Sex differences in risk factors for coronary artery disease and stroke in men and women aged 45–65 years

D Hochner-Celnikier,[1] T Chajek-Shaul,[2] O Manor[3]

[1]Department of Obstetrics and Gynecology, Hadassah University Hospitals, Jerusalem, Israel
[2]Department of Internal Medicine, Hadassah University Hospitals, Jerusalem, Israel
[3]School of Public Health, Hadassah University Hospitals, Jerusalem, Israel

Correspondence to
Professor Drorith Hochner-Celnikier, Department of Obstetrics and Gynecology, Hadassah Mount Scopus University Hospital, Jerusalem 91240, Israel; Hochner@hadassah.org.il

Received 4 March 2013
Revised 22 August 2013
Accepted 10 October 2013

ABSTRACT

Background Coronary artery disease (CAD) and stroke both result from atherosclerosis. Risk factor profiles for CAD and stroke have been reported to differ between middle-aged men and women.

Objective To compare, for men and women aged 45–65 years, between risk factor profiles for CAD and stroke.

Methods This is a retrospective study based on the medical records of 179 women and 270 men diagnosed with CAD, and 114 women and 190 men diagnosed with stroke, hospitalised in one of two medical centres in Jerusalem. We assessed and compared the number of metabolic risk factors (diabetes, hypertension and hypercholesterolaemia) presenting among men and women between the CAD and stroke groups.

Results Among patients with CAD, significantly more women than men presented with diabetes, hypertension and hypercholesterolaemia. In contrast, no statistically significant differences were observed between genders in the prevalence of diabetes, hypertension and hypercholesterolaemia among the stroke patients. Hypertension was more prevalent in both men and women among stroke patients than CAD patients. In the stroke group, 29.1% of the women compared with 14.2% of the men presented with the three metabolic risk factors investigated.

Conclusions In a middle-aged population, CAD risk factor profiles differed between genders while stroke risk factor profiles did not.

INTRODUCTION

Coronary artery disease (CAD) and stroke result from a common disease, atherosclerosis.[1] This disease presents in men and women in later years and results from many endogenous as well as exogenous risk factors. Some risk factors for atherosclerosis are well recognised, such as high blood pressure, diabetes mellitus and hypercholesterolaemia, whereas others such as genetic and psychosocial factors await elucidation.[2 3]

Despite the fact that CAD and stroke result from the same pathological process, studies over the last decade have shown differences in risk factor profiles between the two diseases as well as between the genders. We, and recently a number of others, have reported differences between middle-aged men and women in risk factors for CAD[4–6] and in risk factors for stroke.[7 8]

The aim of the current study was to compare the risk factor profiles for CAD and stroke for men and women aged 45–65 years.

MATERIALS AND METHODS

This is a retrospective study of 179 women and 270 men diagnosed with CAD, and 114 women and 190 men diagnosed with stroke. All 293 women and 460 men were hospitalised in one of two Hadassah Medical Centers (Ein Kerem and Mount Scopus, both in Jerusalem). The diagnosis of CAD was confirmed by coronary angiography and/or revascularisation procedures. The diagnosis of stroke was confirmed by CT scan and/or MRI; carotid artery Doppler ultrasound scanning was used in cases of overt signs of stroke on clinical presentation. Medical background, physical profile and lifestyle information were retrieved from medical records. Profiles of the CAD and stroke groups were described previously.[4 7]

In our study, we considered hypertension as systolic pressure >160 mm Hg and/or diastolic pressure >90 mm Hg. Blood pressure measured at the time of admission was extracted from the patient file as well as any self-report of history of treatment for hypertension.

Hypercholesterolaemia was defined as serum cholesterol >220 mg/dL. Patients with type II non-insulin-dependent diabetes mellitus, as well as insulin-dependent diabetes mellitus, were included. Smoking was considered as accruing 10 packs per year in the present or in the past, as determined by patient report. We assessed and compared the number of metabolic risk factors (diabetes, hypertension and hypercholesterolaemia) presenting among men and women in the CAD and stroke groups.

Statistical analysis

Discrete variables were compared using a χ^2 test. Fisher's exact test was employed in cases of small numbers.

Ethical approval for this study was sought and obtained from the Institutional Ethical Review Board of Hadassah-Hebrew University Medical Centers; according to Institutional Review Board, decision informed consent was not required for this retrospective chart review.

RESULTS

The mean ages of the women and men were similar: 55 and 54, respectively, in the CAD group; 59 and 58, respectively, in the stroke group (table 1). The ethnic distribution differed between men and women in the CAD group but not in the stroke group (table 1). In the CAD group, more women were Israeli born, and only the group of men included South Americans.

To cite: Hochner-Celnikier D, Chajek-Shaul T, Manor O. *Heart Asia* 2013;**5**:229–232. doi:10.1136/heartasia-2013-010258

Table 1 Demographic characteristics of the two study groups

	Coronary artery disease			Stroke		
	Women (N=179)	Men (N=270)	p Value	Women (N=114)	Men (N=190)	p Value
Age in years (mean±SD)	55.1±5.1	54.2±4.9	NS	59±5.1	58.4±5.4	NS
Country of origin	N=177	N=268	<0.001	n=109	N=181	NS
Israel	37%	16%		52%	49%	
Asia	–	–		23%	23%	
North Africa	43%	43%		16%	12%	
Europe	20%	27%		7%	13%	
North America	–	–		1%	2%	
South America	–	14%		1%	1%	

NS, not significant.

Among patients with CAD, significantly more women than men presented with diabetes, hypertension and hypercholesterolaemia (table 2). In contrast, among the stroke patients, differences between the sexes were statistically significant for hypercholesterolaemia but not for diabetes or hypertension (table 2). Hypertension was more prevalent in both men and women among stroke patients than CAD patients. For women, hypercholesterolaemia was more common among patients with CAD than with stroke (table 2). Among CAD patients, 21% of women and 22.6% of men were overweight. Data on overweight were unavailable for the stroke group.

The majority of patients of both genders suffered ischaemic stroke; only about 11% of men and women suffered haemorrhagic stroke.

In the stroke group, 29.1% of the women compared with 14.2% of the men presented with all three metabolic risk factors investigated: diabetes, hypertension and hypercholesterolaemia (table 3). For both sexes, only 4% of those with stroke did not present with any of the three metabolic risk factors investigated. In contrast, for CAD patients, 7.3% of the women with CAD compared with 30% of the men did not present with any of the three risk factors, and 22.9% of the women compared with 5.6% of the men presented with all three metabolic risk factors (table 3). Observed effects were maintained when controlling for age.

Smoking was more prevalent among men than women for both CAD and stroke, with statistical significance for stroke only (table 4). For women, 46.2% who developed CAD smoked compared with 16.4% who developed stroke.

DISCUSSION

Although CAD and stroke root from the same atherosclerotic process, we found considerable differences in their risk factor profiles in a relatively young population, aged 45–65 years. Particularly striking was the marked difference between genders for CAD but not for stroke. The observation that 96% of both men and women afflicted with stroke presented with at least one metabolic risk factor highlights the comorbidity of stroke with metabolic risk factors in relatively young men and women. Similarly for women with CAD, 93% presented with at least one of the metabolic risk factors investigated. In contrast, only 70% of the men presented with a metabolic risk factor.

Diabetes, hypertension and hypercholesterolaemia were all significantly more prevalent among women with CAD than among men. Moreover, four times as many women as men who developed CAD presented with all three risk factors studied compared with only twice as many women as men who developed stroke.

In contrast to the three metabolic factors investigated, smoking differed significantly between men and women who developed stroke but not between men and women who developed CAD. Smoking was almost three times more prevalent among women who developed CAD than among women who developed stroke.

Our findings suggest that the pathological basis of CAD and stroke may be more different than expected, and that differences in the effect of sex-specific factors on these pathologies may be at the base of this difference. We speculate that endogenous oestrogen might play a significant protective role on CAD with no impact on stroke. This provides at least a partial explanation to the observation that almost all women who developed CAD presented with at least one metabolic risk factor. It seems that relatively young women develop CAD only in the presence of risk factors that apparently supersede the 'oestrogen defence'.

Gender-specific differences were also observed when comparing men with CAD versus men with stroke. Almost three times as many men with stroke presented with all three metabolic risk factors studied, while seven times as many men with CAD presented with no risk factor at all.

Differences in genetic factors have also been suggested as explanations for differences between the sexes in risk factor

Table 2 Metabolic risk factors of the patients in the two study groups

	Coronary artery disease			Stroke		
	Women (N=179)	Men (N=270)	p Value	Women (N=114)	Men (N=190)	p Value
Diabetes mellitus	72 (40.2%)	65 (24.1%)	<0.01	45 (40.9%)	60 (31.7%)	NS
Hypertension	113 (63.1%)	128 (47.4%)	<0.01	101 (88.6%)	159 (83.7%)	NS
Hypercholesterolaemia	146 (81.6%)	140 (51.9%)	<0.01	76 (66.7%)	98 (51.6%)	<0.01

NS, not significant.

Table 3 Comparison of the number of metabolic risk factors of the patients in the two study groups

	Coronary artery disease			Stroke		
	Women (N=179)	Men (N=270)	p Value	Women (N=114)	Men (N=190)	p Value
Metabolic risk factors						
0	13 (7.3%)	81 (30%)	<0.01	5 (4.4%)	8 (4.2%)	<0.05
1	53 (29.6%)	105 (38.9%)		29 (25.5%)	75 (39.5%)	
2	72 (40.2%)	69 (25.6%)		47 (40.9%)	80 (42.1%)	
3	41 (22.9%)	15 (5.6%)		22 (29.1%)	27 (14.2%)	

Risk factors assessed: diabetes, hypertension and hypercholesterolaemia.

profiles of atherosclerosis. Significant sexual dimorphism was demonstrated in a large number of complex cardiovascular traits at the haplotype level.[9 10] Male or female sex has also been shown to impact genetic differences, such as in the enhancement of the effects of angiotensinogen gene haplotypes on CAD.[11]

As more studies investigate male and female characteristics, more differences emerge. Factors associated with atherosclerosis that have been found to differ in level or expression between men and women include blood pressure,[12] phosphorous[13] and peroxisome proliferator-activated receptor-γ expression.[14] In a recent study,[15] plasma leptin levels were found to be higher in women than in men, which is not surprising since leptin levels are proportional to body fat. However, in the same study, leptin level was significantly associated with stroke in women, but not in men, after adjustment for age, smoking, body mass index, waist circumference and hypertension. No such association was observed between leptin and coronary heart disease for either sex.

Other studies demonstrate sex-specific differences in the effects of metabolic risk factors on morbidity. For example, diabetes and metabolic syndrome have been found to have greater impact on cardiovascular outcomes[16 17] and on stroke[18 19] in women than in men. The metabolic syndrome has been shown to have a more pronounced effect on early atherosclerosis, also in women.[20]

Sex-specific differences in the prevalence or effect of risk factors for atherosclerosis may also be related to differences in disease presentation. In the Multi-Ethnic Study of Atherosclerosis, lower prevalence and smaller amounts of coronary artery calcification,[8] and lower right ventricular mass and volumes, yet greater right ventricular ejection fraction, were observed in women than in men.[21] In another cohort, a pronounced difference between the sexes in stroke aetiology was observed, namely significantly higher percentages of cardioembolism and lower rates of thromboembolism in women.[22]

Longer time from symptom onset to diagnosis and to medical intervention has been proposed as an explanation for older age of onset and for greater severity of CAD and stroke in women compared with men.[23] In the current study, we do not know if the lower numbers of women compared with men in both CAD and stroke groups result from fewer women diagnosed, and if so, if this reflects less pathology or only less diagnosis. Nevertheless, this would not explain the sex-specific differences in risk profiles for CAD and stroke.

For both men and women in the current study, hypertension was more prevalent among stroke patients than CAD patients; hypercholesterolaemia was less common among women with stroke compared with women with CAD. Reaven[24] recently proposed an explanation for the apparently closer relationship of hypertension and stroke, paralleling that of insulin resistance and cardiovascular disease. Accordingly, while the great majority of individuals with diabetes are insulin resistant, only about half of those with hypertension are insulin resistant. Insulin resistance leads to compensatory hyperinsulinemia. When β cells do not produce enough insulin to control glycaemia, type 2 diabetes develops. While compensatory hyperinsulinemia helps control glycaemia, and may even prevent diabetes, its action on insulin-sensitive tissues is detrimental. Since individuals with insulin resistance also have insulin-sensitive tissues, they are subject to essential hypertension, resulting from compensatory hyperinsulinemia. However, according to Reaven, the aetiology of hypertension is more heterogeneous than that of insulin resistance. About half of those with essential hypertension present with the risk profile of hyperinsulinemia, dyslipidemia and endothelial dysfunction. The other half, who may be insulin sensitive, are also at risk for stroke, but not for CAD. Reaven did not compare between the sex prevalence rates of hypertension that is and is not related to insulin resistance.[24] While our data do not enable such analysis, this is an interesting subject for future research.

The retrospective design of this study is its main limitation. Data were not available for comorbidities, additional risk factors such as obesity/overweight, alcohol consumption, physical activity and family history, as well as menopausal state or use of hormone replacement therapy. Patients were considered to have hypertension only if their blood pressure was above 160/90 at hospital admissions or according to self-report. We aimed thereby to include stage II hypertension.[25] Patients who were well controlled by antihypertensive medications and denied history of hypertension were not considered to have hypertension, thus we may have underestimated the prevalence of hypertension.

In their recently published meta-analysis, comprising more than 250 000 individuals of 18 cohorts, spanning more than 50 years, the Cardiovascular Lifetime Risk Pooling Project[26] constructed risk factor profiles based on the same risk factors assessed in the current study. Their conclusion that differences in the lifetime risk of cardiovascular disease are consistent across

Table 4 Smoking prevalence among patients in the two study groups

Coronary artery disease			Stroke		
Women (N=108)	Men (N=143)	p Value	Women (N=110)	Men (N=189)	p Value
66 (46.25)	50 (53.6%)	NS	18 (16.4%)	83 (43.9%)	<0.01

NS, not significant.

race and birth cohorts[26] diminishes problems of external validity in studies assessing cardiovascular risk factors. They reported that from age 45 to 65, the percentage of men with two or more major risk factors increased only slightly, from 22.0 to 25.0, contrasting with an almost doubling of the percentage of women, from 16.4 to 31.3. It follows that assessment of individuals aged 45–65 as one middle-aged group, as in the current study, may have been valid for men but misrepresentative of women.

CONCLUSIONS

We described gender-specific differences between the risk profiles of CAD and stroke in a relatively young population. We also showed differences in the risk factor profiles for CAD versus stroke, particularly in men. Our findings support the notion that CAD and stroke may have different aetiologies. They may be important for the construction of appropriate multidisciplinary strategies for the prevention of CAD and stroke among men and women. Prospective studies are needed to elucidate observed differences and to trace the sex-specific development of CAD and stroke.

Contributors All authors confirm their contribution to the study was sufficient for authorship. TC-S was responsible for identifying relevant patients, OM reviewed the statistical analysis and DH-C extracted information from the files and performed initial analyses. All authors participated in discussion of the results and drafting of the manuscript.

Competing interests None.

Ethics approval Institutional Review Board.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

1 Ross R. Atherosclerosis—an inflammatory disease. *N Engl J Med* 1999;340:115–26.
2 Chen Y, Rollins J, Paigen B, *et al*. Genetic and genomic insights into the molecular basis of atherosclerosis. *Cell Metab* 2007;6:164–79.
3 Jensen RA, Shea S, Ranjit N, *et al*. Psychosocial risk factors and retinal microvascular signs: the multi-ethnic study of atherosclerosis. *Am J Epidemiol* 2010;171:522–31.
4 Hochner-Celnikier D, Manor O, Gotzman O, *et al*. Gender gap in coronary artery disease: comparison of the extent, severity and risk factors in men and women aged 45–65 years. *Cardiology* 2002;97:18–23.
5 Zafrir N, Mats I, Solodky A, *et al*. Myocardial perfusion profile in a young population with and without known coronary artery disease: comparison by gender. *Clin Cardiol* 2010;33:E39–43.
6 Khawaja FJ, Rihal CS, Lennon RJ, *et al*. Temporal trends (over 30 years), clinical characteristics, outcomes, and gender in patients ≤50 years of age having percutaneous coronary intervention. *Am J Cardiol* 2011;107:668–74.
7 Hochner-Celnikier D, Manor O, Garbi B, *et al*. Gender gap in cerebrovascular accidents: comparison of the extent, severity, and risk factors in men and women aged 45–65. *Int J Fertil Womens Med* 2005;50:122–8.
8 Kim C, Diez-Roux AV, Nettleton JA, *et al*. Sex differences in subclinical atherosclerosis by race/ethnicity in the multi-ethnic study of atherosclerosis. *Am J Epidemiol* 2011;174:165–72.
9 Weiss LA, Pan L, Abney M, *et al*. The sex-specific genetic architecture of quantitative traits in humans. *Nat Genet* 2006;38:218–22.
10 Seda O, Tremblay J, Gaudet D, *et al*. Systematic, genome-wide, sex-specific linkage of cardiovascular traits in French Canadians. *Hypertension* 2008;51:1156–62.
11 Tsai CT, Hwang JJ, Lai LP, *et al*. Interaction of gender, hypertension, and the angiotensinogen gene haplotypes on the risk of coronary artery disease in a large angiographic cohort. *Atherosclerosis* 2009;203:249–56.
12 Ober C, Loisel DA, Gilad Y. Sex-specific genetic architecture of human disease. *Nat Rev Genet* 2008;9:911–22.
13 Onufrak SJ, Bellasi A, Cardarelli F, *et al*. Investigation of gender heterogeneity in the associations of serum phosphorus with incident coronary artery disease and all-cause mortality. *Am J Epidemiol* 2009;169:67–77.
14 Amoruso A, Bardelli C, Fresu LG, *et al*. Enhanced peroxisome proliferator-activated receptor-gamma expression in monocyte/macrophages from coronary artery disease patients and possible gender differences. *J Pharmacol Exp Ther* 2009;331:531–8.
15 Liu J, Butler KR, Buxbaum SG, *et al*. Leptinemia and its association with stroke and coronary heart disease in the Jackson heart study. *Clin Endocrinol (Oxf)* 2010;72:32–7.
16 Kannel WB, McGee DL. Diabetes and cardiovascular disease. The Framingham study. *JAMA* 1979;241:2035–8.
17 Galassi A, Reynolds K, He J. Metabolic syndrome and risk of cardiovascular disease: a meta-analysis. *Am J Med* 2006;119:812–19.
18 Almdal T, Scharling H, Jensen JS, *et al*. The independent effect of type 2 diabetes mellitus on ischemic heart disease, stroke, and death: a population-based study of 13,000 men and women with 20 years of follow-up. *Arch Intern Med* 2004;164:1422–6.
19 Boden-Albala B, Sacco RL, Lee HS, *et al*. Metabolic syndrome and ischemic stroke risk: Northern Manhattan Study. *Stroke* 2008;39:30–5.
20 Iglseder B, Cip P, Malaimare L, *et al*. The metabolic syndrome is a stronger risk factor for early carotid atherosclerosis in women than in men. *Stroke* 2005;36:1212–17.
21 Kawut SM, Lima JA, Barr RG, *et al*. Sex and race differences in right ventricular structure and function: the multi-ethnic study of atherosclerosis-right ventricle study. *Circulation* 2011;123:2542–51.
22 Förster A, Gass A, Kern R, *et al*. Gender differences in acute ischemic stroke: etiology, stroke patterns and response to thrombolysis. *Stroke* 2009;40:2428–32.
23 Lawton JS. Sex and gender differences in coronary artery disease. *Semin Thorac Cardiovasc Surg* 2011;23:126–30.
24 Reaven GM. Relationships among insulin resistance, type 2 diabetes, essential hypertension, and cardiovascular disease: similarities and differences. *J Clin Hypertens (Greenwich)* 2011;13:238–43.
25 Harrison's Online: Harrison's Principles of Internal Medicine, 18th edn, Longo DL, Fauci AS, Kasper DL, Hauser SL, Jameson JL, Loscalzo J, Eds. Part 10: Disorders of the Cardiovascular System. Section 5: Vascular Disease, Chapter 247. Hypertensive Vascular Disease, by Theodore A. Kotchen.
26 Berry JD, Dyer A, Cai X, *et al*. Lifetime risks of cardiovascular disease. *N Engl J Med* 2012;366:321–9.