Ethnicity of Symptomatic Coronary Artery Disease Referred for Coronary Angiography in the Galilee: Prevalence, Risk Factors, and a Case for Screening and Modification

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ABSTRACT: **Background:** Coronary artery disease (CAD) has known risk factors. Individual risks related to specific ethnicities are complex and depend on genetic predisposition and lifestyle.

Objectives: To compare the nature and prevalence of risk factors in Arab and non-Arab ethnic patients with symptomatic obstructive CAD referred for coronary angiography.

Methods: CAD, defined as coronary angiography with a ≥ 50% narrowing in ≥ 1 vessel, was diagnosed in 1029 patients admitted to a medical center between April 2014 and October 2015. Patients were divided into two groups according to ethnic origin: Arab vs. non-Arab. Demographics, clinical presentation, and coronary risk profiles were compared.

Results: The diagnosis of CAD was made during ST-elevation myocardial infarction (STEMI) in 198 patients (19%) who arrived at the clinic, 620 (60%) with unstable angina/non-STEMI, and 211 (21%) with stable angina. Patients with symptomatic CAD and Arab ethnicity were 47% more prevalent than non-Arab patients presenting with CAD. The Arab patients were appoximately 5 years younger, 50% more likely to be active smokers, 25% more likely to be obese, and more likely to have a family history of CAD. Other coronary risk factors were similar between the two groups.

Conclusions: Smoking and obesity, which are potentially modifiable CAD risk factors, stood out as major risk factors, in addition to genetic disposition, among Arab and non-Arab patients with symptomatic CAD. Screening and educational interventions for smoking cessation, obesity control, and compliance to treatment of co-morbidities should be attempted in order to decrease CAD in the Arab population.

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KEY WORDS: coronary artery disease, cardiovascular risk factors, Arab ethnicity, coronary angiography, myocardial infarction

Acute coronary syndrome (ACS) is a major cause of morbidity and mortality worldwide. Although therapy for ACS has greatly improved and mortality has declined substantially in industrialized countries over the past 40 years, mortality from ACS is still rising in some parts of the world [1]. Coronary artery disease (CAD) is a common complex disease, which can lead to ACS or stable angina. Genetics in addition to behavioral and environmental factors are major risk factors for this symptomatic disease. In the INTERHEART study [2], traditional risk factors for CAD, including diabetes mellitus, smoking, and arterial hypertension were found to account for most of the risk of myocardial infarction. Moreover, apart from common risk factors, population-based studies have repeatedly reported that genetic predisposition account for approximately 50% of the risk for CAD, suggesting that genetic background plays an important role in the incidence and progression of CAD [3,4]. People of Middle Eastern background demonstrated higher odds ratio for myocardial infarction for genetic (apoB/apoA1 ratio) and lifestyle (smoking) than most of other populations that have been investigated [2]. Recently, and through large-scale exome-wide screening, a low-frequency coding variant was identified as being associated with protection against CAD and other low-frequency coding variants that were associated with an increased risk of the disease [5]. A meta-analysis indicated that interleukin-10 polymorphisms significantly correlated with CAD risk, as did ethnicity [6]. Yet, in another meta-analysis, adherence to a healthy lifestyle was shown to decrease the risk of CAD (myocardial infarction, coronary revascularization, and cardiac death) by 50% in patients with high genetic risk [7].

In Israel, earlier observational studies have shown that in the Jerusalem area CAD mortality rates of Arab women are higher not only than that of Jewish women but even when compared to Jewish men [8,9].

Our medical facility is located in the Galilee area of northern Israel. We compared several ethnic groups, which are commonly represented in our population of CAD patients, to further explore the specific risk factors associated with ethnicity.

The purpose of this study was to characterize the risk factors associated with symptomatic obstructive CAD patients referred for coronary angiography by comparing adult Arab and non-Arab patients who reside in nearby geographic locations. This analysis enabled us to better identify patients at risk for CAD and to ultimately develop a multidisciplinary preventive strategy.

PATIENTS AND METHODS

Patient medical data were prospectively recorded in the cardiology departmental registry database at the Padeh Medical Center, a university-affiliated hospital located in Poriya, Lower Galilee, Israel.

Data were extracted from the departmental registry. Adult patients (≥ 16 years of age) admitted to our facility between April 2014 and December 2015 were included in our study if they had been diagnosed with CAD (defined by coronary angiography as having ≥ 50% narrowing in at least 1 vessel). Ethnicity (Arab vs. non-Arab origin) was determined by a blinded reviewer (KT) according to given and family names and municipality of residence. Patients were then divided into two groups. We compared patients' clinical characteristics, including demographic data, CAD risk factors, and clinical presentation. In addition, we evaluated patients' echocardiographic and angiographic data, including interventional and procedural characteristics. The study was approved by the hospital's ethics board.

CAD RISK FACTORS, PRE-ADMISSION MEDICAL TREATMENT, AND LABORATORY TEST RESULTS

Admission diagnoses (international classification of disease version 9, ICD9) were taken from patient charts and screened for risk factors including diabetes mellitus, hyperlipidemia, hypertension, smoking (active), obesity (body mass index treated as a continuous variable), and renal failure. Pre-admission medical therapy was recorded. This therapy included cardiovascular medications such as aspirin, β blockers, angiotensin converting enzyme inhibitors and receptor blockers, diuretics, mineralocorticoid receptor antagonists, HMG-CoA inhibitors (statins), oral hypoglycemic treatment, and insulin. Blood pressure, blood glucose, and creatinine levels at admission were recorded. Glycosylated hemoglobin (HbA1C) and lipid profiles were not routinely measured in our study patients.

STATISTICAL ANALYSIS

Categorical variables were expressed as percentages and continuous variables as means ± standard deviations. The Wilcoxon–Mann–Whitney non-parametric test for continuous variables as normal distributions could not be assured. Chi-square or Fisher's exact test was applied for categorical variables, as appropriate. Statistical significance was defined as $P < 0.05$. Statistical analyses were performed using MedCalc Statistical Software version 15.6.1 (MedCalc Software bvba, Ostend, Belgium).

RESULTS

During the 20 month study period, from April 2014 until October 2015, CAD was diagnosed in 1045 patients. We excluded 16 patients of Circassian ethnicity because they represent a specific racial group that could not be identified with either of the predetermined study groups. In total, 1029 patients were included in our analysis. The diagnosis of CAD was made in 198 patients (19%) during an ST-elevation myocardial infarction (STEMI), in 620 (60%) admitted for an unstable angina/non-STEMI (NSTEMI) event, and in 211 (21%) due to stable angina. The study included 457 patients of Arab origin and 572 of non-Arab origin.

ARAB VS. NON-ARAB CAD

There were 223,000 individuals served by our center during the 20 month study period, 30% of whom were of Arab ethnicity [10]. Patients of Arab ethnicity were over-represented in our coronary angiography cohort, comprising 44% of patients (47% higher in representation copared to all served). Compared to non-Arab patients, those of Arab ethnicity were approximately 5 years younger ($P < 0.00001$), 50% more likely to be active smokers, 25% more likely to be obese, and more likely to have a family history of CAD. No other differences were noted in the traditional coronary risk factors, including dyslipidemia and/or the number of significant coronary obstructions [Table 1]. Admission blood pressure was 4 mmHg lower in Arab patients, and they were more likely to use insulin for diabetes. Medication use was similar in the two groups [Table 1]. Arab patients who

Table 1. Clinical characteristics

	Non-Arab (N=572)	Arab (N=457)	*P* value
Age, years	67.4 ± 11.9	62.3 ± 12.1	0.0000
Male gender, n	424 (74%)	348 (76%)	NS
CAD Risk profile			
Smoking (current), n	125 (22%)	156 (34%)	0.0018
Body mass index	28 ± 5	29 ± 5	0.0209
Hypertension, n	354 (62%)	275 (60%)	NS
Systolic blood pressure	136 ± 23	132 ± 22	0.014
Diastolic blood pressure	71 ± 14	74 ± 15	NS
Dyslipidemia, n	287 (50%)	270 (59%)	NS
Diabetes mellitus, n	208 (36%)	188 (41%)	NS
Admission glucose (mg/dl)	151 ± 83	149 ± 83	NS
Family history of CAD, n	69 (12%)	68 (15%)	0.0445
Renal failure, n	30 (5%)	21 (5%)	NS
Admission creatinine (mg/dl)	1.1 ± 1.3	1.0 ± 1.0	NS
Number of risk factors	1.88 ± 1.27	2.14 ± 1.34	0.0013
Medications, n			
Aspirin	459 (80%)	354 (78%)	NS
β blockers	378 (66%)	289 (64%)	NS
ACEi/ARBs	341 (60%)	252 (56%)	NS
Diuretics	73 (13%)	67 (15%)	NS
MRAs	63 (11%)	48 (11%)	NS
Statins	413 (72%)	345 (76%)	NS
Oral hypoglycemic drugs	124 (22%)	102 (22%)	NS
Insulin	63 (11%)	84 (19%)	0.0000
Indication: Cath for STEMI	122 (21%)	76 (17%)	0.0332
Cath: No of vessels ≥ 50%	2.04 ± 0.95	2.00 ± 0.98	NS

ACEi = angiotensin converting enzyme inhibitors, ARB = angiotensin receptor blockers, CAD = coronary artery disease, MRA = mineralocorticoid receptor antagonists, NS = non significant, STEMI = ST-elevation myocardial infarction ($P \geq 0.05$)

presented with STEMI were, on average, younger by approximately 4 years ($P < 0.04$) and were more likely to have dyslipidemia (53% vs. 37% respectively, $P < 0.03$) [Table 2].

EFFECT OF GENDER AND ETHNICITY ON RISK PROFILE

Table 3 compares Arab and non-Arab patients according to gender.

Non-Arab women were the oldest, while Arab male patients were youngest at presentation (72 vs. 60 years, respectively, $P < 0.0001$). Arab women were the least likely to be active smokers, while Arab men were the most (4% vs. 43%, respectively, $P > 0.0001$). Male patients of Arab origin had a higher number of risk factor combinations compared to non-Arab men, while women did not differ in that respect. No other differences were noted in the other traditional coronary risk factors and the number of significant coronary obstructions.

Table 2. ST-elevation myocardial infarction and primary percutaneous coronary intervention analysis

	Non-Arab (n=122)	Arab (n=76)	*P* value
Age, years	62.4 ± 13.2	58.5 ± 11.6	0.0385
Male gender, n	95 (78%)	65 (85%)	NS
CAD risk profile			
Smoking	46 (38%)	33 (43%)	NS
Hypertension	51 (42%)	32 (42%)	NS
Dyslipidemia	45 (37%)	40 (53%)	0.0295
Diabetes mellitus	37 (28%)	23 (30%)	NS
Family history of CAD	19 (16%)	19 (25%)	0.1295
Renal failure	3 (2.5%)	2 (2.6%)	NS
Number of risk factors	1.6 ± 1.3	2.0 ± 1.5	0.0949
Body mass index	29 ± 5	29 ± 5	NS

CAD = coronary artery disease, NS = non significant ($P \geq 0.05$)

Table 3. Gender analysis

	Male gender			Female gender		
	Non-Arab (n=424)	Arab (n=393)	*P* value	Non-Arab (n=146)	Arab (n=107)	*P* value
Age, years	66 ± 12	60 ± 12	0.00000	72 ± 12	69 ± 11	0.05682
Cath for STEMI, n	95 (22%)	65 (19%)	NS	27 (18%)	11 (10%)	0.00822
Previous CABG, n	20 (5%)	9 (3%)	0.00000	4 (3%)	5 (5%)	NS
No. of Vessels >50%	2.10 ± 1.00	2.00 ± 1.00	NS	1.90 ± 0.90	2.00 ± 1.00	NS
CAD risk profile, n						
Smoking	108 (25%)	151 (43%)	0.01158	17 ± 12	4 (4%)	0.00000
Hypertension	252 (59%)	200 (57%)	NS	100 (68%)	74 (69%)	NS
Hypercholesterolemia	217 (51%)	203 (58%)	NS	68 (47%)	66 (62%)	NS
Diabetes mellitus	141 (33%)	129 (37%)	NS	66 (45%)	59 (55%)	NS
Family history	61 (14%)	61 (17%)	NS	8 (5%)	7 (7%)	NS
Renal failure	19 (4%)	15 (4%)	NS	11 (8%)	6 (6%)	NS
Number of risk factors	1.88 ± 1.28	2.17 ± 1.36	0.00217	1.85 ± 1.27	2.02 ± 1.27	NS
BMI	29 ± 5	29 ± 5	NS	28 ± 5	30 ± 4	0.01891

BMI = body mass index, CABG = coronary artery bypass graft, CAD = coronary artery disease, NS = non significant, STEMI = ST-elevation myocardial infarction ($P \geq 0.05$)

DISCUSSION

The burden of symptomatic CAD requiring intervention seems to be higher in the Arab population, as this group was more prevalent in our study than might have been expected from their population share [10]. Previous studies have documented gender and ethnic disparities in the clinical characteristics of patients with respect to CAD. A recent study used a genetic risk score (GRS) to examine the association between 25 CAD-related single nucleotide polymorphisms and myocardial infarction across six ethnic groups (Europeans, South Asians, Southeast Asians, Arabs, Latin Americans, and Africans). The CAD GRS was associated with myocardial infarction across a multi-ethnic cohort, with significant and consistent effects across four distinct ethnicities (Europeans, South Asians, Southeast Asians, and Arabs). However, it only modestly improved myocardial infarction risk prediction beyond clinical factors. This result would probably place most of the CAD risk in the potentially modifiable cultural domain. Our findings of the high prevalence of smoking in Arab males (50% higher than the prevalence in Israeli non-Arab males, 10 times higher than in Arab women), higher levels of obesity (highest among Arab women), and only modest increase in the family history of CAD support behavioral factors as important risk factors. Smoking had potentially the highest impact on outcome as Arab females were the oldest age at presentation (72 ± 12 years) and had the lowest rate of myocardial infarction (11%) as the cause of CAD.

Similar differences in risk factors between Israeli Arab and Jewish populations have been previously reported [12]. Arab women, for example, were reported as being more obese, having a greater prevalence of diabetes, exercising less, being less educated, smoking less, and living in a lower socio-economic and academic status than Jewish women [13-17]. The rates of smoking were similar but not identical. From 1999 until 2001, which is 15 years prior to this study, smoking rates were higher than they currently are [15], decreasing by approximately 29% in Jewish men and by approximately 14% in Arab men. These changes are probably the result of nationwide anti-smoking legislation, such as the 1983 law prohibiting smoking in public spaces, which was amended and widened in 1987, 2004, 2007, and 2014. In addition, the increase in cigarette sales taxation in 2009 and various campaigns launched by Israel heart and cancer associations may have impacted smoking rates. The different rates of decrease in smoking between the Arab and non-Arab populations reflect lower penetrance of these interventions in the Arab society, in addition to reduced compliance [13,18]. The importance of community education and intervention should be emphasized as these programs have shown to effect the incidence of CAD, even in patients with a high genetic risk [7].

The results of this and other studies regarding the effectiveness of campaigns highlighting modifiable risk factors that target the non-Arab population should prompt clinicians and

policy makers to focus on community education programs in the Arab population. These programs should target CAD prevention, smoking secession, and modification of risk factors. Screening of local community risk profiles by healthcare maintenance organizations and local hospitals should be conducted to suggest the goals and targets for such programs.

LIMITATIONS

The main limitation of this study is that it included only patients already diagnosed with CAD at the time of intervention. Apart from a potential referral bias, the full extent of CAD and prevalence of risk factors in the general population was not revealed in this study. Furthermore, except for age and body mass index, all parameters were addressed as binary. Regarding adherence to diabetes treatment, for example, hemoglobin A1C levels in both subgroups might have revealed important information about compliance to treatment information, yet this is not a standard test conducted in patients at the time of admission to our facility.

The very low rate of Arab women with ACS may actually represent lower rates of acute infarction and may be explained by a somewhat better risk profile. Conversely, the findings could also be related to a decrease in ACS symptoms in this group resulting in reduced referrals for primary coronary interventions. This discrepancy should be addressed in a future community-based research, and specifically CAD education.

CONCLUSIONS

In adult patients diagnosed with CAD at the time of coronary intervention, smoking and obesity, both potentially modifiable CAD risk factors, stood out as the major risk factors among younger Arab patients compared with older non-Arab patients. Screening and educational interventions for smoking cessation, obesity control, and assurance of compliance of treatment of co-morbidities should be attempted to decrease CAD in this population.

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Capsule

Memories of exposure

Protective memory B cell responses are shaped through multiple mechanisms, including clonal selection of naïve B cells and affinity maturation. Memory B cell responses are considered critical to the development of a successful malaria vaccine–a goal that has remained remarkably elusive. **Murugan** and colleagues characterized memory B cell responses to the *Plasmodium falciparumcircumsporozoite* (PfCSP) protein in human volunteers immunized with sporozoites. Repeated immunization induced potent responses to the immunodominant PfCSP NANP repeat by the clonal selection of naïve and preexisting memory B cell precursors. B cell responses were less influenced by affinity maturation.

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