Gender differences in cardiovascular risk factors

Giuseppe Mercuro, Sandra Zoncu, Francesco Dragoni*

*Department of Cardiovascular Sciences, University of Cagliari, Cagliari, *Department of Cellular Biotechnologies and Hematology, "La Sapienza" University, Rome, Italy*

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Coronary heart disease is less common in premenopausal women compared to age-matched men. This difference disappears in the post-fertile years, and is presumably related to the reduced levels of female sex hormones, with subsequent metabolic and hemodynamic modifications. Ovarian exhaustion induces a more atherogenic lipid profile, which may partly explain the increased risk of cardiovascular disease observed in post-fertile women as compared to age-matched fertile women. After the menopause, the combination of aging and estrogen deficiency negatively affects glucose metabolism. Diabetes mellitus blunts the beneficial condition associated with the female gender; furthermore, it increases the incidence of myocardial infarction, claudication and stroke in women more than in men. Finally, the unfavorable effects of menopause on the coronary risk seem to be mediated partly by changes in clotting and fibrinolytic factors.

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Address:

Prof. Giuseppe Mercuro

Dipartimento di Scienze Cardiovascolari
Università degli Studi di Cagliari
S.S. 554, bivio di Sestu
09042 Monserrato (CA)
E-mail:
mercuro@pacs.unica.it

Ovarian hormones are thought to play a key role in delaying the development of atherosclerosis during the fertile years. After the menopause, a series of metabolic and hemodynamic changes are thought to nullify the cardioprotective effects of sex hormones and to accelerate the onset of coronary heart disease (CHD), arterial hypertension, and peripheral vasomotor instability. Furthermore, menopause is associated with detrimental changes such as dyslipoproteinemia, obesity and diabetes which enhance the cardiovascular risk.

Lipids

Cross-sectional studies conducted in premenopausal and postmenopausal women[1,2] have conclusively shown that ovarian failure is associated with atherogenic alterations in the lipid profile. After the menopause, the serum concentrations of total cholesterol, low-density-lipoprotein (LDL) cholesterol and lipoprotein(a) [Lp(a)] – which are strongly associated with an altered hemostatic function and with atherosclerotic disease – rise sharply within 6 months of the cessation of menses. On the other hand, high-density-lipoprotein (HDL) cholesterol declines gradually over 2 years, with a concurrent rise in apolipoprotein A-I levels, implying a change in the composition of HDL. Menopause increases the catabolism of very-low-density lipoproteins to LDL, by decreasing their uptake by the liver, and determines the induction of hepatic lipase, which degrades HDL and decreases the rate of LDL removal from plasma[3,4]. The loss of estrogen-stimulated removal of cholesterol from the circulation results in a decreased reverse cholesterol transport. Moreover, menopause enhances the levels of oxidized LDL[5], which can worsen the vasomotor and antithrombotic function of the arterial wall and facilitate atherosclerosis.

Alterations in the lipid profile bear a different relative importance in women and men. High total cholesterol and LDL levels are weakly associated with CHD in women, probably because estrogens protect the arterial wall against LDL deposition. Conversely, HDL levels have a higher cardioprotective effect in women in comparison with men[6] and are clearly correlated with coronary risk. The HDL/total cholesterol ratio is much more predictive of CHD in women than in men. This was evident in a prospective follow-up study in which, within a group of 14 786 middle-aged individuals of both sexes, the difference in the HDL/total cholesterol ratio was the major determinant of the gender difference in coronary risk[7].

In a prospective investigation of 3103 women, Lp(a) was a strong, independent predictor of myocardial infarction, intermittent claudication, and cerebrovascular disease[8]. Similarly, in the Heart and Estrogen/progestin Replacement Study (HERS), increased baseline Lp(a) levels were associated with subsequent CHD events in the placebo group (i.e., women not randomized to estrogen + progestin)[9]. Conversely, hormone replacement therapy significantly reduced Lp(a) levels, with a more favorable effect in women with the highest levels of Lp(a) at baseline[9]. This finding is quite interesting, considering that Lp(a) levels are not reduced by the majority of lipid-lowering drugs, nor by diet or physical exercise.

As to triglycerides, for similar plasma levels, the risk of CHD is higher in women than in men; thus, the atherogenic role of triglycerides could differ according to sex. Particularly negative seems to be the association between elevated triglycerides and reduced HDL plasma concentrations[10].

Diabetes

Diabetes acts as an independent risk factor in several forms of cardiovascular disease, both in women and men, through alterations of arterial functions that predispose to the development and progression of atherosclerosis. Patients with type 2 diabetes mellitus have twice the rate of hypertension, higher levels of triglycerides, of total cholesterol and of LDL, and lower levels of HDL compared to healthy subjects. Women with diabetes seem to lose most of their inherent protection against the development of cardiovascular disease[11]. As early as during the reproductive years, diabetes blunts the beneficial condition associated with female gender. After the menopause, a combination of aging and estrogen deficiency negatively affects pancreatic insulin secretion and blood flow to skeletal muscles[12]. These effects, along with an increase in abdominal adipose tissue due to a loss in lean muscle, enhance the propensity of postmenopausal women towards insulin resistance and a reduced glucose uptake.

A combination of menopause-related factors, such as a greater prevalence of hypertension and hyperlipidemia, as well as central obesity, may magnify the risk for cardiovascular disease in women with type 2 diabetes mellitus. Other common risk markers of cardiovascular disease in aged women with type 2 diabetes mellitus include hyperinsulinemia, increased Lp(a) concentrations, fibrinogen and plasminogen-activator inhibitor-1 (PAI-1) levels, the presence of oxidized/smaller LDL particles and diminished nitric oxide bioavailability. Elderly women are more likely to develop type 2 diabetes mellitus, whose rate increases to 17-18% after 60 years of age, thus determining a 25-30% rise as compared to the previous decade (50 to 59 years)[13].

The presence of diabetes is associated with a worse prognosis after acute myocardial infarction. In patients with acute myocardial infarction enrolled in the GISSI-2 study, insulin-dependent diabetes was recognized as a strong indicator of risk for cardiac death[14], irrespective of the other clinical variables. Moreover, gender appears to be critical in affecting the outcome in diabetic subjects. In women more than in men, diabetes increases the incidence of myocardial infarction, claudication and stroke, even after age adjustment[15-17]. A 10-year survey, carried out amongst US adults, showed that cardiovascular mortality had decreased in nondiabetic individuals of both sexes; this decline applied less to diabetic men, whereas in diabetic women mortality had increased by 23%[18].

The North American Menopausal Society developed a Consensus Opinion[19] on the appropriate evaluation of postmenopausal women who have, or are at risk of developing, type 2 diabetes mellitus. Screening should be considered on a 3-year basis for women aged ≥ 45 years. Besides age, risk factors for type 2 diabetes mellitus include obesity, family history of diabetes in a first-degree relative, hypertension, low HDL or high triglyceride serum level, and a history of gestational diabetes or macrosomia. In the presence of the aforementioned risk factors, screening should be more frequent for women ≥ 45 years and also extended to younger women[19].

Coagulation factors

Vascular thrombosis is a complex multifactorial disease; it has been pointed out that the interaction of various factors is required for the onset of a thrombotic event.

High plasma levels of fibrinogen are an independent risk marker of CHD – with an estimated relative risk of 1.8 (95% confidence interval 1.6-2.0)[20] – and peripheral vascular disease[21]. After a 9-year follow-up, the relative risk of CHD was 2.0 for the highest versus lowest quartiles of fibrinogen levels[22]. Some epidemiological studies reported a positive association between factor VII coagulant activity and CHD in middle-aged men[23,24], but others did not[21,22]. The mean levels of plasma fibrinogen, factor VII coagulant activity and PAI-1 were significantly higher in postmenopausal women not taking hormone replacement therapy than in premenopausal women within the same decade of age[25]. These changes may, at least in part, be secondary to the changes in plasma lipoprotein profile induced by estrogen deprivation. In the Framingham Offspring Study, premenopausal women were found to have lower plasma levels of PAI-1 and higher levels of tissue-type plasminogen activator compared with men of similar age or postmenopausal women[26].

Vascular damage increases the levels of von Willebrand factor, which is primarily synthesized by vascu-

lar endothelial cells, and may reflect excessive endothelial stress. A positive univariate association between the levels of von Willebrand factor and subsequent CHD incidence in men and women was reported in some studies[2], but not in others[21]. An association between factor VIIIc levels and CHD has been reported in older men but not in older women[27]. Prospective controlled studies have strengthened the association of antiphospholipid antibodies with ischemic stroke in young patients[28,29]. In women with polycystic ovary syndrome, a strong positive correlation was observed between the serum concentrations of triglycerides, basal insulin, and abdominal obesity, on the one hand, and the serum levels of PAI-1, fibrinogen, and von Willebrand factor, on the other hand[30].

Some prothrombotic mutations are currently considered as risk factors for deep vein and arterial thrombosis. Factor V Leiden mutation, associated with resistance to activated protein C, is a well recognized risk factor for deep vein thrombosis[31], including cerebral venous thrombosis[32], but its association with ischemic stroke is still debated[33]. Heterozygous carriers of the prothrombin gene G20210A have 30% higher plasma prothrombin levels than noncarriers. Heterozygous carriers have a 3 to 6 times higher risk of deep vein thrombosis than the general population. Moreover, this mutation is relatively frequent in Caucasian populations, its incidence varying from 0.7 to 4%.

In some but not all studies, the prothrombin variant and factor V Leiden have been associated with a significant increase in the risk for myocardial infarction[34]. A 5-fold increase in the risk of stroke among carriers of the prothrombin variant has also been reported by some[35], but not confirmed by other studies[36].

Mild hyperhomocysteinemia is currently considered as an independent risk marker of CHD and cerebral and peripheral vascular disease. Homocysteine levels are influenced by nutritional factors (including daily vitamin intake) and by genetic factors. Homozygosity for a thermolabile variant of methylenetetrahydrofolate reductase (MTHFR C677T) seems to play an important role in determining high homocysteine levels, especially in the presence of folate deficiency[37]. Homozygosity for MTHFR C677T has been associated with both deep vein thrombosis[38] and arterial disease[37], although this association has not been confirmed by others[39].

It has been reported that oral contraceptives and hormone replacement therapy may increase the risk of thrombotic events in women with genetic prothrombotic mutations. Indeed, in two population-based studies, a 20 to 30-fold increased risk was found among factor V Leiden carriers who used oral contraceptives, compared to women without factor V Leiden[40,41]. The prothrombin gene G20210A variant also interacts synergically with oral contraceptives with a 16-fold increased risk of thrombosis in carriers of the prothrombin variant who use oral contraceptives[41]. Factor V Leiden and the prothrombin gene G20210A variant seem to increase the risk of deep vein thrombosis also in women receiving hormone replacement therapy[42]. Since oral contraceptives and hormone replacement therapy are used by hundreds of millions of women worldwide, it is important to identify those subgroups at an increased risk of thrombotic events.

Conclusions

Menopause appears to enhance the development of cardiovascular disease through several unfavorable changes in metabolic and hemodynamic variables. The National Cholesterol Education Program recognizes menopause as an age-independent risk factor for CHD, carrying "a weight similar to that of male sex"[43]. Furthermore, menopause appears to accelerate the onset of other cardiovascular risk factors, thus magnifying their impact. Because the duration of menopause increases in parallel with life expectancy, specific knowledge and adequate treatment of its unfavorable effects on cardiovascular risk are warranted in order to contrast the increasing burden of cardiovascular disease in women > 50 years of age.

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References

1. Matthews KA, Meilahn E, Kuller LH, Kelsey SF, Gaggiula AW, Wing RR. Menopause and risk factors for coronary heart disease. N Engl J Med 1989; 321: 641-6.
2. Wu Z, Wu X, Zhang Y. Relationship of menopausal status and sex hormones to serum lipids and blood pressure. Int J Epidemiol 1990; 19: 297-302.
3. Jensen J, Nilas L, Christiansen C. Influence of menopause on serum lipids and lipoproteins. Maturitas 1990; 12: 321-31.
4. De Aloysio D, Gambacciani M, Maschia M, et al. The effect of menopause on blood lipid and lipoprotein levels. The Icarus Study Group. Atherosclerosis 1999; 147: 147-53.
5. Riedel M, Rafflenbeul W, Lichtlen P. Ovarian sex steroids and atherosclerosis. Clin Investig 1993; 71: 406-12.
6. Legato MJ. Dyslipidemia, gender, and the role of high-density lipoprotein cholesterol: implication for therapy. Am J Cardiol 2000; 86: 15L-18L.
7. Jousilahti P, Vartiainen E, Tuomilehto J, Puska P. Sex, age, cardiovascular risk factors, and coronary heart disease. A prospective follow-up study of 14 786 middle-aged men and women in Finland. Circulation 1999; 99: 1165-72.
8. Bostom AG, Gagnon DR, Cupples A, et al. A prospective investigation of elevated lipoprotein(a) detected by electrophoresis and cardiovascular disease in women. The Framingham Heart Study. Circulation 1994; 90: 1688-95.
9. Shlipak MG, Simon JA, Vittinghoff E, et al. Estrogen and progestin, lipoprotein(a) and the risk of recurrent coronary heart disease after menopause. JAMA 2000; 283: 1845-52.

10. LaRosa JC. Triglycerides and coronary risk in women and the elderly. Arch Intern Med 1997; 157: 961-8.
11. Brezinka V, Padmos I. Coronary heart disease risk factors in women. Eur Heart J 1994; 15: 1571-8.
12. Gaspar UJ, Gotta JM, van den Brule FA. Postmenopausal changes of lipid and glucose metabolism: a review of their main aspects. Maturitas 1995; 21: 171-8.
13. Harris MI, Flegal KM, Cowie CC, et al. Prevalence of diabetes, impaired fasting glucose, and impaired glucose tolerance in US adults: the Third National Health and Nutrition Examination Survey, 1988-1994. Diabetes Care 1998; 21: 518-24.
14. Zuanetti G, Latini R, Maggioni AP, Santoro L, Franzosi MG, on behalf of GISSI-2 Investigators. Influence of diabetes on mortality in acute myocardial infarction: data from the GISSI-2 study. J Am Coll Cardiol 1993; 22: 1788-94.
15. Kannel WB, McGee DL. Update on some epidemiologic features of intermittent claudication: the Framingham Study. J Am Geriatr Soc 1985; 33: 13-8.
16. Kuusisto J, Mykkanen L, Pyorala K, Laakso M. Non-insulin-dependent diabetes and its metabolic control are important predictors of stroke in elderly subjects. Stroke 1994; 25: 1157-64.
17. Hu GB, Stampfer MJ, Solomon CG, et al. The impact of diabetes mellitus on mortality from all causes and coronary heart disease in women. Arch Intern Med 2001; 161: 1717-23.
18. Gu K, Cowie CC, Harris MI. Diabetes and decline in heart disease mortality in US adults. JAMA 1999; 281: 1291-7.
19. Consensus Opinion. Effects of menopause and estrogen replacement therapy or hormone replacement therapy in women with diabetes mellitus: Consensus Opinion of the North American Menopause Society. Menopause 2000; 7: 87-95.
20. Danesh J, Collins R, Appleby P, Peto R. Association of fibrinogen, C-reactive protein, albumin, or leukocyte count with coronary heart disease: meta-analysis of prospective studies. JAMA 1998; 279: 1477-82.
21. Smith FB, Lee AJ, Hau CM, Rumley A, Lowe GD, Fowkes FG. Plasma fibrinogen, hemostatic factors and prediction of peripheral arterial disease in the Edinburgh Artery Study. Blood Coagul Fibrinolysis 2000; 1: 43-50.
22. Folsom AR, Wu KK, Rosamond WD, Sharrett AR, Chambless LE. Prospective study of hemostatic factors and incidence of coronary heart disease: the Atherosclerosis Risk in Communities (ARIC) Study. Circulation 1997; 96: 1102-8.
23. Meade TW, Mellows S, Brozovic M, Miller GJ, et al. Hemostatic function and ischaemic heart disease: principal results of the Northwick Park Heart Study. Lancet 1986; 2: 533-7.
24. Junker R, Heinrich J, Schulte H, Assmann G, van de Loo J. Fibrinogen and factor VII in the prediction of coronary risk: results from the PROCAM study in healthy men. Arterioscler Thromb 1994; 14: 54-9.
25. Scarabin PY, Plu-Bureau G, Bara L, Bonithon-Kopp C, Guize L, Samama MM. Haemostatic variables and menopausal status: influence of hormone replacement therapy. Thromb Haemost 1993; 70: 584-7.
26. Gebara OC, Mittleman MA, Sutherland P. Association between increased estrogen status and increased fibrinolytic potential in the Framingham Offspring Study. Circulation 1995; 91: 1952-8.
27. Tracy RP, Arnold AM, Ettinger W, Fried L, Meilahn E, Savage P. The relationship of fibrinogen and factors VII and VIII to incident cardiovascular disease and death in the elderly: results from the cardiovascular health study. Arterioscler Thromb Vasc Biol 1999; 19: 1776-83.
28. The Antiphospholipid Antibodies and Stroke Study Group. Clinical and laboratory findings in patients with antiphospholipid antibodies and cerebral ischemia. Stroke 1990; 21: 1268-73.
29. Nencini P, Baruffi MC, Abbate R, Massai G, Amaducci L, Inzitari D. Lupus anticoagulant and anticardiolipin antibodies in young adults with cerebral ischemia. Stroke 1992; 23: 189-93.
30. Dahlgren E, Janson PO, Johansson S, Lapidus L, Lindstedt G, Tengborn L. Hemostatic and metabolic variables in women with polycystic ovary syndrome. Fertil Steril 1994; 61: 455-60.
31. Dahlback B, Carlsson M, Svensson PJ. Familial thrombophilia due to a previously unrecognized mechanism characterized by poor anticoagulant response to activated protein C: prediction of a cofactor to activated protein C. Proc Natl Acad Sci USA 1993; 90: 1004-8.
32. Ludemann P, Nabavi DG, Junker R, et al. Factor V Leiden is a risk factor for cerebral venous thrombosis. A case-control study of 55 patients. Stroke 1998; 29: 2507-10.
33. Longstreth WT Jr, Rosendaal FR, Siscovick DS, et al. Risk of stroke in young women and two prothrombotic mutations: factor V Leiden and prothrombin gene variant (G20210A). Stroke 1998; 29: 577-80.
34. Doggen CJM, Cats VM, Bertina RM, Rosendaal FR. Interaction of coagulation defects and cardiovascular risk factors: increased risk of myocardial infarction associated with factor V Leiden or prothrombin G20210A. Circulation 1998; 97: 1037-41.
35. De Stefano V, Chiusolo P, Paciaroni K, et al. Prothrombin G20210A mutant genotype is a risk factor for cerebrovascular ischemic disease in young patients. Blood 1998; 91: 3562-5.
36. Voetsch B, Damasceno BP, Camargo EC, et al. Inherited thrombophilia as a risk factor for the development of ischemic stroke in young adults. Thromb Haemost 2000; 83: 229-33.
37. Fletcher O, Kessling AM. MTHFR association with arteriosclerotic vascular disease? Hum Genet 1998; 103: 11-21.
38. Cattaneo M. Hyperhomocysteinemia, atherosclerosis and thrombosis. Thromb Haemost 1999; 81: 165-76.
39. Kostulas K, Crisby M, Huang WX, et al. A methylenetetrahydrofolate reductase gene polymorphism in ischaemic stroke and in carotid artery stenosis. Eur J Clin Invest 1998; 28: 285-9.
40. Vandenbrouke JP, Koster T, Briet E, Reitsma PH, Bertina RM, Rosendaal FR. Increased risk of venous thrombosis in oral-contraceptive users who are carriers of factor V Leiden mutation. Lancet 1994; 344: 1453-7.
41. Martinelli I, Taioli E, Bucciarelli P, Akhavan S, Mannucci PM. Interaction between the G20210A mutation of the prothrombin gene and oral contraceptive use in deep vein thrombosis. Arterioscler Thromb Vasc Biol 1999; 19: 700-3.
42. Rosendaal FR, Vessey M, Rumley A, et al. Hormonal replacement therapy, prothrombotic mutations and the risk of venous thrombosis. Br J Haematol 2002; 116: 851-4.
43. National Cholesterol Education Program. Second report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel II). Circulation 1994; 89: 1333-45.