Woman´s heart – differences that make a difference

Doença cardíaca na mulher: porque é diferente?

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ABSTRACT

In this article, we analyze the differences between women and men in the setting of coronary artery disease. The main question is whether women are at the same cardiac heart risk as men. Throughout history, the differences between men and women - in sickness and in health - have fascinated researchers and doctors. Female (XX) and male (XY) differ in their genetics. Thus, the influence of an isolated chromosome affects the expression of disease, psychosocial characteristics and behavior, and can protect or increase susceptibility to cardiac heart disease (CHD). There are lots of myths about atherosclerosis, such as that it is a disease of the wealthy, a disease of the elderly or men´s disease. Nowadays, cardiovascular diseases are leading causes of death for American women. One in three women dies from heart disease. It´s the number 1 killer of women, regardles of race or ethnicity. It also strikes women at younger ages than most people think, and the risk rises in middle age. In addition, two-thirds of women who have heart attacks never fully recover. Incidence of cardiac heart disease is age-dependent, in men and women. Despite the advances in treatment of atherosclerosis, several secondary prevention studies have demonstrated that drugs, mainly statins, can significantly reduce cardiovascular events, including coronary death, the need for surgical revascularization, stroke, total mortality, as well as fatal and non-fatal myocardial infarction. Primary prevention studies yielded similar results, although total mortality was not affected. Statins also induce atheroma regression and do not cause cancer. However, many unresolved issues remain, such as partial risk reduction, costs, several potential side effects, and long-term use by young patients. Statins act mainly as lipid-lowering drugs but pleiotropic actions are also present. Healthy lifestyle, on the other hand, is effective and inexpensive and has no harmful effects. Five items are associated with lower cardiac risk both in men and women: non-smoking, body mass index (BMI) ≤25, regular exercise (30 min/day), healthy diet (fruits, vegetables, low-saturated fat, and 5-30 g alcohol/day). Nevertheless, there are difficulties in implementing these measures both at the individual and population levels. Changes in behavior require multidisciplinary care, including medical, nutritional, and psychological counseling. Participation of the entire society is required for such implementation, i.e., universities, schools, media, government, and medical societies. Although these efforts represent a major challenge, such a task must be faced in order to halt the atherosclerosis epidemic that threatens the world, mainly women.

Keywords: Women; Atherosclerosis; Lifestyle; Coronary disease/prevention & control; Cardiovascular diseases/mortality; Body mass index; Hypercholesterolemia/drug therapy; Risk factors

RESUMO

Neste artigo, analisamos as diferenças entre mulheres e homens no cenário da doença arterial coronariana. A principal questão é se as mulheres têm o mesmo risco cardiovascular que os homens. Ao longo da história, as diferenças entre homens e mulheres – na doença e na saúde – têm fascinado pesquisadores e médicos. O gênero feminino (XX) e o masculino (XY) diferem em sua genética. Assim, a influência de um cromossomo isolado afeta a expressão da doença, as características e o comportamento psicossociais, podendo proteger ou aumentar a suscetibilidade a doenças cardíacas. Existem muitos mitos sobre a aterosclerose, como, por exemplo, tratar-se de doença de rico, doença de velho ou de homens. Hoje, as doenças cardiovasculares são as principais causas de morte entre as mulheres americanas. Uma em cada três mulheres morre de doenças do coração**.** É a primeira causa de morte em mulheres, independentemente de raça ou etnia. Elas também ocorrem em idades mais jovens do que a maioria das pessoas pensam, e o risco aumenta na meia-idade. Adicionalmente, dois terços das mulheres que têm ataques cardíacos não se recuperaram totalmente. A incidência de doença cardíaca é dependente da idade em homens e mulheres. Apesar dos avanços no tratamento da aterosclerose e de vários estudos de prevenção secundária terem demonstrado que as drogas, principalmente as estatinas, podem reduzir significativamente os eventos cardiovasculares, incluindo morte coronária, necessidade de revascularização cirúrgica, acidente vascular cerebral,

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mortalidade total, bem como o infarto do miocárdio fatal e não fatal. Também os estudos de prevenção primária produziram resultados semelhantes, embora a mortalidade total não tenha sido afetada. Adicionalmente, as estatinas também induzem à regressão do ateroma e não causam câncer. No entanto, muitas questões permanecem não resolvidas, como a redução parcial de riscos, custos, vários efeitos colaterais, e uso a longo prazo para os pacientes jovens. As estatinas atuam principalmente como hipolipemiantes, mas os efeitos pleiotrópicos também estão presentes. Estilo de vida saudável, por outro lado, é eficaz e barato, além de não ter efeitos prejudiciais. Cinco itens estão associados com risco cardíaco menor, tanto em homens quanto em mulheres: não fumantes, índice de massa corporal ≤25, exercício regular (30 minutos/dia), alimentação saudável (frutas, legumes, baixo teor de gordura saturada) e 5 a 30g de álcool/dia. No entanto, existem dificuldades na implementação dessas medidas, tanto a nível individual quanto populacional. Mudanças no comportamento exigem cuidados multidisciplinares, incluindo médicos, nutricionistas e aconselhamento psicológico. A participação de toda a sociedade é necessária para tal implementação, ou seja, as universidades, as escolas, a mídia, o governo e as sociedades médicas. Embora esses esforços representem um grande desafio, tal tarefa deve ser enfrentada para deter a epidemia de aterosclerose que ameaça o mundo, principalmente em mulheres.

Descritores: Mulheres; Aterosclerose; Estilo de vida; Doença das coronárias/prevenção & controle; Doenças cardiovasculares/mortalidade; Índice de massa corporal; Hipercolesterolemia/quimioterapia; Fatores de risco

INTRODUCTION

Cardiovascular disease (CVD) is the main cause of death in Brazil, as well as in the world, including rich and poor countries. One century ago, CVD accounted for less than 10% of all deaths worldwide, while today it is responsible for approximately 30%, including nearly 40% of deaths in high income countries and about 28% in countries with low or average income[1]. In Brazil, mortality from CVD is estimated to be 33%[2] and there was improvement of 46% from 1977 to 2007 in the admissions from CVD in women with an augment of 16.8% in the number of deaths in the same group[2]. Our country is in the 11th position when compared with other countries regarding male deaths, and in the 8th when it concerns women [3]. The numbers of deaths after bypass surgery is higher in women than in men, independently of the age[4]. As the world population gets older, non-communicable diseases will burden the health care system, and the costs associated with such diseases already account for half the costs of all hospital admissions. Non-communicable diseases account for 66% of all diseases, while contagious diseases account for 24% and injuries for 10%[2]. This rate of non-communicable diseases is not necessarily an inevitable result of modern society, but rather a problem that can be avoided. The main factors behind most of these diseases, i.e., coronary artery disease (CAD), stroke, diabetes, and several types of cancer, are not genetic but rather environmental and behavioral. Women have myocardial infarction on average 10 years later, with mortality up to 79 years being higher than that of men[5], and it is related with atherosclerosis, that is a chronic inflammatory and proliferative disease, which may cause obstructions of the coronary, cerebral and peripheral arteries. Atherosclerosis tends to be a progressive process that begins early in life, probably in childhood. It is typically multifactorial in origin, most often dependent on risk factors such as hypercholesterolemia, diabetes, smoking, hypertension, sedentarism, and obesity. Atherosclerosis results from a complex interaction of hemodynamic and biochemical factors and is determined by circulating blood cells, endothelial cells, smooth muscle cells, blood lipids, and connective tissue of the arterial wall. Once considered to be the result of fat deposition in the arterial wall, it is now viewed as an inflammatory and proliferative process that can lead to arterial wall thickening and eventual complete obstruction that hampers myocardial blood flow. Around 40 years of age women have a risk of cardiovascular disease by 32% and only 50% of them are aware of cardiovascular disease and its risk factors[6]. The risk of atherosclerosis increases when estrogen production ceases, physiologically or after surgery, making women more vulnerable to develop CVD. Menopause is the risk factor that contributes for the development and progression of atherosclerotic lesions and hypertension[7-9].

The purpose of this article is to establish strategies to stop the advance of these diseases in women comparing two latter approaches, drug treatment and lifestyle modification, highlighting the peculiarities of each one and offering practical suggestions for physicians.

Defects of receptors and metabolism as determining cardiovascular disease

Sex hormones are important for CVD development suggesting that the differences in occurrence of the disease among premenopausal women, and men of the same age, disappear when women reach menopause, and evidence suggests that severe endogenous estrogen has protective activity effective against the development of CVD among men and women[10,11]. Estrogen acts in the cardiovascular system causing rapid effects (nongenomic) that augment dilation and release of nitric oxide, and longer-term effects (genomic) reducing atherosclerosis, vascular injury and smooth-muscle-cell growth and improving endothelial-cell growth[11]. Estrogen has anti-inflammatory and vasoprotective effects when administered to young women or experimental animals that appear to be converted to pro-inflammatory and vasotoxic effects in older subjects, particularly those that have been hormone-free for long periods. Clinical studies have raised many important questions about the vascular effects of estrogen that cannot be easily answered in human subjects. Here we review cellular/molecular mechanisms by which estrogen modulates injury-induced inflammation, growth factor expression, and oxidative stress in arteries and isolated vascular smooth muscle cells, with emphasis on the role of estrogen receptors and the Nuclear Factor-κB (NFκB) signaling

pathway, as well as evidence that these protective mechanisms are lost in aging subjects[12]. Inflammation plays an important role in the pathogenesis of many forms of vascular disease, including atherosclerosis and the response to acute vascular injury[13]. Artery balloon injury elicits accumulation of neutrophils and monocyte/macrophages in the adventitia surrounding the injury site within hours after the insult[14]. The appearance of these cells is predated by expression of inflammatory mediators, including adhesion molecules and chemokines and cytokines, in acutely injured arteries[15] as well as in atherosclerotic and restenotic vessels, and is associated with activation of a variety of cell types, including adipocytes and fibroblasts, in adventitial tissues[16]. Medial vascular smooth muscle cells (VSMCs) are activated early following endoluminal injury, releasing cytokines and chemokines that reach the periadventitial space to recruit leukocytes, and appear to be the chief effector cells for initiation of the early inflammatory response[12]. Estrogen plays many roles in immunomodulation, and can be either anti- or pro-inflammatory depending on diverse factors such as the target cell type, the target organ with its specific microenvironment, the timing and concentration of estrogen administered, and cell type- and microenvironment-specific variability in estrogen receptors (ER) expression[17]. However, ER subtype dependence of the anti -inflammatory/vasoprotective effects of estrogen and the signaling pathway(s) involved are incompletely understood. There are at least three, and possibly four distinct ERs: two ligand-activated transcription factors (ERα and ERβ), a G-protein coupled receptor (GPER, GPR30), and a putative receptor (ER-X) that has been studied mainly in the brain[18]. ERα and ERβ are members of the nuclear hormone receptor superfamily that are expressed in the vasculature and play a role in mediating/modulating responses to vascular injury, mainly through transcriptional regulation. GPER (GPR30) is an intracellular transmembrane ER that initiates many rapid nongenomic signaling events, including intracellular calcium mobilization and synthesis of phosphatidyl-inositol 3,4,5-triphosphate in the nucleus of many cell types[19]. GPER has been identified in human internal mammary arteries and saphenous veins, but does not yet have a defined vascular function[12]. Genetic polymorphisms of ERs can affect the transcription of functions and response of the ERs themselves so well as the tissue response to estrogen. An extreme example of dysfunction can be reported in young men who have inactivation of the gene thereby causing ER estrogen resistance. There is premature manifestation of atherosclerosis despite the high levels of circulating estrogen[10]. A study investigated the contribution of alpha and beta estrogen receptors (ERs) for epicardial coronary artery function, vascular NO bioactivity, and superoxide (O(2)(-)) formation. Porcine coronary rings were suspended in organ chambers and precontracted with prostaglandin F(2alpha) to determine direct effects of the selective ER agonists 4,4',4"-(4-propyl-[(1)H]pyrazole-1,3,5-triyl) tris-phenol (PPT) or 2,3-bis (4-hydroxyphenyl)-propionitrile (DPN) or the nonselective ER agonist 17beta-estradiol. Indirect effects on contractility to U46619 and relaxation to bradykinin were assessed and effects on NO, nitrite, and O(2)(-) formation were measured in cultured cells. Within 5 minutes, selective ERalpha activation by PPT, but not 17beta-estradiol or the ERbeta agonist DPN, caused rapid, NO-dependent, and endothelium-dependent relaxation (49+/-5%; P<0.001 versus ethanol). PPT also caused sustained endothelium- and NO-independent vasodilation similar to 17beta-estradiol after 60 minutes (72+/-3%; P<0.001 versus ethanol). DPN induced endothelium-dependent NO-independent relaxation via endothelium-dependent hyperpolarization (40+/-4%; P<0.01 versus ethanol). 17beta-Estradiol and PPT, but not DPN, attenuated the responses to U46619 and bradykinin. All of the ER agonists increased NO and nitrite formation in vascular endothelial but not smooth muscle cells, and attenuated vascular smooth muscle cell O(2)(-) formation (P<0.001). ERalpha activation had the most potent effects on both nitrite formation and inhibiting O(2)(-) (P<0.05). These data demonstrate novel and differential mechanisms by which ERalpha and ERbeta activation controls coronary artery vasoreactivity in males and females and regulates vascular NO and O(2)(-) formation. The findings indicate that coronary vascular effects of sex hormones differ with regard to affinity to ERalpha and ERbeta, which will contribute to beneficial and adverse effects of hormone replacement therapy[20]. In women, kidneys were protected from cardiac arrest through estrogen. Estradiol-mediated renoprotection was not affected by ER deletion or blockade. Estradiol is renoprotective after cardiac arrest. The results indicate that estradiol renoprotection is ER-[alpha] and ER-[beta] independent[21]. Experimental and population-based studies indicate that female gender and estrogens protect the cardiovascular system against aldosterone-induced injury. Understanding the function of estrogens in heart disease requires more precise information on the role of both estrogen receptor (ER) subtypes, ERalpha and ERbeta. Therefore, we determined whether selective activation of ERalpha or of ERbeta would confer redundant, specific, or opposing effects on cardiovascular remodeling in aldosterone salt-treated rats. The ERalpha agonist 16alpha-LE2, the ERbeta agonist 8beta-VE2, and the nonselective estrogen receptor agonist 17beta-estradiol lowered elevated blood pressure, cardiac mass, and cardiac myocyte cross-sectional areas, as well as increased perivascular collagen accumulation and vascular osteopontin expression in ovariectomized rats receiving chronic aldosterone infusion plus a high-salt diet for 8 weeks. Uterus atrophy was prevented by 16alpha-LE2 and 17beta-estradiol but not by 8beta-VE2. Cardiac proteome analyzes by 2D gel electrophoresis, mass spectrometry, and peptide sequencing identified specific subsets of proteins involved in cardiac contractility, energy metabolism, cellular stress response and extracellular matrix formation that were regulated in opposite directions by aldosterone salt treatment and by different estrogen receptor agonists. We conclude that activation of either ERalpha or ERbeta protects the cardiovascular system against the detrimental effects of aldosterone salt treatment and confers redundant, as well as specific, effects on cardiac protein expression. Nonfeminizing

ERbeta agonists such as 8beta-VE2 have a therapeutic potential in the treatment of hypertensive heart disease[22]. Polymorphisms of Estrogen Receptor alpha are associated with the angiographic extent of coronary artery disease[23]. Regarding severity of cardiovascular disease in postmenopausal women, there are many questions to be answered, and a study found evidence that ERs have influence on the action of estrogen and tissue levels and also presented an important development pattern of greater severity of CAD in a high selected group of postmenopausal women[24]. Another study showed that high levels of small low density lipoprotein (LDL) particles are a major risk factor for cardiovascular morbidity and mortality. Both estrogens and smoking, with known anti-estrogenic effects, alter the atherogenic lipid profile. They tested for a role of interaction between smoking and estrogen receptor alpha gene (ESR1) variation in association with plasma concentration of atherogenic small LDL particles and LDL particle size. They studied 1727 unrelated subjects, 854 women and 873 men, mean age 51 years (SD 10), from the population-based Framingham Heart Study. After covariate adjustment, women who smoked and had the common ESR1 c.454-397 TT genotype (in 30% of women, T was present on both chromosomes at position 397 prior to the start of exon 2) had >1.7-fold higher levels of small LDL particles than women with the alternative genotypes (P-value for smoking-genotype interaction was 0.001). Similar results were obtained for three other ESR1 variants including c.454-351A > G, in the same linkage disequilibrium block. A similar substantial gender-specific result was also evident with a fifth variant, in a separate linkage disequilibrium block, in exon 4 (P=0.003). Women who smoked and had specific, common ESR1 genotypes had a substantially higher plasma concentration of atherogenic small LDL particles. Significant results revealed a dose-dependent effect of smoking and were evident in both pre- and postmenopausal women. The reported association has the potential to explain the risks associated with estrogen use in certain women, and a recent report of association between an ESR1 haplotype consisting of c.454-397 T and c.454-351 A alleles with increased myocardial infarction and ischaemic heart disease, independent of the standard, established cardiovascular risk factors[25]. Thus, there is a relationship between the effects of estrogen and pathophysiology of CAD. The coronary calcification, a predictor of future cardiovascular event, may be present in women who entered menopause earlier that do not have presence of risk factors, and treatments with estrogens reduce coronary calcification in postmenopausal women. Estrogen mechanisms for reduction of calcification are multifactorial: differentiated cells modulation, genetic variation of proteins, bone matrix in the activation of osteoclasts and susceptibility to infection by calcification nanoparticles[26]. Ischemic stroke is uncommon in women before menopause and increases substantially with age, leading to the premise that women are protected early in life by reproductive hormones[27]. Estrogen appears to promote the production of energy (oxidative phosphorylation with reduction in the generation of species reactive oxygen (ROS)).

Presentation and management in coronary artery disease

The CLARIFY registry compares cardiovascular clinical outcomes in men and women with stable CAD[28]. They analyzed 1-year outcomes in 30977 outpatients with stable CAD [23 975 (77.4%) men; 7002 (22.6%) women]. Women were older than men, more likely to have hypertension and diabetes, and less likely to exercise or smoke. They had more frequent angina, but were less likely to have undergone diagnostic non-invasive testing or coronary angiography. Women received less optimized treatment for stable CAD. One-year outcomes were similar for men and women for the composite of cardiovascular death, non-fatal myocardial infarction, or stroke [adjusted rates 1.7 *versus* 1.8%, respectively, odds ratio (OR) 0.93, 95% confidence interval (CI) 0.75-1.15]; all-cause death (adjusted 1.5 *versus* 1.6%, OR: 0.91, 95% CI: 0.72-1.13); fatal or non-fatal myocardial infarction (adjusted 1.0 *versus* 0.9%, OR: 0.81, 95 CI: 0.60-1.08); and cardiovascular death or non-fatal myocardial infarction (adjusted 1.4 *versus* 1.4%, OR: 0.89, 95% CI: 0.70-1.12). Fewer women underwent revascularization (2.6 *versus* 2.2%, OR: 0.77, 95% CI: 0.64-0.93), although appropriateness was not analyzed. The authors concluded that the risk profiles of women and men with stable CAD differ substantially. However, 1-year outcomes were similar. Fewer women underwent revascularization. Further research is needed to better understand gender determinants of outcome and devise strategies to minimize bias in the management and treatment of women.

Drugs

Fat consumption has been directly related to cardiac mortality in diferent countries[29]; meaning that the more fat consumed, the greater the coronary mortality. The Framingham Study showed the direct association between plasma cholesterol and cardiac mortality[30], closely associated with the augment in blood pressure. These statements were confirmed by many epidemiological studies, which covered a wide range of cholesterol concentrations. After the correlations were established, the investigation of the natural history of atherosclerosis began to be studied, as well as the ways of changing it with diet and medication. The definitive assessment of LDL reduction being beneficial was facilitated by the development of potent cholesterol-lowering drugs, the 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, termed statins. Afterwards, a series of studies demonstrated the efficacy of those drugs in preventing major cardiovascular events in men and women[31-33].

Healthy lifestyle

A study compared non-obese Americans to moderately and morbidly obese individuals, also featured smokers compared to non-smokers, and concluded that unhealthy lifestyle has devastating effects on survival[34]. The authors noticed that both conditions severely reduced life expectancy, reaching

an incredible 10-year span among smokers. In the Whitehall Study[35], an individual with all three risk factors: smoking, hypertension and hypercholesterolemia showed a decreased lifespan of 10-15 years. Diabetes was other risk fator that showed reduction in life span. Ford et al.,[36] reported on 10 studies that assesed the coronary risk factor. In conclusion, it can be seen that interventions on risk factors were more effective than all drugs and invasive procedures in USA and Europe populations.

Eating habits

Diets

A rather large number of studies regarding diets have been published[37] specialy focusing the Mediterranean diet wich is characterized by low-saturated fat, high intake of vegetables, fruits and legumes plus olive oil and mild/moderate wine consumption. Studies designed to test its efficacy such as de Lorgeril et al.,[38] carried out the Lyon Diet Heart Study in which 605 post-MI patients were randomly assigned to the prudent Western-type diet or to a Mediterranean diet during a mean follow-up of 46 months. The impacts of the Mediterranean diet were significant reduction of the combined endpoint of cardiac death, nonfatal AMI and noncardiac death. An observational study as the European Prospective Investigation into Cancer and Nutrition (EPIC) Trial[39] followed 22,043 adults for an average of 44 months in Greece, and the effects of the diet on mortality were analyzed according to adherence to it using a well-defined score. The results showed that individuals who most adhered to the diet experienced a 25% reduction in general mortality, a 33% decrease in mortality due to CAD and a 24% decrease in cancer mortality. Trichopoulou et al.,[40] showed effects of each component of the diet on the EPIC Study regarding its overall effect on mortality and concluded that high intake of legumes/fruits and monounsaturated fats each contributed with about 10%; high intake of vegetables and low meat, 16%, and moderate alcohol consumption about 23%. Eshghinia, Mohammadzadeh[41] studied the effects of modified alternate-day fasting diet (ADF) on weight loss and its correlation with CAD risk factors in overweight and obese women, and found that in this group short time ADF is a viable dietary option to help obese individuals lose weight and decrease some CAD risk factors. Initial gains in weight reductions are frequently overcome by weight regain over the next 1 to 2 years. Salt is another fundamental component of the Western diet and is responsible in part for hypertension which is a major contributor for strokes. The smallest variations in blood pressure cause a considerable increase in cardiovascular events both in women and men[42]. Tuomilehto et al.,[43] in a study from Finland comparing higher and lower salt intake in 2436 men and women, 25 to 64 years old, observed that higher salt intake increased coronary, cardiovascular and all deaths. In the Intersalt Study, Bibbins-Domingo et al.,[44] calculated the impact of small reductions of salt intake on CVD over a one-year period; the authors investigated the implications of a 3.0-g reduction in salt ingestion in individuals aged 35 to 84 years regarding incidence of CAD, total MI, incidence of stroke, and total death among non-black men and women as well as in black men and women, achieving significant reductions in all parameters. Hence there is a plethora of evidence indicating that high-salt ingestion is deleterious and that even a small salt reduction such as 3-5 g/day has the potential to prevent cardiovascular events, so a low-salt diet of ≤4.0 g/day is usually recommended for hypertension. In heart failure patients, even smaller amounts may be needed.

Wakabayashi[45] studied the relation between alchool consumption and atherogenic indexes in 14.067 women; they were divided by the amount of alcohol intake, and the author concluded that alcohol drinking is inversely associated with atherogenic indices irrespective of smoking status, and the inverse association of alcohol drinking with LDL-C/HDL-C ratio is stronger than that with TG/HDL-C ratio.

Exercise

Exercise has a large impact reducing cardiovascular events[46] through a number of physiological mechanisms. The most striking metabolic effect is a plasma TG reduction, as well as insulin resistance and therefore contributes to diabetes control, decreases blood pressure and increases HDL but has no effect on LDL. Physical activity improves mood, body weight, and inflammatory and hemostatic variables; it improves exercise capacity, increases collaterals in CAD patients, and endothelial function. Following coronary artery bypass grafting (CABG) and percutaneous coronary intervention (PCI), it improves VO2 as well as quality of life. Hence, it is now considered to be part of recovery programs following these interventions. Although in long term it reduces sudden coronary death, the sudden death is more frequent during intense than during moderate exercise. In our group, Casella-Filho et al.,[47] assessed the effects of a 3-month supervised physical training program in 30 patients with metabolic syndrome including low HDL (≤40mg/dL) and noted that brachial arterial flow-mediated dilation improved significantly after exercise although total HDL and LDL remained at the same baseline values. Also, HDL from trained individuals significantly increased LDL resistance to oxidation. They interpreted the data as evidence that exercise can functionally improve HDL even if its total value does not change, probably by interference with its sub-fractions. Thus, even short periods of exercise can substantially ameliorate endothelial function while increasing resistance to LDL oxidation.

Wessel et al.,[48] studied 906 women that were being evaluated for suspected ischemia, to correlate physical fitness and body mass index with CAD and cardiovascular events in women. This study reached the conclusion that among women undergoing coronary angiography for suspected ischemia, higher self-reported physical fitness scores were independently associated with fewer CAD risk factors, less angiographic CAD, and lower risk for adverse CV events.

These lines of evidence justify why cardiologists recommend regular exercise programs for CVD prevention and treatment. Tolerance to exercise through stress testing, however, should be assessed before entering such programs. Performing exercise

within safe ranges of submaximum tolerance rather than at extenuating levels is a salutary practice, since excessive strain may induce sudden death in people with CAD. It is consensual among cardiologists that the optimal frequency of moderate exercise is 30 min/day, 4-5 times/week at least, on a long-term basis, both in men and women.

Smoking

Exposure to tobacco smoke is associated with a higher cardiovascular risk, especially in patients with coronary artery disease (CAD), as demostrated in a study that was performed to evaluate the effect of active and passive tobacco smoking on the activity of endothelial markers in advanced atherosclerosis[49]. They authors studied 181 consecutive patients with advanced CAD (53 women and 128 men) aged 60±8 years, including 102 active self-declared smokers (56.3%). They determined plasma asymmetric dimethylarginine (ADMA), thrombomodulin (TM), and plasminogen activator inhibitor-1 (PAI-1) levels, along with serum cotinine concentrations as a marker of tobacco smoking and observed that plasma ADMA levels were higher in active smokers compared with nonsmokers (0.60±0.09µmol/l *versus* 0.49±0.08µmol/l, P<0.001). There were similar intergroup differences in TM (4.60±2.11ng/mL *versus* 3.0±1.7ng/ml, P<0.0001) and PAI-1 levels (30.3±12.4ng/mL *versus* 23.6±11.3ng/ml, P<0.0001). They observed positive correlations between cotinine and ADMA (r=0.71, P<0.0001), TM (r=0.53, P<0.0001), and PAI-1 (r=0.58, P<0.0001). In 21 patients (26.6%) who declared to be nonsmokers, cotinine levels (mean, 6.30±22.5ng/mL) significantly correlated with ADMA, TM, and PAI-1 (all P<0.001). A multivariate regression analysis showed that cotinine was an independent predictor of ADMA, TM, and PAI-1 in the whole patient group. Despite long-lasting endothelial injury in advanced CAD, continued cigarette smoking is able to further enhance endothelial damage by increasing ADMA levels and resultant inhibition of fibrinolysis. Iestra et al.,[50] reviewing studies on the effects of smoking cessation, estimated at 35% the reduction in mortality among patients with CAD and at 50% in the general population. This greater benefit in the general population is largely attributable to cancer prevention. Although quitting smoking has been a formal cardiologist recommendation for many years, its implementation remains a considerable challenge.

Obesity and diabetes

One of the most prevalent risk factors, obesity is prevalent not only in Brazil but also all over the world. Even children and adolescents are suffering, which is a unique phenomenon in the history of humanity. A body mass index (BMI) above 30 is considered obesity while the normal index ranges from 23 to 25. Causes of obesity are essentially two, the first is excessive caloric ingestion, mainly through foods rich in fats and carbohydrates; and secondly, lack of exercise. Both situations are frequently associated with psychological factors including anxiety, stress and depression. Obesity is frequently associated mainly in women with diabetes and metabolic syndrome, which in turn predispose to CAD; it also reduces life expectancy and greatly impairs quality of life. From the WISE study[51], 780 women referred for coronary angiography to evaluate suspected myocardial ischemia were classified by body mass index (BMI; <24.9=normal, n=184; >or=25.0 to <or=29.9=overweight, n=269; >or =30.0=obese, n=327) and presence (n=451) or absence (n=329) of the metabolic syndrome, further classified by diabetes status. Prevalence of significant angiographic coronary artery disease (CAD; >or =50% stenosis) and 3-year risk of CVD were compared by BMI and metabolic status. The metabolic syndrome and BMI were strongly associated, but only metabolic syndrome was associated with significant CAD. Similarly, unit increases in BMI (normal to overweight to obese) were not associated with 3-year risk of death (adjusted hazard ratio (HR) 0.92, 95% CI 0.59 to 1.51) or major adverse cardiovascular event (MACE: death, nonfatal myocardial infarction, stroke, congestive heart failure; adjusted HR 0.95, 95% CI 0.71 to 1.27), whereas metabolic status (normal to metabolic syndrome to diabetes) conferred an approximate 2-fold adjusted risk of death (HR 2.01, 95% CI 1.26 to 3.20) and MACE (HR 1.88, 95% CI 1.38 to 2.57). Levels of C-reactive protein (hs-CRP) were more strongly associated with metabolic syndrome than BMI but were not independently associated with 3-year risk of death or MACE. The metabolic syndrome but not BMI predicts future cardiovascular risk in women. Although it remains prudent to recommend weight loss in overweight and obese women, control of all modifiable risk factors in both normal and overweight persons to prevent transition to the metabolic syndrome should be considered the ultimate goal. In principle, obesity can be avoided or treated. Several measures, all requiring major changing in lifestyle, are needed for this purpose: a diet with no excessive calories, principally restricting saturated fats and carbohydrates; regular exercise; medications to control excessive anger, and, most recently, bariatric surgery. Cognitive behavioral therapy[52] is of particular value in this respect, as well as counseling by a nutritionist. Unfortunately, the long-term efficacy of weight reducing programs is disappointing, as shown by the Diabetes Prevention Program Research Group[53]; because patients in a long term tend to regain weight mostly over the next 1-2 years.

The five most important factors

As shown above, several factors contribute to a healthy lifestyle. Based on the 16-year follow-up of the Health Professional Study, Chiuve et al.,[54] identified five items associated with lower cardiac risk: non-smoking, BMI≤25, regular exercise (30min/day), healthy diet (fruits, vegetables, low saturated fat) and 5-30g alcohol/day. For each of the items followed there was a corresponding decrease in risk and this was true regardless of medication use, and was applicable to both men and women. Similarly, strokes were also significantly reduced among 43,685 men and 712,423 women who followed the same five recommendations[55]. As seen by Choi et al.,[56] women with a positive family history of coronary artery disease are characterized by a very high risk factor burden that is poorly captured by 10-year risk estimates but better captured by 30-

year estimates. This study also found that consideration of non-traditional factors such as anxiety, low household income, and depression is also pertinent to estimate the risk, and is better use of 30-year risk estimates to do so in young individuals so that the prevention of premature acute coronary syndrome can be improved. Experience shows that it is much easier to adhere to a healthy lifestyle in a preventive fashion, rather than adopting it when atherosclerosis is already present and unhealthy behavior needs correction; it can be more beneficial and easier to follow in a routine.

CONCLUSIONS

The differences between women and men have been assessed above. The setting of coronary artery disease in women increases its risk after menopause despite the advances in treatment of CVD, and several secondary prevention studies have demonstrated that drugs can significantly reduce cardiovascular events. Many unresolved issues remain, such as partial risk reduction, costs, access to treatment and awareness of the risk of development of the disease, and also adopting an active attitude toward regular physical activity. Changes in behavior require multidisciplinary care, including medical, nutritional, and psychological counseling and the participation of the entire society is required for such implementation. Although these efforts represent a major challenge, such a task must be faced in order to halt the CVD epidemic that threatens the world and mainly women.

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