

Study of Serum Levels of IGFBP1 and MMP-9 in Patients with Type 2 Diabetes Mellitus with Coronary Artery Disease: A Cross-Sectional Study

Wael ElSeody ElSayed Wafy¹, Jalaat Abdel Fatah Abdel Aaty¹,
Mohamed Mostafa Ahmed Rizk², Eman Yousef Morsi¹, Mohamed Ahmed Sadaka³, Reem fathallah¹

1. Department of Internal Medicine; Unit of Diabetes, Lipidology & Metabolism. Faculty of Medicine, Alexandria University, Alexandria, Egypt.

2. Department of Clinical Pathology, Faculty of Medicine, University of Alexandria, Alexandria, Egypt.

3. Department of Cardiology; Faculty of Medicine, Alexandria University, Alexandria, Egypt.

Corresponding Author:

Wael elSeody

Postal address: Champollion Street, El-Khartoum Square, Azarita Medical Campus, 21521, Alexandria, Egypt.

Mobile: 01002559722

E-mail address: wael_elsaudi@yahoo.com.

ABSTRACT

Background: Diabetes mellitus (DM) has become a significant health problem in most nations. Coronary artery atherosclerosis is the single most common cause of death in men and women and the leading cause of morbidity and mortality for individuals with diabetes. Studies reported that IGFBP1 affects the prognosis and mortality of cardiovascular diseases in patients without diabetes and glucose intolerance. MMP-9 levels is highly correlated with cardiovascular mortality in patients with atherosclerosis but its role in the development of complications of type 2 diabetes is not fully understood. **The aim** of this was to study serum levels of IGFBP1 and MMP9 and their relation to the severity of atherosclerotic coronary artery disease in patients with type 2 diabetes. **Subjects & Methods:** 100 patients with type 2 diabetes mellitus and atherosclerotic coronary artery disease documented by angiographic analysis which was done by the SYNTAX score. All patients have been evaluated clinically, with coronary angiographically and biochemically investigations including plasma levels of IGFBP-1 and MMP-9. **Result:** IGFBP-1 was negatively correlated with systolic, diastolic,

mean arterial pressure, FBG, HbA1c and LDL. MMP-9 was positively correlated with systolic, diastolic, mean arterial pressure, FBG, HbA1c and LDL. SYNTAX score was positively correlated with systolic, diastolic, mean arterial pressure, FBG, HbA1c and LDL. Statistical analysis of the studied parameters showed that a Significant negative correlation observed between IGFBP-1 and SYNTAX score and a Significant positive correlation was observed between MMP-9 and SYNTAX score. **Conclusion:** A significant negative correlation was observed between IGFBP-1 and SYNTAX score and a Significant positive correlation was observed between MMP-9 and SYNTAX score.

Key words: IGFBP-1, MMP-9, SYNTAX and atherosclerosis,

INTRODUCTION

Diabetes mellitus (DM) has become a significant health problem in most nations with the number of patients dramatically increasing and expected to reach 366 million by the year 2030. Diabetes. Coronary artery atherosclerosis is the single most common cause of death in men and women and the leading cause of morbidity and mortality for individuals with

diabetes. Atherosclerosis is a disease of large and medium-sized muscular arteries and is characterized by endothelial dysfunction, vascular inflammation and buildup of lipids, cholesterol, calcium, and cellular debris within the intima of the vessel wall leading to plaque formation and rupture.⁽¹⁾

The insulin-like growth factor binding proteins (IGFBPs) are a superfamily comprised of six proteins (IGFBP-1 to 6) that bind to IGFs with high affinity. IGFBPs are regulated by proteases released from several tissues,⁽²⁾ and their IGF binding affinity is negatively affected by proteolytic cleavage as well as phosphorylation of IGFBPs⁽³⁾, IGFBP-1, among the IGFBP family, is produced dominantly in the liver and kidney and it is the most important member with regard to insulin and glucose metabolism.⁽⁴⁾ IGFBP-1 level is decreased in the fasting serum of early NIDDM patients with insulin resistance.⁽⁵⁾ Overexpression of IGFBP-1 has been shown to improve impaired glucose tolerance.⁽⁶⁾ On the other hand, serum IGF-1 is reduced while IGFBP-1 level is increased in type 1 diabetic patients. Studies reported that IGFBP1 affects the prognosis and mortality of cardiovascular diseases in patients without diabetes and glucose intolerance; which might be due to an independent direct regulation of vascular endothelial cells (EC) and smooth muscle cells (SMC).⁽⁷⁾

Matrix metalloproteinases (MMPs) are a family of zinc-dependent endopeptidases responsible for both physiological and pathophysiological tissue remodelling. There are 25 family members described in vertebrates, with 22 found in humans.⁽⁸⁾ Normal myocardium possesses several ECM proteins, including collagens, laminins, fibronectin, and low levels of multicellular proteins, all of which play a role in the physiological performance of the heart. MMP-9 plays a major role in the degradation of ECM in a large spectrum of physiology and pathophysiology processes that involve tissue remodelling.⁽⁹⁾ MMP-9 plays divergent roles in the formation and destabilization of atherosclerotic plaques.⁽¹⁰⁾ Plaque ruptures are associated with increased MMP-9 proteolytic

activity, and its levels are highly correlated with cardiovascular mortality in patients with atherosclerosis.⁽¹¹⁾ The role of MMPs in the development of complications of type 2 diabetes is not fully understood.

To date, most studies on IGFBP-1 have focused on diabetes and glucose metabolism. While studies on MMP-9 have focused on atherosclerotic cardiovascular diseases. No sufficient data between the mentioned markers with diabetic atherosclerotic cardiovascular diseases.

AIM OF THE WORK was to study serum levels of IGFBP1 and MMP9 and their relation to the severity of atherosclerotic coronary artery disease in patients with type 2 diabetes.

SUBJECTS & METHODS

This cross-sectional study was conducted on 100 patients with type 2 diabetes mellitus and atherosclerotic coronary artery disease documented by angiographic analysis which was done by the SYNTAX score. Written informed consent of patients and volunteers was obtained following a detailed explanation of the procedures that they will have. The study was approved by the Ethics Review Board of the Faculty of Medicine, Alexandria University

Exclusion criteria: Type 1 diabetes, Pregnancy, Congenital heart disease, Valvular heart disease, Chronic liver disease, chronic kidney disease and definite evidence of recent malignancy.

All patients were evaluated clinically by taking a full history and complete clinical examination. Routine Laboratory studies: Complete blood picture, Serum urea, creatinine, Fasting blood glucose. Glycosylated haemoglobin (HbA1c), Lipid profile, Plasma level of IGFBP-1 and MMP-9 by ELISA technique.

Resting ECG and Echocardiography

The angiographic analysis has been done by the SYNTAX score (SS)

RESULTS

According to age, duration of diabetes and BMI there is no significant relation between these parameters and IGFBP-1 level. According to blood pressure, IGFBP-1 was

negatively correlated with systolic, diastolic and mean arterial pressure. (Table IIa)

According to FBG, HbA1c and LDL, there is a negative relation with IGFBP-1. (Table IIb)

According to age, duration of diabetes and BMI there is no significant relation between these parameters and MMP-9 level. According to blood pressure was positively correlated with systolic, diastolic and mean arterial pressure. (Table IIIa)

According to FBG, HbA1c and LDL, there is a positive relation with MMP-9. (Table IIIb)

According to age, duration of diabetes and BMI there is no significant relation between

these parameters and SYNTAX score level. According to blood pressure, the SYNTAX score was positively correlated with systolic, diastolic and mean arterial pressure. (Table Ia)

According to FBG, HbA1c and LDL, there is a positive relation with SYNTAX score. (Table Ib)

A significant negative correlation was observed between IGFBP-1 and SYNTAX score. (Table IV)

A significant positive correlation was observed between MMP-9 and SYNTAX score. (Table IV)

• **Table (Ia): Relation between syntax score and different parameters (n = 100)**

	N	Syntax score			U	P
		Min. – Max.	Mean ± SD.	Median		
Sex						
Male	9	4.0 – 30.0	15.64 ± 7.75	15.0	123.0	0.544
Female	1	4.0 – 32.0	16.73 ± 8.28	16.0		
Smoking						
Negative	8	4.0 – 32.0	15.58 ± 7.89	15.50	113.0	0.644
Positive	2	4.0 – 32.0	16.40 ± 8.03	15.50		

• **Table (Ib): Correlation between SYNTAX score and different parameters (n = 100)**

	Syntax score	
	r _s	P
Age (years)	-0.080	0.430
Duration (years)	0.011	0.912
BMI (kg/m ²)	0.095	0.347
Systolic	0.547*	<0.001*
Diastolic	0.555*	<0.001*
FBG	0.948*	<0.001*
HbA1c	0.928*	<0.001*
LDL	0.505*	<0.001*

Table (IIa): Relation between IGFBP-1 and different parameters (n = 100)

	N	IGFBP-1			U	P
		Min. – Max.	Mean ± SD.	Median		
Sex						
Male	9	100.0 – 1470.0	421.36 ± 320.22	290.0	092.50	.412
Female	1	70.0 – 1410.0	413.05 ± 376.82	275.0		
Smoking						
Negative	8	75.0 – 1410.0	433.42 ± 364.05	292.50	131.50	.741
Positive	2	70.0 – 1470.0	408.47 ± 331.67	280.0		

Table (IIb): Correlation between IGFBP-1 and different parameters (n = 100)

	IGFBP-1 (ng/ml)	
	r_s	P
Age (years)	0.082	0.418
Duration (years)	-0.036	0.721
BMI (kg/m ²)	-0.148	0.142
Systolic mmHg	-0.532*	<0.001*
Diastolic mmHg	-0.549*	<0.001*
FBG mg/dl	-0.930*	<0.001*
HbA1c %	-0.914*	<0.001*
LDL mg/dl	-0.518*	<0.001*

Table (IIIa): Relation between MMP-9 and different parameters (n = 100)

	N	MMP-9			U	p
		Min. – Max.	Mean ± SD	Median		
Sex						
Male	9	250.0 – 1850.0	932.29 ± 351.82	990.0	140.0	0.626
Female	1	210.0 – 1950.0	974.63 ± 406.22	990.0		
Smoking						
Negative	8	210.0 – 1900.0	917.37 ± 364.72	980.0	112.50	.642
Positive	2	250.0 – 1950.0	969.44 ± 380.63	990.		

Table (IIIb): Correlation between MMP-9 and different parameters (n = 100)

	MMP-9 (ng/L)	
	r_s	P
Age (years)	-0.062	0.541
Duration (years)	0.013	0.897
BMI (kg/m ²)	0.100	0.324
Systolic mmHg	0.555*	<0.001*
Diastolic mmHg	0.550*	<0.001*
FBG mg/dl	0.944*	<0.001*
HbA1c %	0.919*	<0.001*
LDL mg/dl	0.513*	<0.001*

Table (IV): Correlation between SYNTAX score with IGFBP-1 and MMP-9 (n = 100)

	Syntax score	
	r_s	P
IGFBP-1 (ng/ml)	0.975*	<0.001*
MMP-9 (ng/L)	0.983*	<0.001*

DISCUSSION:

We tried to find the relationship between the serum level of IGFBP-1 and MMP-9 with the degree of severity of CAD measured by SYNTAX score in patients with type 2 DM.

Coming to the present study, was a cross-sectional observational study conducted on 100 CAD patients with type 2 DM.

According to age, duration of diabetes and BMI there is no significant relation between these parameters and IGFBP-1 level. E M Rutanen, T Kärkkäinen, U H Stenman et al suggest that there was no significant relation between age and IGFBP-1⁽¹²⁾. Mujde Akturk, Metin Arslan, Alev Altinova et al. show that there is a positive relationship between IGFBP-1 and the duration of diabetes mellitus⁽¹³⁾. Tanya L Alderete, Courtney E Byrd-Williams, Claudia M Toledo-Corral et al show a negative relationship between IGFBP-1 and BMI⁽¹⁴⁾. According to blood pressure, IGFBP-1 was negatively correlated with systolic, diastolic and mean arterial pressure. Adrian H Heald, K W Siddals, and William Fraser et al support the same finding⁽¹⁵⁾. Also regarding FBG and HbA1c the current study shows a negative correlation with IGFBP-1, Golam Kabir, Mosaraf Hossainan, Omar Faruque et al show the same conclusion.⁽¹⁶⁾ Paul Pettersson-Pablo, Torbjörn K. Nilsson, Lars H et al also conclude the same⁽¹⁷⁾. LDL also shows negative correlation with IGFBP-1

In this study we investigate MMP-9 with different parameters and the following results observed, No significant relation between MMP-9 level and the following parameters (age, duration of diabetes and BMI) Patrizia Cancemi, Anna Aiello, Giulia Accardi et al shows that is no significant relation between age and MMP-9⁽¹⁸⁾. While Marta Kollarova, Angelika Puzserova, and Peter Balis et al. report a positive correlation⁽¹⁹⁾. G Derosa, A D'Angelo, C Tinelli et al. found a positive correlation between MMP-9 and BMI⁽²⁰⁾. But Alireza Rastgoo Haghi, Nasrin Khorami, Mahtab Fotoohi et al. found that MMP-9 did not have a significant relationship with age, sex, duration of disease and BMI⁽²¹⁾.

According to blood pressure (systolic and diastolic) a significant positive correlation was

observed with MMP-9 Katerina Vitlianova, Janeta Georgieva, Maria Milanova et al. also found a positive correlation between elevated blood pressure and MMP-9.⁽²²⁾

According to FBG and HbA1c, a significant positive correlation was observed with MMP-9. Alireza Rastgoo Haghi, Nasrin Khorami, Mahtab Fotoohi et al. found also positive correlation.⁽²³⁾

According to LDL, a significant positive correlation was observed with MMP-9 the same findings were also noted by Mike Sampson, Isabel Davies, Jelena Gavrilovic et al⁽²⁴⁾

SYNTAX score also correlated with different parameters and the following data has been observed, no significant relation between SYNTAX score and the following parameters (age, sex, duration of diabetes and BMI). Wenjia Yang, Xiaoling Cai, Xueyao. Han et al. found a positive correlation between age and degree of coronary atherosclerosis they also found a significant positive correlation and male sex⁽²⁵⁾. Lynne E. Wagenknecht, Ralph D'Agostino Jr, Peter J. Savage et al found that there is no significant relation between diabetes and degree of atherosclerosis⁽²⁶⁾. Robert J Henning found a positive correlation between BMI and the degree of atherosclerosis in patients with diabetes⁽²⁷⁾.

According to blood pressure (systolic and diastolic) a significant positive correlation was observed with SYNTAX score John R. Petrie, Tomasz J. Guzik, and Rhian M. Touyz. found a positive correlation between hypertension and the degree of atherosclerosis in patients with diabetes⁽²⁸⁾

According to FBG and HbA1c, a significant positive correlation was observed with the SYNTAX score. Debora Sitnik, Itamar S Santos, Alessandra C Goulart et al found a positive significant correlation between FBG HbA1c and atherosclerosis.⁽²⁹⁾

According to LDL a significant positive correlation was observed with the SYNTAX score. The same correlation was also noticed by Elham Hasheminasabgorji and Jay C. Jha.⁽³⁰⁾

In current study a significant negative correlation was observed between IGFBP-1 and SYNTEX score.

The role of IGFBP-1 in cardiovascular prognosis and atherosclerosis remains controversial. A H Heald et al⁽³¹⁾, Rajwani A et al⁽³²⁾ and Wang J et al⁽³³⁾ found a negative correlation between IGFBP-1 and degree of atherosclerosis. While J. A. Janssen et al⁽³⁴⁾ found that there is no significant correlation between the above-mentioned parameters. Xiaojing Wu et al found a positive correlation between IGFBP-1 and the degree of atherosclerosis.⁽³⁵⁾

The positive correlation observed between MMP-9 and SYNTEX score was found in the current study. Its relation is also controversial Srdjan Popović et al.⁽³⁶⁾ and Razvan Daniel Macarie et al.⁽³⁷⁾ found positive relation between MMP-9 and atherosclerosis. On the other side Osman Beton et al⁽³⁸⁾ found that there is no significant correlation between the above-mentioned parameters.

CONCLUSION:

IGFBP-1 is significantly lower in diabetic patients with atherosclerotic cardiovascular diseases. It is negatively correlated to blood pressure, FBG, HbA1c and LDL. MMP-9 is significantly higher in diabetic patients with atherosclerotic cardiovascular diseases. It is positively correlated to blood pressure, FBG, HbA1c and LDL. Negative correlation between IGFBP-1 and degree of atherosclerosis in diabetic patients. Positive correlation between MMP-9 and degree of atherosclerosis in diabetic patients.

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