Impact of insulin like growth factor-1 in development of coronary artery ectasia

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ABSTRACT

Coronary artery ectasia (CAE) is characterized by inappropriate dilatation of the coronary vasculature. The mechanisms of CAE are not well known. Insulin-like growth factor-1 (IGF-1) may make endothelial cells and smooth muscle cells more sensitive to the effects of growth hormone. In the present study, we hypothesized that IGF-1 may have an impact on the formation of ectasia and aneurysm in arterial system, and aimed to investigate the associations between the presence of CAE and serum IGF-1 levels in patients undergoing coronary angiography. The study included 2.980 subjects undergoing elective diagnostic coronary angiography. We selected 40 patients diagnosed with CAE as CAE group and 44 subjects with absolutely normal coronary arteries were assigned as normal control group. IGF-1 levels were measured in both groups of patients. Groups were similar in terms of age, sex and coronary artery disease risk factors. The serum IGF-1 levels were significantly higher in CAE patients with 109.64±54.64 ng/mL than in controls with 84.76±34.01 ng/mL (p=0.016). HDL levels were lower in ectasia group with 41.5±10.7 mg/dL than controls with 47.7±10.4 mg/dL (p=0.018). By means of logistic regression analysis, high IGF-1 and low HDL levels were found to be independent risk factors for the presence of CAE (p<0.02, p<0.016, respectively). The study revealed that there was a positive correlation between serum IGF-1 levels and presence of CAE, and high IGF-1 levels and low HDL levels were independent risk factors for the presence of CAE. Future studies are needed to confirm these results.

KEY WORDS: insulin like growth factor 1, IGF-1; coronary artery ectasia, CAE

INTRODUCTION

Coronary artery ectasia (CAE) is an abnormal dilatation of coronary arteries in which the ectatic segment exceeds the diameter of the normal adjacent segments or the diameter of the patient's largest coronary vessel by 1.5 times [1]. It is a rare clinical entity. The incidence of CAE ranges from 0.3 to 5.3% in coronary angiographic series [1,2]. Severity of CAE is defined by the involvement of a single vessel or multiple vessels [3]. CAE is characterized by inappropriately localized or diffuse dilatation of the coronary vasculature. The main coronary angiographic characteristics of CAE are impaired coronary blood flow, delayed antegrade coronary dye filling, segmental back flow phenomenon and stasis with local deposition of dye in dilated coronary segments [4]. Patients with CAE may be totally asymptomatic or present with atherosclerotic heart disease-like symptoms, about 50% of CAE patients present with atypical anginal pain, as the ectatic lesions can interfere with the coronary blood flow and CAE may cause myocardial ischemia or myocardial infarction without significant coronary artery stenosis due to intracoronary thrombosis within the ectatic segment and distal embolization of this thrombotic material [5]. The etiology and pathophysiology of CAE remains unclear. It is believed that CAE is a specific form of atherosclerotic coronary artery disease (CAD), and in approximately 20-30% of patients, it maybe congenital in origin. In most cases, CAE is found to coexist with CAD, whereas in 10-20% of cases, it is associated with cocaine abuse, toxins, inflammation, infections, inflammatory diseases, cardiac lymphoma and connective tissue disorders such as Kawasaki disease, systemic lupus erythematosus, Marfan syndrome, and Ehlers-Danlos syndrome [6-10]. In histopathological appearance of the disease, marked destruction and reduction of the medial elastic fibers with disruption of the internal and external elastic lamina, smooth muscle hyalinization of the coronary

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fibro-muscular media, excessive nitric oxide (NO) production which leads to hyalinization by indirect acetylcholine production have been found [6-10]. Severe coronary wall inflammation may play a role in CAE pathogenesis [10,11]. Insulin-like growth factor-1 (IGF-1) has anti-inflammatory and pro-repairing properties that make it antiatherogenic [12,13]. Circulating IGF-1 is mainly released by the liver under the regulation of growth hormone and executes all of its physiological effects via binding to its receptor [13]. Up to date, several studies have already described the importance of IGF-1 on atherosclerosis with its large biological effects. Although the results of these trials are inconclusive; in general, there is an inverse relation between IGF-1 levels and atherosclerosis, and IGF-1 reduces oxidative stress, inflammation and atherogenesis in the vasculature and plays a major role in vasodilatory responses by regulating (NO) production in the endothelium [13,14]. On the other hand, some cross-sectional and prospective studies suggest a positive association between IGF-1 and its binding proteins and atherosclerosis [15,16]. Accumulating evidence now indicates that IGFs and their regulatory proteins, secreted by cells of the cardiovascular system, are growth promoters for arterial cells and mediators of cardiovascular diseases and IGF-1 molecule may make endothelial cells (EC) and smooth muscle cells more sensitive to the effects of growth hormone (GH) [14-18]. Total circulating IGF-1 concentrations are not influenced by diurnal or circadian variation, which is an advantage for biomarker research [19]. The underlying mechanisms of CAE formation have not been entirely explained yet. Role of IGF-1 molecule on the development of CAE has not been studied up to date. In the present study, we hypothesized that IGF-1 may have an impact on the formation of ectasia and aneurysm in arterial system, and aimed to investigate the associations between the presence of CAE and serum IGF-1 levels in patients undergoing coronary angiography.

MATERIALS AND METHODS

Subjects

The present observational, case-control comparative study was conducted in a high volume tertiary heart center. Approximately, 3000 subjects undergoing elective diagnostic coronary angiography in our institution were scanned to find patients with apparent CAE. We selected 40 patients diagnosed with CAE, and they were labeled as CAE group, and we selected 44 patients with absolutely normal coronary arteries; those were assigned as normal control group. Patients with coronary aneurysms associated with balloon angioplasty, coronary stent placement, brachytherapy or atherectomy, Kawasaki disease, known collagen vascular diseases, patients with previous myocardial infarction, undergoing coronary

artery by-pass grafting surgery, patients with disorders affecting IGF-1 levels such as diabetes mellitus on insulin therapy, poorly controlled diabetes mellitus, acromegaly, growth hormone deficiency, patients on steroid therapy and patients diagnosed with malignant disease were excluded from the study. A detailed medical history was obtained from all patients and a complete physical examination was performed. A detailed transthoracic echocardiography was performed by two experienced specialists. The diagnosis of hypertension was established if a systolic blood pressure was 140 mmHg or higher; or a diastolic blood pressure of 90 mmHg or higher, measured in at least three separate measurements; or the use of anti-hypertensive medication. The diagnosis of diabetes mellitus was established by a fasting blood glucose of 126 mg/dL or higher, or the use of anti-diabetic medication. Fasting blood glucose of 100 mg/dL to 126 mg/dL was defined as impaired fasting glucose. Hyperlipidemia was defined as total cholesterol levels of 200 mg/dL or higher, or a history of statin use except in the last 3 month. Patients who were smoking before hospitalization were accepted as smokers. The study protocol was approved by the local ethics committee and all patients signed a written informed consent. The study was conducted in accordance with the Declaration of Helsinki, good clinical practice (GCP) and International Conference on Harmonization (ICH) guidelines.

Blood sampling and biochemical measurements

Fasting venous blood samples of all individuals were collected following an overnight fasting state just after coronary angiography. For the measurement of IGF-1, after the collection, the tubes were centrifuged at 3000 rpm for 10 min and the serum transferred to capped-tubes for storage. All aliquots were anonymized and stored frozen at −40°C for 6 months until analyze. All analyzes were performed using IGF-1 assay kits (Immulite 2000°, Siemens, Germany) with solid-phase enzyme labeled chemiluminescent immunometric assay provided by authors [20], which is the method that employs selected reaction monitoring of two triptych peptides derived from IGF-1 and utilized solid phase extraction for enrichment of the peptide fraction containing IGF-1 rather than immunocapture to reduce assay interference. Hemolyzed, lipemic and icteric serums were not used for analysis. Results of IGF-1 tests were given as ng/mL. Glucose, creatinine level, and lipid profile were measured for all patients with a Cobas-C 501 biochemical analyzer (Roche Diagnostics, Mannheim, Germany) using Roche kits. Hematological indices were evaluated from complete blood count analysis performed using a Mindray device BC-5800 (Mindray Bio-Medical Electronics Co. Ltd., Shenzhen, China) by the optical laser method.

Coronary angiography and transthoracic echocardiography

Coronary angiography was performed by the Judkins technique through femoral artery access. Coronary angiograms were analyzed by two experienced interventional cardiologists who were blinded for the laboratory measurements and clinical status of the participants. CAE was defined as the segmental or diffuse dilatation of the coronary arteries more than 1.5 fold of the diameter of the adjacent segments of the same artery or of different arteries. CAE was classified according to a classification system proposed by Markis et al. in 1976 [3]. According to this classification, CAE was graded as follows type 1, diffuse ectasia of ≥ 2 coronary arteries; type 2, diffuse ectasia in one coronary artery and localized ectasia in another coronary artery; type 3, diffuse ectasia of one coronary artery, and type 4, localized or segmental ectasia of only one coronary artery [3]. Transthoracic echocardiography was performed before discharge using a System V device (General Electric, Horten, Norway) with a 2.5 MHz phased-array transducer. The left ventricular ejection fraction (LVEF) was measured using the modified Simpson's rule [21].

Statistical analysis

Statistical calculations were performed with Number Cruncher Statistical System 2007 Statistical Software program for Windows (Utah, USA). Besides standard descriptive statistical calculations (mean and standard deviation, median, interquartile range), in the comparisons between groups, one way ANOVA test was used. Independent Samples T test was used in the comparison of two groups. Chi square test and Fisher' exact test were used during the evaluation of qualitative data. Logistic regression analysis was used to identify factors that may affect presence of CAE. A p value< 0.05 was accepted to be statistically significant. Because no study on the associations between IGF-1 and CAE has been reported to date, partly referencing other previous IGF-1 and CAE studies, we arbitrarily calculated that at least 40 patients with CAE were required for 80% power and 5% significance assuming that 20 to 41% difference between groups for IGF-1 is estimated to be.

RESULTS

Demographic and clinical characteristics of the patients and the results of laboratory investigations were presented in Table 1 and 2, respectively. Both groups were similar in terms of sex, age and cardiovascular risk factors such as smoking, family history of CAD, presence of diabetes, hypertension, alcohol abuse and metabolic syndrome (Table 1).

Serum IGF-1 levels were significantly higher in patients with CAE than in patients with normal coronary arteries (p=0.016), and serum HDL level was statistically lower in CAE group (p=0.018) (Table 2).

Although, serum aspartate transaminase (AST) levels were in normal ranges in both groups, AST levels were significantly higher in patients with CAE compared to the patients with normal coronary arteries. In the present study, we found no correlation between the degree of CAE and IGF-1 levels (Table 3).

In logistic regression analysis, high IGF-1 levels and low HDL levels were found to be independent risk factors for the presence of CAE (p<0.02, p<0.016, respectively) (Table 4).

TABLE 1. Demographic and clinical characteristics of study groups.

	CAE (n=40)	Normal (n=44)
Age (years)	58.6±10.3	55.4±9.5
Gender (M) (n %)	28 (70.0)	25 (56.8)
BMI (kg/m²)	29.0±4.7	28.8±4.0
Diabetes mellitus (n %)	8 (20.0)	11 (25.0)
Hypertension (n %)	21 (52.5)	18 (40.9)
Alcohol (n %)	7 (17.5)	2 (4.5)
Smoking (n %)	12 (30.0)	13 (29.5)
Family history of CAD (n %)	21 (52.5)	18 (40.9)
Metabolic syndrome (n %)	13 (32.5)	13 (29.5)

TABLE 2. Laboratory findings of study groups.

	CAE (n=40)	Normal (n=44)	P value
IGF-1 levels (ng/mL)	109.64±54.64	84.76±34.01	0,016
Total cholesterol (mg/dL)	189.6±35.6	199.9±29.2	0.178
HDL cholesterol (mg/dL)	41.5±10.7	47.7±10.4	0.018
LDL cholesterol (mg/dL)	115.8±3 4.7	126.5±31.6	0.194
Triglycerides (mg/dL)	146.7±79.6	175.0±87.2	0.162
Glucose (mg/dL)	119.3±50.0	123.4±65.1	0.754
Creatinine (mg/dL)	0.9±0.2	0.8±0.2	0.152
Uric acid (mg/dL)	5.7±1.4	5.6±1.5	0.817
Leukocyte (10³/mL)	8.4±2.5	8.0±1.7	0.382
Ejection fraction (%)	58.9±9.4	60.5±6.7	0.716

TABLE 3. Logistic regression analysis of variables.

	B	S.E.	Wald	df	p	Exp (B)
Constant	0.23	0.241	0.91	1	0.034	1.26
					95.0% C.I. EXP (B)	
	B	S.E.	p	Exp (B)	Lower	Upper
IGF-1	0.02	0.01	0.02	1.02	1.00	1.03
HDL	–0.07	0.03	0.016	0.93	0.88	0.99

TABLE 4. Correlations between disease severity and IGF-1 levels.

Disease severity	n (%)	IGF-1 (ng/mL)	p value
Class 1	8 (20)	100.19±38.87	
Class 2	9 (22.5)	75.08±25.96	0.102
Class 3	6 (15)	120.25±37.7	
Class 4	17 (42.5)	128.64±68.5	
Diffuse	23 (57.5)	95.6±37.34	
Focal	17 (42.5)	128.64±68.5	0.085

DISCUSSION

In our study we found a positive correlation between serum IGF-1 levels and the presence of CAE, and high IGF-1 levels and low HDL levels were independent risk factors for the presence of CAE. The serum IGF-1 levels were significantly higher in patients with CAE but we found no correlation between disease severity and IGF-1 levels. In addition, we found a negative correlation between HDL levels and CAE, and HDL levels were lower in patients with CAE.

Several studies have evaluated the traditional cardiovascular risk factors in patients with CAE, and male dominance, younger age, hypertension, dyslipidemia, smoking, cocaine use, low prevalence of diabetes and persisting congenital anomaly, which included bicuspid aortic valve, aortic root dilatation, ventricular septal defect, pulmonary stenosis or cyanotic congenital heart disease have been implicated [6]. The frequent coexistence of CAE with CAD and histopathological findings resembling those of atherosclerosis have led to the conclusion that the mechanism underlying the pathogenesis of CAE is a variant of atherosclerosis but there are some differences between CAE and CAD. CAE is associated with risk factors such as diabetes mellitus and age, elevated inflammatory parameters, changes in extracellular matrix remodeling, matrix metalloproteinase (MMP)-3 5A polymorphism, increased plasma levels of MMP-3, more pronounced involvement of right coronary artery, lower incidence of increased carotid intima-media thickness, decreased endothelium independent dilatation, possible association with vein involvement and possible hazardous effects of nitrate treatment [6]. The pathogenesis of CAE has not yet been clear. There are also obvious similarities between the pathogenesis of CAE and CAD. Regarding the high coexistence of CAE and CAD, positive remodeling described as enlargement of the area within the external elastic membrane may play a role in the pathogenesis of CAE [22]. On the other hand, histological examinations have revealed significant destruction and reduction of the media elastic fibers with disruption of the internal and external elastic membrane, usually not matching the degree of the involvement of vessel intima, the loss of musculoelastic arterial wall components in CAE, which was noticed to be unrelated to local atheromatous burden [1,3,6,9]. Non-atherosclerotic forms of CEA have been described with an intact vessel intima, but with extensive media degeneration and smooth muscle cell replacement by hyalinized collagen [1,3,6,9]. Thus, a functional loss of the musculoelastic components of the coronary artery media is considered to be the predominant aspect in the pathogenesis of CAE [1,3,6,9]. Chronic overstimulation of endothelium by NO or NO donors and enhanced NO production have also been documented and have been suspected to be an underlying pathophysiological mechanism

of CAE [23]. Lamblin et al. [24] have proposed other possible culprits in CAE pathogenesis: the system of metalloproteinases, which are actively involved in the proteolysis of the extracellular matrix proteins. Chronic vascular inflammation has been stressed as the common denominator in all cases with CAE [1, 3, 6, 9]. Conventional inflammatory markers like cytokines, tumor necrosis factor (TNF), interleukins and T helper (Th) lymphocyte activation have been found elevated in CAE patients, and the abovementioned markers are considered as good markers of systemic inflammation [25,26]. On the other hand, markers like inflammatory cells e.g. leucocytes count, monocyte count and C-reactive protein are closely linked to the presence of CAE [27]. Furthermore, levels of soluble adhesion molecules (e.g. intracellular adhesion molecules - ICAM and vascular cell adhesion molecules - VCAM) were also found to be higher in isolated CAE as well as in CAE with occlusive CAD compared with occlusive coronaries without CAE; these findings suggest that more severe coronary wall inflammation may play a role in CAE pathogenesis [11]. On the other hand, Liu et al. recently reported that IGF-1 can rescue endothelial nitric oxide synthase (e-NOS) activity and decrease ICAM-1 and VCAM-1 secretion influenced by CRP and can diminish the effect of CRP [28].

Pathophysiological background of CAE is not clear. Despite the close relationship between CAE and atherosclerosis, the histological variances and conflicting reports of the role of traditional cardiovascular risk factors weaken the significance of such association [9]. Vascular smooth muscle cell (VSMC) proliferation and positive remodeling are important steps of CAE development. IGF-1 is a potent mitogen and anti-apoptotic factor for VSMCs, and it also stimulates migration of VSMCs [29]. VSMC proliferation is regulated by numerous growth factors, including IGF-1, platelet derived growth factor (PDGF), basic and acidic fibroblast growth factor (FGF), epidermal growth factor (EGF), endothelin-1, angiotensin II; and of these, IGF-1 seems to play a pivotal role because neutralizing with anti–IGF-1 antibodies can prevent VSMC proliferation induced by other growth factors such as angiotensin II, thrombin and b-FGF [30]. IGF-1 binds to IGF-1R, and the diverse physiological effects of IGF-1R activation include differentiation, proliferation, inhibition of apoptosis, reactive oxygen species (ROS) production and cellular transformation [30,31]. IGF-1 also regulates migration and angiogenesis; also, it enhances inflammatory and vasodilatory responses in ECs [32-34]. The effects of IGF-1 on ECs are also mediated via regulation of e-NOS expression and vascular endothelial growth factor signaling, and IGF-1 increases vascular e-NOS expression and stimulates vascular NO production [28,29,34]. Production of endothelial NO promotes the vasodilatation of arterial and venous vessels. IGF-1 induced VSMC and EC proliferation, migration, angiogenesis, increased inflammation and overt NO production leading

smooth muscle hyalinization of the coronary fibro-muscular media may contribute to vascular positive remodeling and development of CAE [6-10]. This suggested mechanism for development of CAE may be supported by other clinical trials. Lindholt et al. showed that baseline serum IGF-1 correlated positively with abdominal aortic aneurysm (AAA) size and growth rate [35]. Yeap et al. showed that higher IGF-1 and an increased ratio of IGF-1/IGF binding protein (IGFBP) 3 are associated with AAA, while IGFBP-1 is independently associated with increased aortic diameter, and components of the IGF-1 system may contribute to, or be a marker for, aortic dilation in elderly patients [36]. Casini et al. have reported that acromegaly was associated with aortic ectasia, suggesting the GH and IGF-1 excess might have effects on the cardiovascular system [37]. Oshino et al. have reported that a significantly higher prevalence of cerebral aneurysm was detected in male patients with acromegaly, and this finding indicates that excess growth hormone or IGF-1 affects the cerebral vascular wall, resulting in aneurysm formation [38]. Ramos-Mozo et al. reported that IGFBP-1 has been identified by a protein array approach as a potential novel biomarker of AAA [39]. There are numerous studies on the associations between CAE and hematologic parameters such as mean platelet volume, red cell distribution width, neutrophil/lymphocyte ratio, platelet/lymphocyte ratio and inflammatory markers such as YKL 40, hs-CRP, matrix metalloproteinases [6,9,10]. Most of these studies support the idea that inflammation may play a role in CAE pathogenesis, which may be related to increasing effect of IGF-1 on inflammation.

In the present study, we also found significantly lower HDL levels in patients with CAE compatible with previous studies. In previous studies, Sudhir et al. and Altiparmak et al. pointed out lower HDL levels in patients with CAE [40,41]. Buchart et al. reported that there was no relationship between IGF-1 and HDL levels [42]. Friedrich et al. pointed that IGF-1 reduces HDL levels [43] but Elbornsson et al. showed that IGF-1 increases HDL-1 levels [44]. We found that there was no association between IGF-1 and low HDL levels in this very study.

The present study has some limitations. It was a single centered study and limited to native vessels. A major limitation was a small number of patients involved. We only measured free IGF-1 but were not able to measure IGFBPs, which also represents an important limitation of the study.

We cannot yet speculate whether IGF-1 itself would be the only pathogenic factor in the development of CAE but it may be an important factor in the pathogenesis of CAE.

In our study, we have found a positive correlation between IGF-1 levels and CAE. Our findings suggest that elevated levels of IGF-1 may have a pivotal role in the development of CAE, and may indicate the direction for further investigation aiming on the development of novel diagnostic and therapeutic approaches for CAE.

CONCLUSIONS

The present study revealed that there was a positive correlation between serum IGF-1 levels and the presence of CAE, and high IGF-1 levels and low HDL levels were independent risk factors for the presence of CAE. Future studies are needed to confirm these results.

DECLARATION OF INTEREST

The authors declare no conflicts of interest, and have received no financial support for the research.

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