Variance in Biomarker Usefulness as Indicators for Carotid and Coronary Atherosclerosis

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ABSTRACT: **Background:** Atherosclerosis is a systemic disease. Nevertheless, the role of specific biomarkers as indicators for both coronary and carotid diseases is debatable.

Objectives: To evaluate the association of biomarkers with coronary and carotid disease.

Methods: We studied 522 consecutive patients with stable angina. All underwent coronary angiography and carotid duplex study on the same day. Patients with no apparent carotid plaques were evaluated for carotid intima-media thickness (CIMT) using an automated system that sampled over 100 samples in each carotid artery. Biochemical markers of cardiovascular disease risk were obtained at the time of coronary angiography, including serum lipid levels, hemoglobin A1C (HbA1c), white blood cell count, fibrinogen and high sensitivity C-reactive protein (hs-CRP).

Results: The mean age of the patients was 66 ± 11; 73% were males. Significant carotid stenosis was associated with higher hs-CRP (9.4 ± 17 vs. 6.3 ± 13 mg/L, $P = 0.001$), while high HbA1c (6.7 ± 1.6 vs. 5.8 ± 0.8%, $P < 0.001$) and low high density lipoprotein levels (40 ± 9 vs. 47 ± 14 mg/dl, $P < 0.001$) were linked with advanced coronary artery disease severity. In contrast, CIMT was not related to any of the biomarkers evaluated.

Conclusions: Although atherosclerosis is considered a systemic disease, different biomarkers are associated with coronary and carotid artery disease. Identifying the specific biomarkers for each disease is important for both prevention and for exposing the underlying pathophysiologic mechanism.

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KEY WORDS: biomarkers, C-reactive protein (CRP), hemoglobin A1c (HBA1c), high density lipoprotein (HDL), carotid intima-media thickness (CIMT), atherosclerosis

In 2010, cardiovascular disease still accounted for 31.9% of all deaths [1]. Coronary artery disease (CAD) and stroke constitute the two leading causes of death in the world, with a mean 30% increase in crude mortality rates over the past 20 years [2]. Since atherosclerosis is a systemic condition, a relationship is commonly recognized between coronary and carotid arterial disease [3,4]. However, the role of biomarkers for coronary artery disease as indicators also for carotid disease is not clear.

Biomarkers such as high serum levels of low density lipoprotein (LDL)-cholesterol, hemoglobin A1c (HbA1c), high sensitive C-reactive protein (hs-CRP), fibrinogen and low serum levels of high density lipoprotein (HDL) are associated with coronary artery disease; however, their role in risk stratification and as indicators of carotid artery stenosis (CAS) is controversial [3,5]. Past studies have evaluated the association of a specific biomarker on either CAD or CAS but never included all of the mentioned biomarkers of both diseases in the same population at the same time [6,7]. Greater understanding of these artery-specific biomarkers may give us better insight to the underlying pathophysiologic mechanisms of the disease, which will assist in the prevention and treatment of CAD and CAS.

The aim of this study was to evaluate the association of commonly used biomarkers with coronary and carotid artery disease severity, and to evaluate if they are equally associated with both vascular beds, in consecutive patients with stable angina who underwent elective coronary angiography and carotid Doppler on the same day.

PATIENTS AND METHODS

The data in this study were collected from the Tel Aviv Prospective Angiographic Survey (TAPAS) database. TAPAS is a prospective single-center registry that enrolls all patients undergoing cardiac catheterization at the Tel Aviv Medical Center [8]. The study cohort consisted of consecutive patients referred for elective coronary angiography in our institution for stable angina and who had carotid Doppler study and CIMT measurement on the same day. There were no exclusion criteria. All the enrollees signed a written informed consent for participation in the study, which was approved by the institutional ethics committee.

ASSESSMENT OF THE SEVERITY OF CAD

CAD was defined by an epicardial coronary artery narrowing of ≥ 50% or a history of coronary intervention (stent or angioplasty) to an epicardial coronary artery, or by past bypass sur-

gery. CAD severity was divided into four categories according to the number of diseased vessels, i.e., 0, 1, 2, or 3 (groups 1–4) [9]. Significant left main coronary artery narrowing was considered as the equivalent of triple-vessel CAD. Every patient was given a score by the interventional cardiologist who performed the procedure and was unaware of the laboratory results and the nature of the study.

DEFINITIONS OF CAROTID ARTERY DISEASE

Atherosclerosis of both the left and right internal carotid arteries (ICA) was assessed by a sonography technician who was blinded to clinical and coronary angiographic data. The ICAs were scanned with carotid duplex equipment (HD11 XE, Philips Healthcare, Andover, MA, USA) with a 3–12 MHz linear array transducer, using a previously described protocol [10]. ICA atherosclerosis was evaluated by the maximum percentage of diameter reduction recorded by B-mode ultrasound, and by the peak systolic velocity (PSV) and peak diastolic velocity (PDV) per Doppler. Lesion severity was defined as the greatest internal carotid artery stenosis (CAS) observed on either the right or left ICA. Ultrasound and Doppler findings were classified into one of the following five categories [11]: normal (PSV < 125 cm/sec with no signs of atherosclerotic lesions), mild CAS (PSV < 125 cm/sec in the presence of an atherosclerotic lesion), moderate CAS (PSV 125–230 cm/sec, corresponding to 50–70% diameter stenosis), severe CAS (PSV > 230 cm/sec, > 70% diameter stenosis), and total or near occlusion (defined as zero PSV and no visible flow). For the present analysis total or near occlusion, present in 5 patients (0.2%), was grouped with severe CAS. Moderate to severe CAS was considered > 50% diameter stenosis.

CAROTID INTIMA-MEDIA THICKNESS

Carotid intima-media thickness (CIMT) was measured in patients with normal carotid ultrasound and Doppler findings, as previously described [12]. Briefly, CIMT was measured by ultrasound at the common carotid arteries (CCA) using carotid duplex equipment (HD11 XE, Philips Healthcare) with a 7.5 MHz linear array transducer.

CIMT was measured using the M'Ath software (Intelligence in Medical Technologies, Paris, France) to automatically measure CIMT using 100 samples in a 10 mm segment and calculating mean CIMT. Measurement of far wall CCA IMT followed the conventions established by the Mannheim intima-media thickness consensus [13]. All the measurements were conducted by a single technician with high intra-observer correlation ($r = 0.9$, $P < 0.001$). The measurements of CIMT were checked by a sonographer who was required to get a quality index > 0.8 on a 10 mm length of the far wall of the CCA to validate proper data acquisition. Reproducibility of the method, published previously, showed an intra-class correlation coefficient of 0.97 [14].

DEFINITION OF CARDIOVASCULAR RISK FACTORS

Diabetes mellitus was defined as the patient either being informed of this diagnosis by a physician prior to admission or by receiving hypoglycemic treatments (dietary, oral antidiabetic agents, or insulin). Hypertension was defined as known elevation of blood pressure on at least two separate occasions according to the medical history or the use of antihypertensive medications in a patient with known controlled hypertension. Dyslipidemia was defined by medical history or the use of lipid-lowering medications in order to reduce lipids or fasting serum LDL levels > 160 mg/dl. Smoking status was ascertained by the medical history.

LABORATORY TESTS

Arterial blood was obtained from all participants via their arterial access puncture site as a part of the coronary angiography procedure. All subjects underwent angiography after a night's fast. Biochemical markers of cardiovascular disease risk, obtained at the time of coronary angiography, including serum lipid levels, hemoglobin A1C (HbA1c), white blood cell count (WBC), fibrinogen and high sensitivity C-reactive protein (hs-CRP), were measured by standard laboratory techniques. The WBC count was determined by the Coulter STKS (Beckman Coulter, Nyon, Switzerland) electronic cell analyzer, and the neutrophil/lymphocyte ratio (NLR) was computed using the absolute neutrophil count divided by the absolute lymphocyte count [9].

STATISTICAL ANALYSIS

Categorical variables were compared using chi-square test and continuous variables by ANOVA/*t*-test or Kruksal-Wallis/Mann-Whitney test. We present the data using means and standard deviations for reader ease. Continuous variables were tested for normal distribution using the Kolmogorov-Smirnov test and Q-Q plots. Multivariate binary logistic regression was used to assess the association of metabolic and inflammatory biomarkers, as depicted in Table 1, with the severity of carotid and coronary disease. We adjusted for all the mentioned biomarkers. We used the probability of CAD or CAS given by the logistic regression to evaluate the ability of the biomarkers to discriminate between patients with and without CAD or CAS. Area under the receiver operating characteristic curve (AUC) and discrimination slope (DS) were used for this purpose.

A two-tailed $P < 0.05$ was considered statistically significant. All analyses were performed with the SPSS 19.0 software (SPSS Inc., Chicago, IL).

RESULTS

A total of 522 consecutive patients referred for coronary angiography due to stable angina at the Tel Aviv Medical Center were prospectively enrolled. The mean age was 66 ± 11 (range 31–97 years) and 73% were males. Their baseline clinical characteris-

Table 1. Clinical characteristics of the study population (total n=522)

	No. of patients (%)
Hypertension	377 (72%)
Diabetes mellitus	191 (36%)
Dyslipidemia	417 (80%)
Peripheral vascular disease	112 (22%)
Known ischemic heart disease	217 (42%)
History of myocardial infarction	108 (21%)
History of stroke	48 (9%)
History of coronary artery bypass surgery	53 (10%)
Current smokers	229 (43%)
Past smokers	193 (37%)
Medications	
Aspirin	443 (85%)
Statins	396 (76%)
β-blockers	278 (53%)
Clopidogrel	180 (35%)
Angiotensin-converting enzyme inhibitors	72 (14%)
Angiotensin II receptor blockers	213 (41%)
Insulin	26 (5%)
Oral hypoglycemics	119 (23%)

Table 2. Mean levels of inflammatory and metabolic biomarkers according to coronary artery disease severity

Biomarker	0 vessel CAD N=171	1 vessel CAD N=86	2 vessel CAD N=115	3 vessel CAD N=150	*P* value
Glucose (mg/dl)	99 ± 33	95 ± 33	116 ± 55	120 ± 59	‹ 0.001
Hs-CRP (mg/L)	4.5 ± 7.8	7 ± 16	7.9 ± 17	8.2 ± 16	0.18
Cholesterol (mg/dl)	166 ± 34	158 ± 36	161 ± 40	155 ± 36	0.005
Triglycerides (mg/dl)	134 ± 100	118 ± 58	139 ± 99	139 ± 83	0.27
LDL (mg/dl)	92 ± 26	90 ± 30	91 ± 32	86 ± 29	0.13
HDL (mg/dl)	47 ± 14	45 ± 13	43 ± 12	40 ± 9	‹ 0.001
Non-HDL-C (mg/dl)	118 ± 32	113 ± 34	119 ± 39	115 ± 34	0.38
HbA1c (%)	5.8 ± 0.8	6.0 ± 0.8	6.5 ± 1.2	6.7 ± 1.6	‹ 0.001
Fibrinogen (mg/dl)	296 ± 67	321 ± 81	318 ± 80	325 ± 76	0.002
NLR (10^3/µl)	3 ± 2.5	3 ± 1.96	3.3 ± 2.8	3.8 ± 3.6	0.09

P values between two groups: 0 vessel CAD vs. triple vessel CAD

Hs-CRP = high sensitivity C-reactive protein, LDL = low density lipoprotein, HDL = high density lipoprotein, NLR = neutrophil/lymphocyte ratio

tics are presented in Table 1. Coronary angiography revealed normal or non-obstructive CAD in 33% of the patients, and single, double or triple vessel CAD was found in 16%, 22% and 29% of the patients, respectively. Same-day carotid duplex was available for all. Moderate to severe carotid stenosis (> 50% diameter stenosis) was present in 77 (18%) of the patients.

Patients with triple vessel CAD had higher fasting serum glucose levels (120 ± 59 vs. 99 ± 33 mg/dl, $P = 0.001$), lower serum HDL levels (40 ± 9 vs. 47 ± 14 mg/dl, $P < 0.001$), higher HbA1c (6.7 ± 1.6% vs. 5.8 ± 0.8%, $P = 0.001$) and higher fibrinogen levels (325 ± 76 vs. 296 ± 67 mg/dl, $P < 0.001$) compared to patients with no CAD. They did not demonstrate a significant difference in hs-CRP or NLR compared with patients without obstructive CAD [Table 2].

Table 3. Mean levels of inflammatory and metabolic biomarkers in non-significant carotid vessel disease compared to significant carotid diseases (› 50%)

Biomarker	Non-significant CAS N=445	Significant CAS N=77	*P* value
Glucose (mg/dl)	105 ± 44	125 ± 63	0.003
Hs-CRP (mg/L)	6.3 ± 13	9.4 ± 17	0.001
Cholesterol (mg/dl)	161 ± 36	156 ± 38	0.09
LDL (mg/dl)	91 ± 29	86 ± 28	0.19
HDL (mg/dl)	44 ± 13	42 ± 10	0.38
Non-HDL-C (mg/dl)	117 ± 34	114 ± 38	0.23
HbA1c (%)	6.2 ± 1.2	6.6 ± 1.5	0.06
Fibrinogen (mg/dl)	309 ± 73	340 ± 87	0.007
NLR (10^3/µl)	3.2 ± 2.6	3.5 ± 4.1	0.79

Hs-CRP = high sensitivity C-reactive protein, LDL = low density lipoprotein, HDL = high density lipoprotein, NLR = neutrophil/lymphocyte ratio

Table 4. Mean levels of inflammatory and metabolic biomarkers in patients according to intima media thickness

Biomarker	Lower IMT tertile N=130	Middle IMT tertile N=119	Higher IMT tertile N=111	*P* value
Mean IMT (mm)	0.65 ± 0.055	0.779 ± 0.03	0.92 ± 0.067	‹ 0.001
Glucose (mg/dl)	102 ± 42	107 ± 47	111 ± 53	0.36
Hs-CRP (mg/L)	7 ± 17	4.3 ± 5	6.5 ± 13	0.71
Cholesterol (mg/dl)	165 ± 41	158 ± 28	162 ± 39	0.39
LDL (mg/dl)	95 ± 32	90 ± 23	90 ± 31	0.42
HDL (mg/dl)	45 ± 13	43 ± 10	46 ± 14	0.35
Non HDL-C (mg/dl)	120 ± 38	115 ± 26	116 ± 36	0.55
HbA1c (%)	6.2 ± 1.1	6.1 ± 1.0	6.2 ± 1.1	0.34
Fibrinogen (mg/dl)	312 ± 75	302 ± 72	301 ± 66	0.74
NLR (10^3/µl)	3.4 ± 2.5	3.3 ± 2.6	3 ± 2.8	0.17

Hs-CRP = high sensitivity C-reactive protein, LDL = low density lipoprotein, HDL = high density lipoprotein, NLR = neutrophil/lymphocyte ratio

CAS was mainly related to higher hs-CRP (9.4 ± 17 vs. 6.3 ± 13 mg/L, $P = 0.001$), glucose (125 ± 63 vs.105 ± 44 mg/dl, $P = 0.003$) and fibrinogen (340 ± 87 vs. 309 ± 7 3 mg/dl, $P = 0.007$), compared with patients with no CAS. They did not show a significant difference in cholesterol or HbA1c levels [Table 3]. CIMT was not related to any of the biomarkers evaluated [Table 4].

In multivariate analysis, triple vessel CAD was associated with increased HbA1c levels [odds ratio (OR) 2.03, 95% con-

fidence interval (CI95%) 1.19–3.45, $P = 0.009$] for every 1% increment and higher levels of fibrinogen (OR 1.07, CI95% 1.01–1.10, $P = 0.01$) for every 10 mg/dl increment.

Significant carotid stenosis was associated with higher fibrinogen values (OR 1.06, CI95% 1.02–1.10, $P = 0.009$) for every 10 mg/dl increment. All other biomarkers were found to be non-significant.

HbA1c, fibrinogen, glucose and HDL demonstrated discriminatory ability between patients with triple vessel CAD and without obstructive CAD (HbA1c AUC = 0.698, $P < 0.001$, DS = 0.11; fibrinogen AUC = 0.653, $P < 0.001$, DS = 0.03; glucose AUC = 0.635, $P = 0.001$, DS = 0.05; HDL AUC = 0.634, $P = 0.001$, DS = 0.07). We did not find any discriminatory variables when we evaluated CAS or CIMT.

DISCUSSION

In the present study, we evaluated the association of inflammatory and metabolic biomarkers with both coronary and carotid artery disease in a relatively large cohort of patients who underwent coronary angiography and carotid duplex study on the same day. We demonstrated that hs-CRP was linked to significant carotid disease while HbA1c and serum HDL-cholesterol levels were linked to CAD severity. Interestingly, fibrinogen and glucose were the only variables indicative of disease in both vascular beds. In addition, none of the biomarkers tested was found to be indicative of preclinical atherosclerosis as measured by CIMT.

Biomarkers have been incorporated into clinically used risk scores such as the Reynolds score, which includes hs-CRP, HbA1c, and family history of premature MI. These risk scores have shown better risk prediction compared with conventional risk scores such as the Framingham and Adult Treatment Panel III scores [15].

Carotid and coronary disease are considered part of a systemic atherosclerotic process [3] and are therefore believed to share common risk factors [16]. However, past studies suggested that the classic cardiovascular and cerebrovascular risk factors have a different impact in different arterial systems [3,5]. The reason for these differences may be explained by the complex physiology of atherosclerosis, which comprises many processes and can by influenced by the type, size and function of the involved artery. The potential differences between the shear forces, artery size, arterial wall components as well as the angulations and the blood velocity between the coronary and carotid arteries might explain differences in the atherosclerotic process and the differences seen in the prediction value of different biomarkers [17].

INFLAMMATION

In the Rotterdam study, hs-CRP was found to be independently associated with the extent and progression of carotid plaques [18], as we demonstrated in our study. Furthermore, intensive atorvastatin therapy resulted in regression of carotid atherosclerotic disease, with concomitant reduction in CRP levels [19], supporting the importance of inflammation in carotid artery disease. Hs-CRP was not significantly associated with CAD in our cohort. This finding is controversial among researchers, with the Rotterdam study [18] supporting our finding while other studies showed a strong relationship between hs-CRP and CAD [20] and a higher risk score of CHD [5]. The difference in the results might be explained by the different populations studied, which consisted of post-menopausal women in the first [20] and hypertensive patients in the latter [5].

Fibrinogen has been repeatedly shown to be highly correlated with both coronary and carotid atherosclerosis [21]. Our results reaffirm these findings by showing that higher fibrinogen levels were significantly associated with the severity of both coronary and carotid disease. Nevertheless, fibrinogen is not routinely used for risk stratification either for CAD or for CAS.

METABOLIC ABNORMALITIES

The association between abnormal lipid profile and CAD has been known from the first Framingham studies [22]. We demonstrate an association between low HDL and CAD severity but not with CAS. The association between HbA1c and CAD is still controversial. Few studies have demonstrated an association between HbA1c levels and CAD severity [23], while others showed such an association only in women [24]. Our study demonstrated that HbA1c is associated with CAD severity but not with CAS.

CIMT

In contrast to several past studies that found an association between maximum CIMT and inflammatory activity, including hs-CRP, we could not find such an association [6]. The difference between our study and the previous works can be explained by the accurate measurement of CIMT in our study, which included over 100 samples for each patient compared to 1–4 samples in previous studies [14]. It is important to mention that examination of only the common carotid artery, as in our study, may not detect plaques in the bifurcation or in the internal carotid artery and thus may result in misdiagnosis.

LIMITATIONS

Our findings may be limited to broader populations both by the specific patient subset analyzed and by its design. This was a single-center retrospective observational study, and as such may have been subject to bias, even though we included consecutive patients and attempted to adjust for multiple confounding factors using multivariate models. It is important to mention that a substantial number of patients were treated with statins (76%) and aspirin (85%), which may influence the biomarker

levels. Furthermore, the diagnosis of diabetes was not based on HBA1C levels, thus undiagnosed diabetic patients might have been missed.

CONCLUSIONS

Although atherosclerosis is considered a systemic disease, the commonly used biomarkers are not equally predictive of the risk for both coronary and carotid artery disease. While the inflammatory biomarkers were linked to carotid artery disease severity, the metabolic biomarkers were linked to coronary artery disease. Identifying the specific biomarkers for each disease is important for exposing the underlying pathophysiologic mechanism and for use in clinical practice as accessible markers both for prevention and for early detection of the disease, which will help to provide better treatment and perhaps a better prognosis. It is important to mention that there are several other biomarkers associated with atherosclerosis [25], such as interleukin-6 and tumor necrosis factor-alpha, which were not evaluated in our study and further studies are needed.

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"Words should be weighed, not counted"

Yiddish proverb

"Start where you are. Use what you have. Do what you can"

Arthur Ashe (1943-1993), American professional tennis player and the first black player selected to the United States Davis Cup team and the only black man ever to win the singles title at Wimbledon, the US Open, or the Australian Open. He was ranked World No. 1 in 1968 and 1975. In the early 1980s, Ashe is believed to have contracted HIV from a blood transfusion he received during heart bypass surgery. He publicly announced his illness in April 1992 and began working to educate others about HIV and AIDS. He founded the Arthur Ashe Foundation for the Defeat of AIDS and the Arthur Ashe Institute for Urban Health. He was posthumously awarded the Presidential Medal of Freedom by then United States President Bill Clinton