Role Of Insulin Like Growth Factor-1 and Insulin Like Growth Factor Binding Protein-3 In Patients Of Coronary Artery Disease Attending Suez Canal University Hospital

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ABSTRACT

*Cardiovascular disease is the leading cause of mortality, not only in the Western world, but also in developing countries. It has been suggested that circulating insulin like growth factor-1 (IGF-I) and insulin like growth factor binding protein-3(IGFBP-3) are involved in the pathophysiological processes underlying coronary artery disease. We evaluated the relationship between the levels of IGF-I and IGFBP-3 nd coronary atherosclerosis in sixty two patients attending Cardiac Clinic and Coronary Care Unit at Suez Canal University Hospital, and 30 healthy controls. IGF-1 and IGFBP-3 were measured using Immulite 1000. Fasting blood glucose and lipid profile were measured for all subjects. Coronary artery disease was more frequent among males compared to females (67.7%, and 32.3% respectively). Total cholesterol (TC), low density lipoprotein cholesterol (LDLc) and triacylglycerol (TAG) levels were significantly higher, while HDL was significantly lower in patients than controls. The means of IGF-1 and IGFBP-3 were significantly higher among control group compared to patients group (212.5 ± 109.1 ng/ml and 6.4 ± 2.3 ng/ml versus 129.5 ± 66.2 ng/ml., 4.4 ± 1.6 ng/ml respectively, p= 0.001 for each). Thirty (48.4%) of patients had 3 stenosed vessels. The mean percent of stenosis was 74.7 ± 14.2 %. IGF-1 and IGFBP-3 were lower in the group of three affected vessels but there was no significant correlation between both parameters and severity of the disease. There was significant correlation between IGF-1 and HDL (**r =0.254,** p-value = 0.046) in patients group while no significant correlation between IGF-1 and other parameters in both groups. There was no significant correlation between IGFBP-3 and other parameters in both groups. In conclusion, IGF-1, IGFBP-3 may be used to determine the risk of coronary artery disease in Egyptian population living in Suez Canal area.*

Key Words: *IGF-1, IGFBP-3and CAD.*

INTRODUCTION

Traditionally, atherosclerotic disease is considered a typical middle-age disease. The most common heart disease is coronary artery disease (CAD), which often appears as a heart attack [(1)].

The atherosclerotic process starts decades before the appearance of clinical symptoms (myocardial infarction, cerebral vascular accident and peripheral vascular disease). The progression and the severity of the atherosclerotic process are related to the presence, number, magnitude and duration of a series of risk factors[2].

Cardiovascular disease is the leading cause of mortality, not only in the Western world, but also in developing countries. Coronary artery disease is a global health concern today, with limited treatment options available to address that disorder. Extensive efforts have been devoted to molecular therapies to enhance perfusion and function of the ischemic myocardium[3].

Insulin-like growth factor I (IGF-I) is a peptide hormone that shares sequence homology with insulin and has a fundamental role in somatic growth and cellular differentiation, metabolism and survival [4].

IGF-1 is expressed, under GH (growth hormone) control, by the liver in an endocrine form or ubiquitously in a relevant 'paracrine/autocrine' fashion[5].

Besides the liver, important contributions to serum IGF-1 levels come from bone, vascular endothelium and exercising skeletal muscle[6] to give a total daily secretion of approx. 3−10 mg/day [7].

Daily IGF-1 serum preservation/tissue delivery is supervised by six different specific high-affinity binding proteins (IGFBP-1to IGFBP-6), synthesized mainly by the liver, which can bind IGF-1 in biological fluids, regulating its movement between intravascular and extravascular compartments, increasing its half-life, and managing IGF delivery to tissues by fine-tuning its concentrations in the interstitial fluid and its affinity for receptors[8].

The majority of IGFs in the circulation are bound to IGF binding proteins, of which IGF binding protein 3 (IGFBP-3) is the most predominant, carrying > 80% of circulating IGF-I. But, although IGFBP-3 is an important regulator of the bioactivity of IGF-I, there is evidence to suggest that IGFBP-3 possesses functions independent of its role as an IGF-I carrier protein [9].

It has been suggested that circulating IGF-I is involved in the pathophysiological processes underlying coronary artery disease (CAD). Experimental data in animals have shown that overexpression or administration of IGF-I after myocardial infarction (MI) prevents cardiomyocytes death and improves cardiac function [10,11].

Evidence for improvement of cardiac function and increased ventricular mass has been shown in individuals with growth hormone deficiency after short-term IGF-I therapy [12]. Improved cardiac performance has also been demonstrated following administration of recombinant IGF-I to individuals with chronic heart failure [13].

Several potential protective mechanisms of IGF-I on vascular disease processes have been described. Experimental infarction models suggest that IGF-I may promote survival of myocytes exposed to ischemic injury in part by enhancing glucose uptake[14].

Cross sectional observational studies have reported that circulating IGF-I concentrations are lower in individuals with CAD and MI [15-17], but the opposite has been reported as well [18]. Furthermore, increments in IGF-I levels are associated with reduced prevalence of atherosclerotic plaques, as measured by arterial ultrasound [19].

The prospective association between circulating levels of IGF-I and IGFBP-3 and subsequent risk of future CAD, however, remains uncertain [20-25].

Several population-based prospective studies have suggested that low circulating levels of IGF-I within the normal range may predict increased risk of ischemic heart disease [22,26] and ischemic stroke. IGFBP-3 levels have been both directly and inversely associated with prevalent and incident CVD [27,28].

IGF-1 deficiency may precipitate the apoptosis of smooth muscle cells migrating to the endothelial layer, as well as the cells found in the media of the vessel. This probably contributes to the destabilization of atherosclerotic plaque [29]. IGF-1 prevents the dilatation of heart muscle by activating cardiac progenitor cells and inhibiting apoptosis of cardiomyocytes and VSMC hypertrophy [30].

IGF-1 has also been shown to play a critical role in the reduction of ischemia/reperfusion damage, LV (left ventricular) dysfunction remodeling and in the recovery of ischemic cardiomyopathy through a reduction in apoptosis and apoptosis-induced inflammation. Moreover, IGF-1 enhances cardiomyocyte contractility and relaxation [8].

In a mouse model of diabetic cardiomyopathy, the induced expression of the IGF-1R gene prevented the onset of diastolic dysfunction, fibrosis and preserved cardiac function [31]. That low serum IGF-1 levels are able to predict the future onset of ischemic heart disease (IHD), heart failure (HF), and cardiovascular and all-cause mortality [21,22,32-37].

Two isolated exceptions have described no (n = 1122)[38] or inverse (n = 642)[20] prospective associations between IGF-1 levels and all-cause and cardiovascular mortality.

A third case is that of a prospective study (n = 1273) describing a more complex relation, in which low IGF-1 levels predicted all-cause mortality, and both low-normal and high-normal IGF-1 levels predicted IHD mortality[39].

Delafontaine et al.,[30] have reported that low systemic levels of IGF-1 and high systemic levels of IGF binding protein- 3 (IGFBP3) were direct risk factors for coronary artery disease[30].

The role of IGF-1 in the progression of coronary atherosclerosis is unclear[29].

These conflicting results leave the role of IGF-1 levels in coronary atherosclerosis an unresolved question. So, the aim of the present work is to determine the relationship between the levels of IGF--1 and IGFBP3-3 and coronary atherosclerosis in Suez Canal area.

MATERIALS & METHODS

Sixty two patients presented with coronary artery disease were recruited from Cardiac Clinic and Coronary Care Unit at Suez Canal University Hospital in the period from October 2011 to February 2012. Coronary artery disease was diagnosed by coronary angiography. Patient´s age ranged 36-75 years. Control group consisted of 30 volunteers with no history of coronary artery disease or family history of that disease. Their age ranged 35-67 years. The protocol was approved by the local Ethical Committee. They were enrolled in the study after obtaining informed consent. The two groups were subjected to the following: Detailed history taking including (personal history, present history of coronary artery disease, presence of chronic diseases {as diabetes mellitus, hypertension ...} and family history). Clinical examination included anthropometric measurements weight, height measurements and the body mass index was calculated as weight (Kg) / square of height (m^2).

Laboratory investigations including**:**

- Measurements of IGF-1 and IGFBP-3 using Immulite/Immulite1000 IGF-1kit (PILKGF-9,2005-10-12) and IGFBP-3 kit (PILKGB-6,2005-08-08) (Siemens, Immulite).
- Fasting blood glucose was determined by glucose oxidase method **(40).**
- Lipid profile: Serum total cholesterol (TC)**(41)**, and triacylglycerol (TAG) **42), were estimated colorimetrically and** HDL- cholesterol (HDLc)**(44)** was determined enzymatically**(43), while** LDL- cholesterol (LDLc) was calculated by the Friedewald formula**(44).**

Statistical analysis:

The obtained data were processed using SPSS version 15 (SPSS Inc., Chicago, IL, USA). Quantitative data were expressed as means ± SD while qualitative data were expressed as numbers and percentages (%).Chi square (χ^2) and Fisher's exact tests were used to test significance of difference between qualitative variables. Unpaired Student t test and analysis of variance (ANOVA) was used to test significance of difference between two or more qualitative variables respectively. Spearman correlation coefficient (r) was used to analyze correlation between different quantitative variables. ROC (Receiver Operating Characteristic) curve was used to set a cut off value for IGF and IGF BP-3 for detection of coronary artery disease. A probability value of p-value < 0.05 was considered statistically significant.

RESULTS

The current study aimed to determine the role of IGF-1 and IGFBP-3 in patients with CAD compared to healthy controls. It included 62 patients presented with CAD attending Suez Canal University Hospital in Ismailia and 30 apparently healthy controls. The mean age of CAD patients was 54.56±8.9 years, with a range of 36 -75 years. Controls´ age ranged 36-73 years, with a mean of 49.6 ± 10.2 years.

There was no significant difference between patients and control groups regarding to smoking, hypertension and diabetes mellitus (P>0.05). Coronary artery disease was more frequent among males compared to females (67.7%, versus 32.3% respectively). Both groups were matched for age and sex with no significant difference between patients and control regarding to smoking, hypertension and diabetes mellitus (p-value >0.05) as shown in table (1).Table (2) showed that TC, LDLc, and TAG were significantly higher, while HDLc was significantly lower in patients than controls. Table (3) showed that the mean IGF-1 was significantly higher among controls group (212.5 ± 109.1ng/ml) compared to patients group (129.5 ± 66.2 ng/ml) (p= 0.001). Moreover, the mean IGFBP-3 was higher among controls group (6.4 ± 2.3ng/ml) than patients group (4.4 ± 1.6ng/ml), with significant difference (p= 0.001). Table (4) showed severity of the disease where 48.4% of patients had 3 stenosed vessels, 21% had 2 stenosed vessels while 30.6% had one vessel affected. The mean percent of stenosis was 74.7 ± 14.2 %. Table (5) showed the correlation between the means of IGF-1 and IGFBP-3 in the patients group and the severity of disease. IGF-1 and IGFBP-3 were lower in the group of three affected vessels but there was no significant correlation between both parameters and severity of the disease. Table (6) showed significant correlation between IGF-1 and HDLc (p-value = 0.046) in patients group while no significant correlation between IGF-1 and age, lipid profile, and percentage of stenosis in both groups. Table (7) showed that there was no significant correlation between IGFBP-3 and age, lipid profile, and percentage of stenosis in both groups. Based on receiver operating characteristic (ROC) curve, we calculated best cut off points for investigated parameters (table 8).

Table (1): Comparison between both groups regarding risk factors

Variables		**Patient group (n=62)**	**Control group (n= 30)**
Age (years)m, Mean ± SD		54.56 ± 8.9	49.6 ± 10.2
Sex	Male	67.7%	60%
	Female	32.3%	40%
Smoking	yes/	58.1 %	40 %
	no	41.9 %	60 %
Diabetes	yes/	41.9 %	36.7 %
	no	58.1 %	63.3 %
Hypertension	yes	51.6 %	40%
	no	48.4 %	60%

No statistically significant difference (p-value > 0.05 for each)

Table (2): Comparison between both groups regarding lipid profile

Variables		**CAD patients group (n=62)**	**Control group (n=30)**	**p-value**
HDLc (mg/dl)	Mean ± SD	40.4 ± 8.6	46.15 ± 8.9	0.004*
	Range	22 – 68	22 – 65	
Total Cholesterol (mg/dl)	Mean ± SD	230.0 ± 65.0	174.13 ± 59.9	0.001*
	Range	102 – 362	97 – 300	
Triacylglycerol (mg/dl)	Mean ± SD	178.5 ± 62.4	146.1 ± 40.3	0.01*
	Range	85 – 400	85 – 305	
LDLc (mg/dl)	Mean ± SD	126.7 ± 42.0	104.3 ± 43.8	0.02*
	Range	55 – 219	42 – 188	

HDLc= High density lipoprotein cholesterol.
LDLc= Low density lipoprotein cholesterol.
*Significant difference (p-value < 0.05)

Table (3): Comparison between both groups regarding IGF-1 and IGFBP-3

Parameters		**Study group (n=62)**	**Control group (n=30)**	**p-value**
IGF-1 (ng/ml)	Mean ± SD	129.5 ± 66.2	212.5 ± 109.1	0.001*
	Range	25 – 351	30 – 388	
IGFBP-3 (ng/ml)	Mean ± SD	4.4 ± 1.6	6.4 ± 2.3	0.001*
	Range	0.5 – 9.8	2.2 – 11.3	

*Statistically significant difference (p-value < 0.05).
IGF-1= insulin like growth factor-1.
IGFBP-3 = Insulin like growth factor Binding Protein-3

Table (4): Distribution of patients group according to coronary angiography findings

Variables		**Number (n=62)**	**Percentage**
Severity	1 vessels	19	30.6%
	2 vessels	13	21.0%
	3 vessels	30	48.4%
Percence of stenosis	Mean ± SD	74.7 ± 14.2	

Table (5): Relation between IGF-1, IGFBP-3 and severity of CAD in patients group:

Parameters	Severity of disease		
	1 vessel	**2 vessels**	**3 vessels**
IGF (ng/ml) Mean ± SD	137.1 ± 68.7	148.2 ± 78.9	116.6 ± 56.7
IGFBP-3 (ng/ml) Mean ± SD	4.3 ± 2.0	5.2 ± 1.7	4.0 ± 1.3

No statistically significant difference (p-value > 0.05)

Table (6): Correlation between IGF-1 and age, lipid profile, and percentage of stenosis in each of the two studies groups

Variables	Patients group, (n=62)		Control group, (n=30)	
	R	**p-value**	**r**	**p-value**
Age, years	0.001	0.9 (NS)	0.23	0.205(NS)
HDLc, mg/dl	0.254	0.046*	0.22	0.24 (NS)
Total Cholesterol, ,	0.09	0.518 (NS)	-0.129	0.49 (NS)
Triacylglycerol, ,	0.11	0.39 (NS)	0.06	0.72 (NS)
LDLc, , mg/dl	-0.08	0.5 (NS)	-0.20	0.26 (NS)
Percent of stenosis	0.09	0.47 (NS)	-	-

HDLc= High density lipoprotein cholesterol. LDLc= Low density lipoprotein cholesterol.

r :Spearman Correlation coefficient NS: no significant difference (p-value > 0.05)

*Significant difference (p-value < 0.05)

Table (7): Correlation between IGFBP-3 and age, lipid profile, and percent of stenosis in both groups

Variables	CAD group (n=62)		Control group (n=30)	
	r	**p-value**	**r**	**p-value**
Age, years	0.297	0.11 (NS)	0.29	0.111 (NS)
HDLc, mg/dl	-0.067	0.60 (NS)	-0.17	0.344 (NS)
Total Cholesterol , mg/dl	0.167	0.19 (NS)	-0.12	0.52 (NS)
Triacylglycerol, , mg/dl	0.213	0.09 (NS)	-0.16	0.39 (NS)
LDLc, , mg/dl	0.054	0.67 (NS)	-0.04	0.83 (NS)
Percent of stenosis	0.06	0.6 (NS)	-	-

HDLc= High density lipoprotein cholesterol. LDLc= Low density lipoprotein cholesterol.

r :Spearman Correlation coefficient NS: no significant difference (p-value > 0.05)

Table (8): Sensitivity and specificity of investigated parameters by using Receiver Operating Characteristic (ROC) curve

Parameters	Cut-off	Sensitivity	Specificity	Area under ROC curve
IGF-1	173	71%	63%	0.72
IGFBP-3	5.1	77%	77%	0.77

DISCUSSION

Coronary artery diseases (CAD) constitute a major health problem in many parts of the world and are an important cause of morbidity and mortality. It is predicted that by the year 2020, CAD will be the main cause of disability worldwide [(45)].

There is evidence that IGF-1 plays a role in cardiovascular disorders such as atherosclerosis [(46,47)].

The present study was undertaken to determine the relationship between the levels of IGF-1 and IGFBP-3 with coronary atherosclerosis in patients living in Suez canal area attending at Cardiology Unit, Suez Canal University Hospital. There was no significant difference between patients group and control group regarding to smoking, hypertension and diabetes mellitus (p>0.05). However, significant differences were found between both groups regarding to HDLc, LDLc, TC, and TAG (p<0.004, ?0.02, <0.001 and <0.01 respectively). Similar results have been reported by other studies [(48,49)]. **Shankar et al.,**[(50)] reported significant difference between CAD patients and controls (p<0.001) as regard TC, LDLc and TAG but no significant difference between both groups regarding to HDLc[(50)]. In a prospective cardiovascular Munster study, HDLc in CHD patients was reported to be lower as compared to that in controls but not statistically significant[(51)].

Jousilahti *et al.*, [(52)] stated that in male cases there was an increased levels around age 45 to 50 years, while in female cases, there was increase that continues sharply until age of 60 to 65 years [(52)].

In the present study, there was significant difference between both groups regarding IGF-1 and IGFBP-3 (p< 0.001 for each) which were lower in patients group than control. In fact, these results were in agreement with previous studies which demonstrated decreased circulating levels of total or free IGF-1 or IGFBP-3 in patients with CAD [(27,53)]. **Bøtker et al. (1997) and Ruotolo et al. (2000)** demonstrated that circulating levels of IGF-1 and/or IGFBP were decreased in patients with manifest CAD due to decreased activity of the GH–IGF-1 axis [(54,55)]. **Kawachi et al. (2005)** found that increased serum IGF-1 and IGFBP-3 levels were associated with CAD in Japanese men[(28)], while **Juul*et al.* (2002)** demonstrated that the low IGF-1 and high IGFPP-3 predicted increased risk of ischemic heart disease in a case control study which was conducted in a large

prospective study on cardiovascular epidemiology[26].

The present study showed no relation between IGF-1, IGFBP-3 and severity of IHD in the study group. **Schuler-Lüttmann et al. (2000)** examined the associations of IGF-1 and IGFBP-3 with three coronary scores: a vessel score, a stenosis score, and an extent score and found IGFBP-3 to be significantly inversely associated with all three scores. They also reported that IGF-1 was inversely associated with arteriosclerosis in unadjusted analysis, but in multivariate analysis the association between vessel score and IGF-1 became positive and marginally significant and the associations for stenosis score and extent score became non-significant [27]. **Schuler-Lüttmann et al. (2000)** speculated that IGFBP-3 may be part of the insulin resistance cluster, which would underlie the physiologic basis of the associations between IGFBP-3 and arteriosclerosis [27].

Burchardt et al. (2010) noticed significantly elevated circulating levels of IGF-1 in patients with significant obstructive lesions in all three coronary arteries in contrast to those without changes [29].

In this study there was significant inverse correlation between IGF-1 and HDLc (r = -0.254, P=0.046), while there was no significant correlation between IGF-1 and TC and LDLc (P>0.5 &>0.3 respectively). These results are in accordance with a study of elderly men and women, performed by **Ceda et al. (1998)** who found no association between IGF-1 and total or LDLc [56]. On the other hand, in a dietary intervention study, **Prewitt et al. (1992)** found significant inverse associations between IGF-1 and TC and LDLc in hypercholesterolemic women with a mean age of 32 years (range, 20–48 years) both after a 4-week high-fat diet and after a 20-week low-fat diet. They did not find an association between IGF-1 and HDLc [57]. Also, in a clinical study of 132 healthy elderly men and women, **laura et al. (2004)** found a significant positive correlation between IGFBP-3 and HDLc after adjustment for age and body mass index but no association between either IGF-1 and TC or LDLc or IGFBP-3 and TC or LDLc [58]. In a large cross-sectional study of men and women in the Singapore Chinese Health Study [59], there were positive correlations of TC and LDLc with both IGF-1 and IGFBP-3, but there were no associations for HDLc. Colangelo **et al. (2004)**, stated that their finding of a positive correlation between HDLc and IGFBP-3 suggests that growth hormone, which activates IGF formation and secretion, plays a role in lipid metabolism [58].

In conclusion, IGF-1 and IGFBP-3 may be used as risk factors in CAD in Egyptian patients in Suez Canal area. Further studies using larger series and different population might lead to more significant results.

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دور عامل النموالشبيه بالانسولين-١والبروتينات المرتبطة بعامل النمو الشبيه بالانسولين-٣ بمرضى الشريان التاجى المترددين على مستشفى جامعه قناه السويس

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انسداد الشريان التاجي من الأمراض الشائعة عالميا ، ومن الأسباب الرئيسية للوفيات في المجتمعات الغربية والعالم النامي. و قد أظهرت الدراسات أهمية عامل النمو الشبيه بالانسولين-١ ، والبروتين المرتبط بعامل النمو الشبيه بالانسولين-٣ في أمراض الشريان التاجي. لذا هدفت هذه الدراسة الى التحقق من امكانية العلاقة بين عامل النمو الشبيه بالانسولين-١ والبروتين المرتبط بعامل النمو الشبيه بالانسولين-٣ وأمراض الشريان التاجي.

اشتملت الدراسة على ٦٢ مصريا مريضا بامراض الشريان التاجى من الجنسين والمترددين على قسم أمراض القلب ووحدة رعاية القلب في مستشفى جامعة قناة السويس ، والمقيمين فى منطقة القناة و ٣٠ من الأفراد الأصحاء كمجموعة شابطة. و قد تم قياس مستوى كل من عامل النمو الشبيه بالانسولين-١ والبروتين المرتبط بعامل النمو الشبيه بالانسولين-٣ فى المجموعتين ، كما تم قياس مستوى الدهون والسكر فى الدم.

وبعد التحليل الاحصائى للنتائج أوضحت الدراسة انخفاض مستوي كل من عامل النمو الشبيه بالانسولين-١ والبروتين المرتبط بعامل النمو الشبيه بالانسولين-٣ فى مجموعة المرضى مقارنة بالمجموعة الضابطة من الأصحاء وكان هذا الانخفاض ذو دلالة احصائية. وقد انخفض كلا منهما انخفاضا لم يكن ذو دلالة احصائية في المرضى المصابين بانسداد في ثلاثة شرايين تاجية مقارنة بالمرضي المصابين بانسداد فى عدد أقل من الشرايين التاجية. و لم يكن هناك علاقة ذو دلالة احصائية بين كل من عامل النمو الشبيه بالانسولين-١ والبروتين المرتبط بعامل النمو الشبيه بالانسولين-٣ ومستوى الدهون والسكر فى الدم فى المجموعتين.

ولذلك ربما يكون لكل من عامل النمو الشبيه بالانسولين-١ والبروتين المرتبط بعامل النمو الشبيه بالانسولين-٣ دور في قابلية الاصابة بامراض الشريان التاجى.