mellitus occurs throughout the world but is more common (especially type 2) in more developed countries [2].

There are many medical conditions which can potentially give rise to, or exacerbate T2D. These include obesity, hypertension, elevated cholesterol and triglycerides levels (combined hyperlipidemia), and with the condition often termed metabolic syndrome. Additional factors that may increase the risk of T2D include aging, high-fat diets and a less active lifestyle [3].

Milk fat globule-epidermal growth factor 8 (MFG-E8), also referred to as lactadherin, is a peripherally secreted glycoprotein that is mainly secreted by activated macrophages or immature dendritic cells, and acts as a bridging molecule between apoptotic cells and phagocytes [4].

MFG-E8 has been shown to be involved in various biological functions including the phagocytic clearance of apoptotic cells, neovascularization and epithelial restitution. Recently, emerging studies have reported that MFG-E8 plays a role in inflammatory responses and inflammatory/autoimmune diseases [5].
Some studies demonstrated that exogenous MFG-E8 could attenuate inflammation by reducing pro-inflammatory cytokines, such as TNF-a, IL-6, and IL-1β, in sepsis and in renal, hepatic, and intestinal ischemia/ reperfusion conditions. Although these results came from animal experiments, given that these inflammatory factors are also highly expressed in patients with T2D, it is likely that MFG-E8 might also prevent the development of diabetic microvascular complications by reducing these factors in the context of diabetes [6].

The aim of this work is to investigate the probable role of Milk Fat Globule-Epidermal Growth Factor 8 (MFG-E8) in early diagnosis of microvascular complications in type 2 diabetic patients.

2. PATIENTS AND METHODS

The study included 80 patients from the Internal Medicine Department, divided in to 4 groups depending on the value of clinical and laboratory parameters. Group A: included 20 patients with T2D free of any vascular complications (carotid intima media thickness [CIMT] < 0.9 mm). Group B: included 20 patients with T2D with subclinical atherosclerosis (CIMT≥0.9 mm) and free of any microvascular complications. Group C: included 20 patients with T2D with early microvascular complications without subclinical atherosclerosis (CIMT< 0.9 mm). Group D: included 20 patients with T2DM with both subclinical atherosclerosis (CIMT≥0.9 mm) and early microvascular complications.

2.1 Inclusion Criteria

1. Type2 diabetes patients who were fulfilled the diagnostic criteria of the American Diabetes Association (ADA).
2. Patients with age range (40-70 years).
3. Diabetic patients with early microvascular complications:

    a. Early diabetic nephropathy was diagnosed by urinary albumin

excretion rate (UAER) between 30 and 299 mg/day in the absence of hematuria or infection.

b. Early diabetic retinopathy was diagnosed by findings of dilated pupil on fundoscopy carried out by an ophthalmologist which include microaneurysms, intraretinal haemorrhages, intraretinal microvascular abnormalities (IRMA) or cotton wool spots.

c. Early diabetic peripheral neuropathy (DPN) was diagnosed by symptoms which include (intermittent pain, tingling sensations or numbness in toes, fingers, feet and hands) and signs which include (decreased pinprick or temperature sensations with distal to proximal pattern) that appeared through physical examination carried out by a neurologist.

2.2 Exclusion Criteria

1. Patients with hypertension, previously diagnosed cardiovascular disease (CVD), malignancy, inflammatory diseases, chronic hepatic or renal disease other than diabetic kidney disease.
2. Patients with overt diabetic nephropathy (UAER > 300 mg/day), proliferative diabetic retinopathy and severe diabetic neuropathy.

All patients included in this study were subjected to complete medical history, clinical examination including BMI, neurological and ophthalmological examination. Radiological investigation including CIMT that was measured for all patients to define macrovascular injury and subclinical atherosclerosis. Routine lab investigations as fasting and post prandial plasma glucose, Hb A1c level, urinary albumin excretion rate, serum hs-CRP, lipid profile including: serum Triglycerides, Total cholesterol, HDL cholesterol, LDL cholesterol and specific investigations as serum (MFG-E8) was measured by ELISA technique.

2.3 Estimation of serum Milk Fat Globule Epidermal Growth Factor 8 (MFG-E8) level Using ELIZA Method

A double antibody sandwich enzyme linked immunosorbent assay was used to assay the level of human MFG-E8 in samples. Samples and standard were added to monoclonal antibody enzyme well which was pre-coated with human MFG-E8 monoclonal antibody, incubation was done; then MFG-E8 antibodies labeled with biotin, and combined with streptavidin-HRP were added to form immune complex; then incubation and washing were carried out to remove the uncombined enzyme. Then chromogen solution A, B were added, the color of the liquid changed into the blue, and at the effect of acid, the color finally became yellow. The chroma of color and the concentration of the substance MFG-E8 of sample were positively correlated. (Fig. 1)

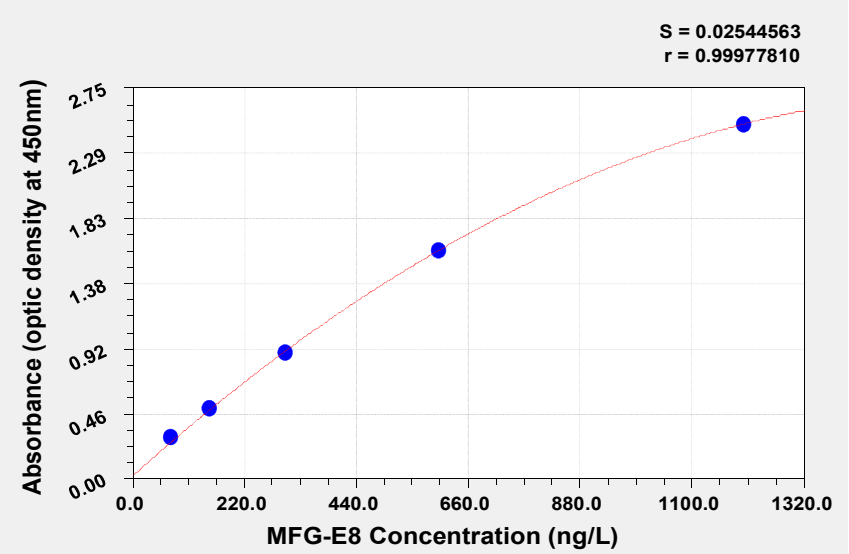

Fig. 1. Standard ELIZA curve for MFG-E8

2.4 Statistical Analysis

Statistical presentation and analysis of the present study was conducted, using SPSS V.22. Quantitative variables were expressed as mean and standard deviation (SD) and were compared using F test among the three groups with post hoc (LSD) test to compare each two groups. Categorial variables were expressed as frequency and percentage and were statistically analyzed by Chi-square test. Pearson coefficient was used to show the degree of correlation between two variable. The overall diagnostic performance was assessed by ROC curve analysis. A two-tailed P value ≤ 0.05 was considered statistically significant.

3. RESULTS

There was a significant difference in age between groups (A-B) p1=0.001, (A-C) p2=0.001, (A-D) p3=0.001, (B-D) p5=0.001, (C-D) p6=0.001. There was no significant difference in age between groups (B-C) p4=0.091. There was no significant difference as regard gender and BMI between the studied groups with p value >0.05. Table 1.

There was a significant difference in FPG levels between the studied groups with p value=0.001. There was a significant difference in FPG levels between groups (A-B) p1=0.001, (A-C) p2=0.001, (A-D) p3=0.001, (B-C) p4=0.001, (B-D) p5=0.001, (C-D) p6=0.007. **Table 2**.

There was a significant difference in PPG levels between groups (A-B) p1=0.001, (A-C) p2=0.001, (A-D) p3=0.001, (B-C) p4=0.001, (C-D) p6=0.001. There was no significant difference in PPG levels between groups (B-D) p5=0.071. Table 2.

There was a significant difference in HbA1c percentage between groups (A-B) p1=0.001, (A-C) p2=0.001 and (A-D) p3=0.001. There was no significant difference in HbA1c percentage between groups (B-C) p4=0.506, (B-D) p5=0.805 and (C-D) p6=0.363. Table 2.

There was a significant difference in UAER between groups (A-C) p2=0.001, (A-D) p3=0.001, (B-C) p4=0.001, (B-D) p5=0.001. There was no significant difference in UAER between groups (A-B) p1=0.059 and (C-D) p6=0.390. Table 2.

There was a significant difference in hs-CRP levels between groups (A-B) p1=0.001, (A-D) p3=0.001, (B-C) p4=0.001, (B-D) p5=0.001, (C-D) p6=0.001. There was no significant difference in hs-CRP levels between groups (A-C) p2=0.493. Table 2.

Table 1. Comparison between the studied groups regarding demographic data

		Group A	Group B	Group C	Group D
Age (years)					
Range		40 – 50	52 – 62	52 – 65	61 – 70
Mean ± SD		46.30 ± 2.39	57.00 ± 2.32	60.00 ± 3.61	66.70 ± 2.87
F. test		178.603			
p. value		0.001*			
P1		**P2**	**P3**	**P4** **P5**	**P6**
0.001*		0.001*	0.001*	0.091 0.001*	0.001*
Sex					
Male	**N**	10	8	10	11
	%	50.0%	40.0%	50.0%	55.0%
Female	**N**	10	12	10	9
	%	50.0%	60.0%	50.0%	45.0%
Chi-square	**X^2**	0.951			
	P-value	0.813			
BMI					
Range		24 - 35	25 - 35	24 - 34	25 – 34
Mean ± SD		28.10 ± 2.94	30.00 ± 2.71	28.30 ± 3.06	28.90 ± 2.79
F. test		1.760			
p. value		0.162			

P value >0.05= non-significant *P value <0.05= significant*
P1 comparison between (GA& GB) *P2 comparison between (GA& GC)*
P3 comparison between (GA& GD) *P4 comparison between (GB& GC)*
P5 comparison between (GB& GD) *P6 comparison between (GC& GD)*

There was a significant difference in TG levels between groups (A-B) p1=0.001, (A-C) p2=0.001, (A-D) p3=0.001, (B-C) p4=0.001, (B-D) p5=0.001. There was no significant difference in TG levels between groups (C-D) p6=0.336. Table 2.

There was a significant difference in TC levels between groups (A-B) p1=0.001, (A-D) p3=0.005, (B-C) p4=0.001, (B-D) p5=0.001, (C-D) p6=0.005. There was no significant difference in TC levels between groups (A-C) p2=0.991. Table 2.

There was a significant difference in HDL levels between groups (A-B) p1=0.001, (A-C) p2=0.001, (A-D) p3=0.001, (B-C) p4=0.001, (C-D) p6=0.001. There was no significant difference in HDL levels between groups (B-D) p5=0.566. Table 2.

There was a significant difference in LDL levels between groups (A-B) p1=0.001, (A-D) p3=0.001, (B-C) p4=0.001, (B-D) p5=0.001, (C-D) p6=0.001. There was no significant difference in LDL levels between groups (A-C) p2=0.543. Table 2.

There was a significant difference in CIMT between groups (A-B) p1=0.001, (A-D) p3=0.001, (B-C) p4=0.001, (C-D) p6=0.001. There was no significant difference in CIMT between groups (A-C) p2=0.375 and (B-D) p5=585. Table 2.

There was a significant difference in serum MFG-E8 level between groups (A-C) p2=0.001, (A-D) p3=0.001, (B-C) p4=0.001, (B-D) p5=0.001, (C-D) p6=0.001. There was no significant difference in serum MFG-E8 level between groups (A-B) p1=0.068. Table 2.

Table 2. Comparison between the studied groups regarding laboratory tests

	Group A	**Group B**	**Group C**	**Group D**
FPG				
Range	**133 - 175**	**176 - 265**	**153 - 226**	**185 - 256**
Mean ± SD	**153.50 ± 12.83**	**237.40 ± 23.95**	**193.30 ± 21.78**	**210.90 ± 19.47**
F. test	62.286			
p. value	0.001*			
P1	**P2**	**P3**	**P4**	**P5**	**P6**
0.001*	0.001*	0.001*	0.001*	0.001*	0.007*
		PPG			
Range	180 - 277	270 - 420	215 - 370	250 – 440
Mean ± SD	211.70 ± 20.21	354.15 ± 39.60	283.45 ± 39.30	332.80 ± 43.58
F. test	59.027			
p. value	0.001*			
P1	**P2**	**P3**	**P4**	**P5**	**P6**
0.001*	**0.001***	**0.001***	**0.001***	0.071	**0.001***
		HbA1c			
Range	7.1 – 8.4	8.5 – 11.3	8.2 – 11.6	8.7 – 12.1
Mean± SD	7.50 ± 0.37	9.79 ± 0.71	9.97 ± 1.18	9.73 ± 0.84
F. test	39.853			
p. value	0.001*			
P1	**P2**	**P3**	**P4**	**P5**	**P6**
0.001*	**0.001***	**0.001***	0.506	0.805	0.363
		UAER			
Range	7.2 – 19.4	13.5 – 27.4	38.6 – 115.5	40 – 90
Mean ± SD	14.83 ± 3.62	21.17 ± 4.28	58.52 ± 16.36	55.65 ± 11.78
F. test	94.493			
p. value	0.001*			
P1	**P2**	**P3**	**P4**	**P5**	**P6**
0.059	**0.001***	**0.001***	**0.001***	**0.001***	0.390
		high sensitivity C- reactive protein (hs-CRP)			
Range	0.9 – 2.4	1.4 – 2.8	1.2 – 2.4	2 – 3.3

	Group A	Group B	Group C	Group D
Mean ± SD	1.80 ± 0.40	2.35 ± 0.32	1.87 ± 0.27	2.87 ± 0.28
F. test	47.189			
p. value	0.001*			
P1	**P2**	**P3**	**P4**	**P5**	**P6**
0.001*	0.493	**0.001***	**0.001***	**0.001***	**0.001***
serum triglycerides (TG)				
Range	150 - 180	190 - 300	157 - 235	170 – 200
Mean ± SD	161.15 ± 7.49	248.50 ± 33.33	194.70 ± 29.55	187.65 ± 9.03
F. test	50.601			
p. value	0.001*			
P1	**P2**	**P3**	**P4**	**P5**	**P6**
0.001*	**0.001***	**0.001***	**0.001***	**0.001***	0.336
total cholesterol (TC)				
Range	172 - 215	196 - 266	170 – 223	188 – 226
Mean ± SD	199.5 ± 12.13	239.0 ± 17.47	199.50± 16.53	212.5 ± 10.05
F. test	33.520			
p. value	0.001*			
P1	**P2**	**P3**	**P4**	**P5**	**P6**
0.001*	0.991	**0.005***	**0.001***	**0.001***	**0.005***
HDL				
Range	48 - 57	38 - 48	41 - 58	37 – 46
Mean ± SD	52.35 ± 2.76	42.05 ± 3.07	48.00 ± 4.47	41.45 ± 2.50
F. test	49.667			
p. value	0.001*			
P1	**P2**	**P3**	**P4**	**P5**	**P6**
0.001*	0.001*	0.001*	0.001*	0.566*	0.001*
LDL-C				
Range	92 – 130	110 - 170	89 - 132	110 – 150
Mean ± SD	115.15 ± 11.58	147.25 ± 12.04	112.85 ± 13.66	133.65 ± 10.06
F. test	37.376			
p. value	0.001*			
P1	**P2**	**P3**	**P4**	**P5**	**P6**
0.001*	0.543	**0.001***	**0.001***	**0.001***	**0.001***
carotid intima media thickness (CIMT)				
Range	0.64 – 0.84	0.95 – 1.82	0.71 – 0.83	0.98 – 1.57
Mean ± SD	0.74 ± 0.05	1.15 ± 0.20	0.78 ± 0.05	1.13 ± 0.16
F. test	55.620			
p. value	**0.001***			
P1	**P2**	**P3**	**P4**	**P5**	**P6**
0.001*	0.375	**0.001***	**0.001***	**0.585**	**0.001***
MFG-E8				
Range	553 - 750	520 - 730	266 - 358	135 – 207
Mean ± SD	645.70 ± 56.77	630.85 ± 52.87	310.30 ± 26.89	179.70 ± 21.15
F. test	592.003			
p. value	0.001*			
P1	**P2**	**P3**	**P4**	**P5**	**P6**
0.068	**0.001***	**0.001***	**0.001***	**0.001***	**0.001***

P value <0.05= significant, P1 comparison between (GA& GB), P2 comparison between (GA& GC), P3 comparison between (GA& GD), P4 comparison between (GB& GC), P5 comparison between (GB& GD), P6 comparison between (GC& GD)

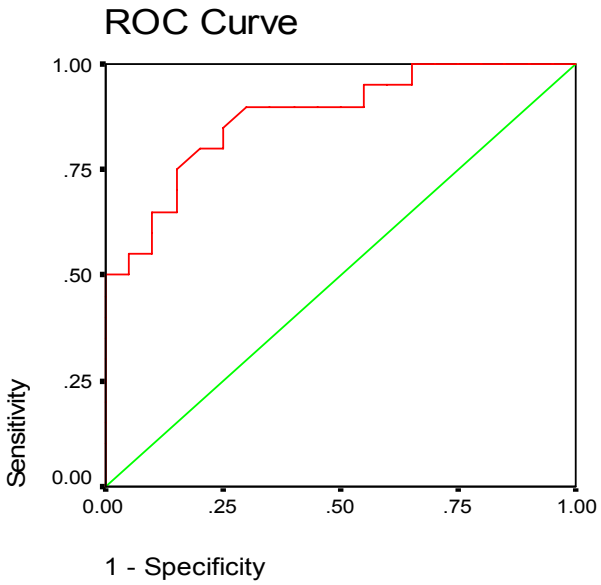

Fig. 2. ROC curve of MFG-E8 as a diagnostic marker of early microvascular complications in T2D patients

There was a negative association between serum MFG-E8 levels and presence of NPDR and DPN 3.

Table 3. Association between serum MFG-E8 levels and (NPDR and DPN)

	MFG-E8	
	r.	**P**
NPDR	- 0.837	0.001*
DPN	- 0.825	0.001*

Table 4. Correlation between serum MFG-E8 levels and (age, BMI, FPG, PPG, HbA1C, UAER, hs-CRP, TG, TC, HDL-C, LDL-C and CIMT)

	MFG-E8	
	r.	**P**
Age	- 0.883	0.001*
BMI	0.040	0.723
FPG	- 0.231	0.040*
PPG	- 0.356	0.001*
HbA1c	- 0.516	0.001*
UAER	- 0.848	0.001*
hs-CRP	- 0.473	0.001*
TG	0.088	0.438
TC	0.053	0.641
HDL-C	+ 0.395	0.001*
LDL-C	0.030	0.788
CIMT	0.125	0.145

There was a negative correlation between serum MFG-E8 and age, FPG, PPG, HbA1C, UAER and hs-CRP (p value <0.05), while positive correlation was found between serum MFG-E8 and HDL-C levels (p value <0.05). Also there was no correlation between serum MFG-E8 and BMI, TG, TC, LDL-C and CIMT (p value >0.05). Table 4.

The cut-off value was selected to achieve the highest sensitivity and specificity for predicting early microvascular complications. The selected cut-off was 610ng/L, the area under the curve (AUC) was 0.878 and this cut-off achieves sensitivity 75% and specificity 90%. Fig. 2.

4. DISCUSSION

MFG-E8 is a secreted integrin-binding glycoprotein with multifunctional domains. In healthy and diseased vessels, MFG-E8 is expressed by endothelial cells, VSMCs, and macrophages [7].

T2DM is associated with a chronic state of low-grade inflammation, which has been implicated in the pathogenesis of both macrovascular and microvascular complications of diabetes. Previous studies have shown that MFG-E8 mediates the clearance of apoptotic cells, by acting as a bridging molecule between apoptotic cells and phagocytes, and is implicated in the

pathogenesis of atherosclerosis and inflammatory diseases [8]. However, little is known about MFG-E8 role in microvascular complications in patients with T2DM.

Our study agreed with Leticia F. et al. [9] who proved that there was a strong association between age and subclinical atherosclerosis, and Piepoli M.F. et al. [10] who proved that age is the most significant risk factor for cardiovascular events. In patients with subclinical atherosclerosis, there was a significant increase in serum level of total cholesterol in groups B and D (239.00±17.47, 212.55±10.05 respectively) and serum level of LDL-C in groups B and D (147.25±12.04 and 133.65±10.06 respectively). Also, there was a significant decrease in serum level of HDL-c in groups B and D (42.05±3.07 and 41.45±2.50 respectively) compared to other groups.

Our results were in consistence with the results of Sunil K. et al. [11] who proved that total cholesterol and LDL cholesterol significantly and positively correlated with cIMT which is an important biomarker of subclinical atherosclerosis; while HDL cholesterol had a negative correlation with CIMT.

Our results showed that there was a significant increase in serum level of triglycerides in diabetic patients with subclinical atherosclerosis in group B (248.50±33.33) compared to other groups.

This is consistent with the results of Qamar A. et al. [12] who proved that higher TG levels in T2DM subjects are associated with subclinical atherosclerosis that may lead to increased cardiovascular disease mortality.

Also, this was in agreement with Shimizu Y. et al. [13] who proved that diabetes, especially in association with high TG- HDL ratio, was a significant risk factor for atherosclerosis and increased arterial stiffness for Japanese men.

In diabetic patients with subclinical atherosclerosis group B, there was a significant increase in serum level of FPG (237.40±23.95), serum level of PPG (354.15±39.60) and $HbA_{1c\%}$ (9.79±0.71) compared to diabetic patients free from any vascular complications (group A).

This was in agreement with Sunil K. et al. [11] who proved that FPG, PPG and HbA_{1c} significantly and positively correlated with cIMT.

On the other hand our results were different from the study conducted on patients with diabetes mellitus by Du HW et al. [14] who found no significant relationship between HbA_{1c} and cIMT values.

Our negative correlation between serum MFG-E8 and hs-CRP was consistent with Dai w. et al. [15] who reported that the serum MFG-E8 concentrations are negatively associated with both the hs-CRP concentration and the severity of coronary artery stenosis in patients with coronary heart disease and explained this by increasing MFG-E8 consumption during the removal of the large numbers of apoptotic cells present in atherosclerotic lesions.

Ridker PM. and Tomiyama H. et al. [16,17] agreed with us and reported that hs-CRP is a parameter that is used to assess inflammation and high hs-CRP is a risk factor for cardiovascular events and elevated arterial stiffness. Also, Pleskovic A. et al. [18].have described an association between carotid atherosclerosis and hs-CRP.

Tanaka M. [19] agreed with us and proved that elevated plasma glucose levels, both fasting and 2-h postprandial, can be considered as risk factors for microvascular complications in patients with type 2 diabetes mellitus.

Chang H. et al. [20] agreed with us and proved that higher HbA_{1c} variability is associated with the development of microalbuminuria in type 2 diabetes patients, and also the study done by Bosnyak z. et al. [21] who reported that achieving glycemic control, as determined by HbA_{1c} levels, is effective in reducing the risk of microvascular type 2 diabetes complications.

Our results were in line with Nalysnyk L. et al., [22] who proved that glycemic control, especially in the postprandial period, may reduce the development of diabetic micro and macrovascular complications. Also, a study done by Sheyu L. et al. [23] proved that a higher HbA_{1c} variability is associated with increased risks of cardiovascular events and microvascular complications of diabetes.

Current study findings were in consistence with the study done by Suresh K. et al. [24] which proved that microalbuminuria may be considered as an early risk marker of nephropathy in type 2 diabetes mellitus.

Sun G. et al. [25] agreed with us and proved that reduced serum MFG-E8 concentrations are associated with increased risk of microvascular complications in patients with type 2 diabetes.

Matsuda A. et al. [26] demonstrated that exogenous MFG-E8 administration could attenuate inflammation by reducing pro-inflammatory cytokines, such as TNF-a, IL-6, and IL-1β, in sepsis and in renal, hepatic, and intestinal ischemia/reperfusion conditions. This suggests that MFG-E8 has important anti-inflammatory properties. These inflammatory cytokines are also highly expressed in patients with diabetic nephropathy, diabetic retinopathy and coronary heart disease according to a study done by Schram M.T. et al. [27]. So, MFG-E8 might prevent the development of diabetic microvascular complications by reducing these inflammatory factors.

According to our findings we suggest that serum MFG-E8 concentrations are negatively associated with the risk of microvascular complications in T2DM patients, thus it may be a potential candidate of diabetic microvascular complications and can be used as an early diagnostic marker of microvascular complications in type 2 diabetic patients.

Further studies on a wide scale on type 2 diabetic patients with microvascular complications are recommended for accurate assessment of using serum MFG-E8 concentration as an early diagnostic marker of diabetic microvascular complications. Also, it is recommended to study the possibility of using MFG-E8 in prophylaxis and treatment of diabetic microvascular complications.

5. CONCLUSIONS

There was a negative association between serum MFG-E8 concentration and early microvascular complications in T2DM patients. There was no correlation between serum MFG-E8 and CIMT. So, MFG-E8 seems not to be a sensitive biomarker for early diagnosis of subclinical atherosclerosis in T2DM. Serum MFG-E8 might be used as an early diagnostic marker of microvascular complications in type 2 diabetic patients.

CONSENT AND ETHICAL APPROVAL

This study was carried out at clinical pathology department, Faculty of Medicine, Tanta University Hospitals, Egypt after approval from Ethical Committee and obtaining informed written consent.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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