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Insulin-like growth factor-1 in early-onset coronary artery disease: Insights into the pathophysiology of atherosclerosis

Andrea De Lorenzo [a,b,*], Annie S.B. Moreira [a], Elaine G. Souza [b], Glaucia M.M. Oliveira [b]

[a] Instituto Nacional de Cardiologia, Rio de Janeiro, RJ, Brazil
[b] Universidade Federal do Rio de Janeiro, Rio de Janeiro, RJ, Brazil

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Coronary artery disease (CAD) is more frequent in older adults but may affect younger patients. Recent data show an annual incidence of myocardial infarction or fatal coronary heart disease in US patients <45 years of 35 per 1000 [1]. Insulin-like growth factor-1 (IGF-1) is a peptide that shares sequence homology with insulin and has endocrine, paracrine and autocrine functions, acts on endothelial cells, and stimulates angiogenesis [2]. However, the association between low circulating IGF-1 and CAD is controversial [3,4]. Carotid atherosclerosis, another phenotype of the systemic atherosclerotic process, has also been linked with CAD and adverse prognosis [5], and correlated with low IGF-1 levels in adults [6]. Due to multiple actions in the vascular system and controversial effects on the pathophysiology of atherosclerosis, the study of IGF-1 in the setting of early-onset CAD is of potential value. This study aimed to evaluate serum levels of IGF-1 in nondiabetic patients with early-onset CAD and their association with traditional risk markers and carotid intima–media thickness (CIMT). Although diabetes mellitus has a well-known association with CAD, with the latter appearing as a major cause of morbidity and the leading cause of death in diabetics [1], we decided not to include diabetic patients because of the complex interplay between insulin and IGF-1 [7].

Early-onset CAD was defined as the detection, before age 45, of any ≥50% coronary obstruction on coronary angiography, or the occurrence of documented myocardial infarction, coronary artery bypass surgery or percutaneous coronary intervention. Patients with acute coronary syndromes or coronary interventions in the previous 6 months were not considered eligible for the study. Controls were nondiabetic adults ≤45 years without cardiac symptoms or known CAD. Blood was collected after a 12-hour fast for glucose, total cholesterol, LDL and HDL-cholesterol, triglycerides, IGF-1 and insulin measurements. IGF-1 was measured by chemiluminescent enzyme-labeled immunometric assays (Immulite 2000, Diagnostic Products Corporation, USA), and serum insulin was measured by radioimmunoassay (ImmuChemTM Coated Tube, MP Biomedicals, USA). CIMT measurement was performed with a 7.5-MHz ultrasound system (GE Healthcare, Wisconsin, USA) by 2 trained sonographers. Scans of the right and left last distal centimeter of common carotid arteries and bifurcation and of the first proximal centimeter of internal carotid arteries in 3 different projections (anterior, lateral, and posterior) were performed. Measurements were made on longitudinal scans by using the machine's electronic caliper. Values for the 3 different projections and for right and left carotid arteries were averaged to obtain the mean maximum CIMT. For the analysis of agreement between observers, a Bland–Altman analysis was employed. There was good concordance between observers (0.73–0.91).

The study complied with the Declaration of Helsinki. All participants gave informed written consent and study approval was obtained from the local ethics committee. Categorical variables were expressed as number and percentage and compared with a chi-square test. Continuous variables were expressed as mean ± SD or median and interquartile range and compared with the Student's t test or Mann-Whitney's test according to their distribution (normal or skewed). Correlations between CIMT and candidate variables of interest were studied with the Pearson's test. Linear regression analysis was employed to evaluate variables independently associated with CIMT in the entire population; traditional risk factors were entered into the model, and IGF-1 and insulin were then separately entered to assess their contribution over and above the other risk factors. A value of $p < 0.05$ was considered statistically significant.

Nineteen patients (84.2% with prior myocardial infarction, 26.3% with prior coronary artery bypass surgery and 68.4% with prior percutaneous coronary intervention) and 17 controls were studied. Table 1 depicts their characteristics. There was a small, statistically significant difference in age, which was not considered biologically important since patients remained at the "young for coronary artery disease" age range and very close to controls. Early-onset CAD patients had higher body mass index, fasting glucose and triglycerides and lower HDL-cholesterol. Of note, total cholesterol and LDL-cholesterol were not significantly

* Corresponding author at: Instituto Nacional de Cardiologia, Rua das Laranjeiras 743, Rio de Janeiro, RJ ZIP 22240-000, Brazil.

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Table 1
Characteristics of patients and controls.

	Early-onset CAD (n = 19)	Control (n = 17)
Age (years)	42.8 ± 3.0	40.3 ± 3.8*
Male	11 (57.9)	8 (47.1)
Hypertension	17 (89.5)	0*
Smoking	6 (31.6)	5 (29.4)
Metabolic syndrome	18 (94.7)	13 (76.5)*
Medications		
Aspirin	19 (100.0)	0*
Statin	19 (100.0)	0*
Nitrates	9 (47.3)	0*
Beta-blockers	14 (73.7)	0*
Angiotensin-converting enzyme inhibitors	16 (84.2)	0*
Body mass index (mg/kg^2)	31.9 ± 5.7	26.4 ± 3.2*
Waist-to-hip ratio	0.94 ± 0.07	0.87 ± 0.09*
Fasting glucose (mg/dl)	102.1 ± 15.5	88.8 ± 8.9*
Total cholesterol (mg/dl)	209.6 ± 58.9	192.8 ± 31.4
LDL cholesterol (mg/dl)	133.8 ± 43.9	129.5 ± 29.3
HDL-cholesterol (mg/dl)	37.4 ± 6.8	43.8 ± 8.9*
Triglycerides (mg/dl)	152 (128)	95 (57)*
Insulin (μU/ml)	19.0 ± 11.4	8.9 ± 3.9*
IGF-1 (ng/ml)	137.9 ± 35.0	171.5 ± 44.8*
CIMT (mm)	0.94 ± 0.18	0.79 ± 0.07*

Values are n (%), mean ± standard deviation or median and interquartile range.
CAD, coronary artery disease; CIMT, carotid intima-media thickness; HDL, high-density lipoprotein; IGF-1, insulin-like growth factor 1; LDL, low-density lipoprotein.
* $p < 0.05$.

different between patients and controls, possibly due to statin use by all patients with prior CAD. IGF-1 levels were lower and insulin levels higher in patients with early-onset CAD, who also had higher CIMT. Table 2 depicts the significant correlations between CIMT and atherosclerotic risk factors in the whole study population (patients and controls). As expected, smoking was strongly correlated with CIMT; IGF-1 correlated negatively with CIMT, and insulin had a borderline positive association. In the linear regression analysis, the final model showed smoking burden (beta = 0.53, $p < 0.001$) and triglycerides (beta = 0.41, $p < 0.001$) as significantly associated with CIMT, with a trend towards an association between IGF-1 and CIMT (beta = −0.19, $p = 0.08$).

Despite advances in knowledge, there is much more left to learn in order to understand the pathogenesis of early-onset CAD. In this study, patients with early-onset CAD had significantly lower IGF-1 levels than controls of the same age *stratum*. Patients had higher body mass index and waist-to-hip ratio, fasting glycemia and triglycerides, and lower HDL, which when put together with high insulin levels merge in the metabolic syndrome, which was indeed more frequent in this group. Of note, it has been shown that low IGF-1 levels are linked to insulin resistance and obesity [8]. Interestingly, although medication use (especially concerning statins) could have influenced IGF-1 levels, it is worth noting that statins have been linked to increases in IGF-1 levels [9], while in the current study CAD patients (100% of whom took statins) had lower IGF-1 serum levels. Therefore, we do not believe there was a significant influence of medications on our results. Finally, IGF-1 was inversely correlated with CIMT, as well as other established risk factors, similar to that previously described by El-Hafez et al. [6].

Table 2
Correlations between carotid intima–media thickness and atherosclerotic risk factors.

	Pearson correlation coefficient	Value of p
Smoking burden	0.61	<0.001
Body mass index	0.33	0.04
Waist-to-hip ratio	0.32	0.05
Triglycerides (mg/dl)	0.56	0.002
HDL (mg/dl)	−0.39	0.01
IGF-1 (ng/ml)	−0.36	0.03
Insulin	0.43	0.05

HDL, high-density lipoprotein; IGF-1, insulin-like growth factor 1.

This study suggests that low IGF-1 may play an important role in early-onset coronary and carotid atherosclerosis. In view of the controversy regarding the role of IGF-1 in the cardiovascular system, our results, which are limited by the small sample, may stimulate further research. If the influence of IGF-1 on the pathogenesis of atherosclerosis is confirmed, IGF-1 may be a target for interventions, as growth hormone treatment has been shown to increase IGF-1 levels, with beneficial effects on endothelial progenitor cells [10].

Conflict of interest

None.

Disclosures

All authors have approved the final article. Authors' contributions: Andrea De Lorenzo — conception and design of the study, analysis and interpretation of data, drafting the article; Elaine G Souza — acquisition of data; Annie SB Moreira — conception and design of the study, revision of the draft; Glaucia MM Oliveira — conception and design of the study, critical revision of the final article.

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References

[1] D. Mozaffarian, E.J. Benjamin, A.S. Go, D.K. Arnett, M.J. Blaha, M. Cushman, et al., Heart disease and stroke statistics—2015 update. A report from the American Heart Association, Circulation 131 (2015) e29–e322.
[2] J. Nakao-Hayashi, I. Hideki, T. Kaneyasu, I. Morita, S. Murota, Stimulatory effects of insulin and insulin-like growth factor I on migration and tube formation by vascular endothelial cells, Arteriosclerosis 92 (1992) 141–149.
[3] A. Juul, T. Scheike, M. Davidsen, J. Gyllenborg, T. Jorgensen, Low serum insulin-like growth factor I is associated with increased risk of ischemic heart disease: a population-based case–control study, Circulation 106 (2002) 939–944.
[4] S. Saydah, B. Graubard, R. Ballard-Barbash, D. Berrigan, Insulin-like growth factors and subsequent risk of mortality in the United States, Am. J. Epidemiol. 166 (2007) 518–526.
[5] S.C. van den Oord, E.J. Sijbrands, G.L. ten Kate, D. van Klaveren, R.T. van Domburg, A.F. van der Steen, et al., Carotid intima-media thickness for cardiovascular risk assessment: systematic review and meta-analysis, Atherosclerosis 228 (2013) 1–11.
[6] H.A. El-Hafez, M.M. Elrakhawy, A.A. El-Baiomy, M.M. El-Eshmawy, Carotid intima media thickness is independently associated with male gender, middle age, and IGF-1 in metabolically healthy obese individuals, ISRN Obes. (2014) 1–7 (Article ID 545804).
[7] T. Kadowaki, K. Tobe, R.K. Honda-Yamamoto, H. Tamemoto, Y. Kaburagi, K. Momomura, et al., Signal transduction mechanism of insulin and insulin-like growth factor, Endocr. J. 43 (1996) S33–S41 (Suppl.).
[8] V.K. Gatenby, M.T. Kearney, The role of IGF-1 resistance in obesity and type 2 diabetes mellitus-related insulin resistance and vascular disease, Expert Opin. Ther. Targets 14 (2010) 1333–1342.
[9] O. Shaker, D.A. Sourour, M. Taha, Effects of statins on insulin-like growth factor-1 gene expression in fructose induced metabolic syndrome in rats, Open Endocrinol. J. 3 (2009) 28–33.
[10] T. Thum, S. Hoeber, S. Froese, I. Klink, D.O. Stichtenoth, P. Galuppo, et al., Age-dependent impairment of endothelial progenitor cells is corrected by growth hormone-mediated increase of insulin-like growth-factor-1, Circ. Res. 100 (2007) 434–443.