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Gender Differences in Cardiovascular Disease: Hormonal and Biochemical Influences

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Abstract

Objective—Atherosclerosis is a complex process characterized by an increase in vascular wall thickness owing to the accumulation of cells and extracellular matrix between the endothelium and the smooth muscle cell wall. There is evidence that females are at lower risk of developing cardiovascular disease (CVD) as compared to males. This has led to an interest in examining the contribution of genetic background and sex hormones to the development of CVD. The objective of this review is to provide an overview of factors, including those related to gender, that influence CVD.

Methods—Evidence analysis from PubMed and individual searches concerning biochemical and endocrine influences and gender differences, which affect the origin and development of CVD.

Results—Although still controversial, evidence suggests that hormones including estradiol and androgens are responsible for subtle cardiovascular changes long before the development of overt atherosclerosis.

Conclusion—Exposure to sex hormones throughout an individual's lifespan modulates many endocrine factors involved in atherosclerosis.

Keywords

Cardiovascular disease; atherosclerosis; hormones; factors; gender

INTRODUCTION

The association between atherosclerosis and cardiovascular health has long been a source of investigation. As early as 1933, an association between dietary changes and female serum cholesterol levels was reported.[1] In 1958, during a conference on “Hormones and Atherosclerosis,” researchers concluded that cholesterol deposition was directly linked to blood cholesterol levels, although other factors, including gender, hormones, diet, lipid levels, and stress, were deemed important as well. In particular, it was reported that ethinyl estradiol reduced plasma lipid levels in a group of men with previous myocardial infarction

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(MI), although there was no significant reduction in morbidity or mortality from coronary events as compared to the control group.[2]

Despite years of research, however, the relationships between cholesterol, atherosclerosis and cardiovascular risk (CVR) remain controversial.[3-8] The popularity of statins and other cholesterol-lowering medications is a testament to the notion that elevated cholesterol is linked to heart disease. The real connection, however, is likely not so straightforward. Half of individuals who have a heart attack do not have high cholesterol levels, and some of the cardioprotective effects of statins seem to be mediated via a reduction in arterial inflammation[9,10] and effects on vitamin D rather than through a simple lowering of cholesterol.[11,12] Furthermore, there is not enough information regarding the long-term impact of pharmacologic treatment of cholesterol levels. It is known that statins inhibit cerebral cholesterol synthesis by blocking the growth of new nerve cell synapses; this may account for some of their reported adverse effects such as amnesia, confusion, disorientation, and dementia.[13,14] Statins also inhibit the production of other vital biochemicals, notably the potentially cardioprotective co-enzyme Q10.[15]

Because the connection between hypercholesterolemia and CVD is not a straightforward one, researchers have been actively investigating other potential contributors. The role of sex hormones in cardiovascular disease (CVD) is an emerging field of interest. A small series of men with deficient estrogen action (due to mutations in the genes for estrogen receptor [ER] or aromatase) developed early-onset atherosclerosis, increased visceral adipose tissue, hyperinsulinemia, and the constellation of risk factors known as metabolic syndrome. These same abnormalities have also been reported in men with sufficient estrogen action but low testosterone (T) levels.[16] It has been postulated that the described alterations in sex hormone alterations may cause these cardiovascular abnormalities and that, ultimately, atherosclerotic CVD may be an endocrinological disorder.[16]

In the last decade, newer hormones, including leptin, adiponectin, and vitamin D, have also been linked to different phases of vascular dysfunction.[17-19] Despite 50 years of research, however, there is no unifying theory for the pathophysiology of CVD, which might allow for development of effective therapies with fewer side effects than those currently available. We present a review of recent evidence regarding influencing factors, with a focus on gender-specific influences that may be involved in the genesis of CVD.

THE CARDIOVASCULAR GENDER GAP

Epidemiological, clinical, and experimental data have provided evidence that there are gender-specific variations in CVR. From a broad perspective, many medical comorbidities, including endocrine disorders such as hypothyroidism and diabetes and psychiatric disorders such as depression, manifest a gender predilection and are associated with increased CVR.[20] For example, women are more likely than men to experience an episode of depression and to be subsequently diagnosed with the metabolic syndrome.[21] The prevalence of subclinical hypothyroidism increases with age and is higher in women, and several studies have suggested an association between thyroid disease and coronary artery disease.[22] Finally, women with diabetes are less likely to be well-controlled (as manifested by glycosylated hemoglobin [HbA1C] levels less than 7%) and are more likely to develop and die from CVD.[23]

Apart from these and other comorbidities, the menopausal period in itself appears to be a time of transition to increased CVR.[24] The incidence of nondiabetic CVD is lower in premenopausal women than in age-matched men.[25] Ovarian hormone insufficiency at the time of the menopause is associated with increased cardiovascular events. Thus, CVD develops, on average, 10 years later in women compared to men.[26] These observations have

led to the development of the hypothesis that estrogens protect women against atherosclerotic complications.

At the cellular and biochemical level, gender differences in the regulation of physiological mechanisms are directly influenced by genetic polymorphisms. Some studies have linked CVD with variations in the nuclear hormone family of ER genes, including ER-α gene (ESR1) and ER-β gene (ESR2).[27] These receptors function as ligand-dependent transcription factors and predominate in vascular endothelial and smooth muscle cells.[28] Estrogen receptor α gene polymorphisms may influence response to peripheral estradiol and, indirectly, the prevalence of different menopause-related conditions.[29] Postmenopausal women who carry a particular ESR1 variant (haplotype 1, c.454–397 T allele and c.454–351 A allele) are at increased risk of MI and ischemic heart disease (IHD), independent of known CVR factors.[30] This association has not been observed in men.[31]

Estrogen receptor β gene expression predominates in human vascular smooth muscle cells (VSMCs).[32] In rat models, expression of ESR2 was induced after vascular injury and its expression is associated with increased coronary artery plaque surface area in both women and men.[33,34] Some ESR2 polymorphisms are associated with gender-specific increased risk of CVD (particularly MI). For example, women with a particular variant allele (RS127152) had significantly increased risk of CVD and MI, while men with a different rare variant (RS1256049) were at reduced risk. Other variants, however (such as RS127152), confer increased risk of MI upon men only.[35] In postmenopausal women, a near-significant association was found between some ESR2 haplotypes and obesity—a related CVD condition.[36]

Selective stimulation of a second type of ER, the intracellular G protein-coupled ER (GPER), decreases rat blood pressure and dilates human arterial blood vessels.[37] In GPER knockout mice, this effect is abolished and visceral obesity is observed. Female GPER knockout mice had impaired glucose tolerance (hyperglycemia), reduced body growth, increased blood pressure, and reduced insulin-like growth factor blood levels.[38]

In women, endogenous female sex hormones, especially estrogens, are cardioprotective via multiple mechanisms: increased high-density lipoprotein (HDL), decreased low-density lipoprotein (LDL), and release of vasodilators such as nitric oxide (NO) and prostacyclin (PGI_2) from vessel walls, which results in inhibition of vascular constriction and lowering of blood pressure as well as decreased platelet aggregation.[39] In a study in which men and women underwent 24-hour ambulatory blood pressure monitoring, men had higher blood pressure than their age-matched, premenopausal female counterparts. However, after menopause, blood pressure increased in women to levels even higher than those observed in men.[40] In addition, during the menopausal transition, there is an increase in the prevalence of the metabolic syndrome, elevated body weight, dyslipidemia, hyperinsulinemia, and hypertension.[41,42] Hormone therapy (HT), in most cases, does not significantly reduce blood pressure in postmenopausal women, suggesting that estrogen deficiency may not be the only component involved in postmenopausal hypertension.[42]

The lower prevalence of CVD in premenopausal women, in comparison to age-matched men, has been explained by differences in body fat distribution, plasma lipoprotein levels, and indices of plasma glucose-insulin homeostasis.[43,44] Women generally have a higher plasma HDL levels and lower plasma insulin, apolipoprotein B, and triglyceride (TG) levels (which have been associated with abdominal visceral adipose tissue).[45] Additionally, estrogen seems to contribute to glucose homeostasis via increased glucose transport into the cell, and studies have suggested a positive effect of hormone replacement therapy on HbA1C levels in postmenopausal women.[46]

SEX HORMONES AND LIPOPROTEINS

Although the mechanism by which exogenous estrogen may prevent CVD is most likely multifactorial, during the last decades, increased emphasis has been given to estrogen's effect on the lipid profile and the process by which alterations in the lipid profile lead to CVD. High serum lipid levels (especially LDL) contribute to atherosclerosis.[47,48] This process seems to be initiated at the level of the intima via macrophage uptake of oxidatively modified LDL, which results in release of the proinflammatory cytokine tumor necrosis factor α (TNF-α) from monocytes and macrophages.[49] Oxidized LDL induces apoptosis in cultured endothelial cells and promotes inflammation via enhancement of in vitro endothelial cell monocyte adhesion.[50] In vitro preparations, 17β estradiol at high local concentrations inhibits LDL oxidation and reduces cholesterol ester formation[51,52]; T does not have the same effect.[52]

However, estrogen's LDL-lowering effect accounts only for 25% of the observed reduction in CVR.[53] A high fraction (66%) of women included in the Framingham Cohort, who had incident coronary heart disease, did not have either hypercholesterolemia or elevated serum LDL. These women did, however, have elevated TG levels and low HDL levels.[53] The combination of elevated LDL and elevated TG levels predicts a heightened risk of CVD, beyond the prediction obtained by elevated LDL alone.[54] Hypertriglyceridemia also decreases high-density lipoprotein cholesterol (HDL-C) while increasing insulin resistance, glucose intolerance, hypertension, and prothrombotic states with the overall effect of further increasing CVR.[54] There was also a trend for men to have higher LDL concentrations than women and for women to have higher HDL concentrations than men.[54] This difference in HDL particle size decreased with age, with a concomitant increase in CVR.[54] An additional CVD risk factor is elevated apolipoprotein (a) levels that tend to increase after menopause.[55]

Gender differences in endogenous sex hormones and lipoprotein subfractions were confirmed via nuclear magnetic resonance (NMR) spectroscopy.[56] When VLDL, LDL, and HDL particle size and numbers were measured in men and non-HT-using postmenopausal women included in the Multi-Ethnic Study of Atherosclerosis (MESA) baseline examination, a more atherogenic lipo-protein particle profile was associated with higher endogenous estradiol and lower sex hormone binding globulin (SHBG) levels.[57]

The Women's Health Initiative (WHI) investigated the role of conjugated equine estrogen (CEE), alone or in combination with progestin, in decreasing cardiovascular events in women.[58] While the trials were discontinued early due to an increased risk of CHD and stroke,[59] the trials are limited by the choice of an older population (with a mean age of 63 years at the time of initiation of HRT: hormone replacement therapy (or hormone therapy)).[60] Subsequent subgroup analyses suggest that women who initiate HT in the early postmenopausal period have lower CVR than those who initiate HT more than 20 years after menopause.[61] In addition, an analysis of the WHI trial has found that younger postmenopausal women treated with the estrogen-only regimen had significantly less coronary artery calcification than their counterparts taking placebo.[62] These data suggest that estrogen may decelerate the early stages of atherosclerosis. Women in the early postmenopausal years undergo fewer thrombotic modifications to the vasculature during HT, because the endothelium is healthier and more resistant to thrombosis.[63-65] Disappointingly, late initiation of HT has not been associated with cardiovascular benefits.[58,59] Furthermore, when ET has been used in men (eg, as an adjuvant component for prostate cancer chemotherapy), it has been associated with serious adverse vascular effects and increased cardiovascular-related deaths.[66] The appropriate route of administration is also controversial. Some of the adverse effects of estrogen are related to the “first-pass effect” through the portal circulation, an effect that can be avoided by

transdermal estrogen administration, thus avoiding hepatic enzyme induction.[67] Additionally, there are data to suggest that transdermal estrogen may be more effective at lowering blood pressure.[67] However, the hepatic effects of oral estrogens are also responsible for the improved lipoprotein levels seen after initiation of HT. The Kronos Early Estrogen Prevention Study (KEEPS) trial will address many of these issues in younger, recently postmenopausal women, comparing transdermal and oral estrogen in a blended trial.[68]

ESTROGEN's EFFECTS ON THE VASCULATURE

Estrogen-induced lipoprotein profile changes partly explains estrogen's cardioprotective effect in premenopausal women.[69] In addition, estrogen and its receptors are involved in multiple other biochemical pathways, including stimulation of angiogenesis, endothelial NO production, and regulation of cytokines and inflammatory markers that may help to explain their antiatherosclerotic effects.[70-72] Steroid receptors—and specially ERs—interact with a wide range of coregulatory factors that may change depending on endothelial age and alteration. This physiological cross talk and biological equilibrium may be abruptly interrupted by estrogen deprivation and can ultimately increase an individual's risk of CVD.[73-76]

Estrogens exert direct effects on arterial wall smooth muscle to cause vasodilation.[77,78,87,88] Estrogens produce rapid vasodilatory effects by increasing endothelial nitric oxide synthase (eNOS) activity, an effect that does not require changes in gene expression.[79] In the long term, estrogen's effects on vasodilatation are mediated, at least partly, by changes in expression of the estrogen-specific receptors ESR1 and ESR2. Estrogen mediates arterial vasodilatation and blood flow through this pathway via stimulation of endothelial PGI_2 synthesis and inhibition of endothelin-1 (ET-1), a substance that has a vasoconstrictive effect on arterial subendothelial smooth muscle cells.[80,81] Also notably, in vitro studies using porcine coronary arteries contracted with a thromboxane A_2 (TXA_2) analogue showed direct relaxation after addition of increasing concentrations of estradiol and estrone.[82]

Surgically induced menopause causes an increase in peripheral vascular resistance and blood pressure. The observation that blood pressure often returns to baseline after initiation of HT suggests that ovarian (and primarily estrogenic) insufficiency accelerates development of hypertension.[83] The effect of exogenous estrogen on blood pressure may depend on the type, route, and dose of estrogen administered. In normotensive postmenopausal women, transdermal estradiol decreases sympathetic nerve discharge without augmenting arterial baroreflexes, causing a small but significant decrease in ambulatory blood pressure.[84,85] Sympathetic inhibition is evident only with chronic rather than acute estrogen administration, implying a genomic mechanism of action.[85-88]

Estradiol also acutely modulates vascular activity of vasoconstrictors such as angiotensin or serotonin, regulating venous endothelin receptor expression and stimulating vasoconstrictor prostanoids. In nonatherosclerotic human coronary arteries, estradiol induces rapid endothelium-independent vasodilatation and enhances bradykinin endothelium-dependent relaxation.[89,90] As will be further discussed, all these data point out to the fact that nongenomic estradiol pathways are relevant to normal vasodilation.

ANDROGENS AND THE CARDIOVASCULAR SYSTEM

Links between androgens and the cardiovascular system, in both men and women, remain controversial.[91,92] Testosterone levels fall as men grow older, with a steeper decline in free T compared with total T concentrations.[91] In healthy women, total and free T levels, as well as levels of dehydroepiandrosterone sulfate (DHEAS) and androstenedione, decrease with

age. The steepest decline in androgen levels occurs in the early reproductive years.[93] It is generally accepted that androgen levels do not change significantly in the perimenopausal period, although some researchers have challenged this assertion, reporting a decline in T, androstenedione, and SHBG during the menopausal transition.[93]

Experimental evidence suggests that androgen deficiency contributes to the onset and progression of CVD in men.[94,95] Androgen deficiency is associated with endothelial dysfunction, adverse lipid profiles, inflammatory responses, altered smooth muscle, and hypertension. Lower T levels have been associated with poor cognitive function, sexual dysfunction, metabolic syndrome, and type 2 diabetes.[94] These last 2 conditions are associated with CVD. In older men, lower total T levels predict increased incidence of stroke and transient ischemic attacks even after adjusting for conventional CVD risk factors, and observational studies show that blood T concentrations are lower among men with CVD, suggesting a possible preventive role for T therapy.[95]

Androgen treatment may prevent or ameliorate these age-related declines in T.[96] Short-term effects of various T doses on vascular function have been studied in isolated porcine contracted coronary artery strips. Testosterone produces vasorelaxation of the contracted system in an endothelium-independent manner and without the participation of androgen receptors (ARs). Interestingly, T receptor antagonists flutamide and cyproterone acetate did not interfere with the observed response, again suggesting that the response is independent of ARs.[97] Indeed, T supplementation restores arterial vasoreactivity, reduces levels of proinflammatory cytokines, cholesterol, and TG, and improves overall endothelial function, although it may also reduce HDL levels.[98] Human arteries and veins (in both males and females) can locally convert T to estradiol and provide important atheroprotective effects via the mechanisms described above.[99] It is likely, then, that estradiol's protective vascular effects (either directly due to presence of estrogen or indirectly due to peripheral conversion of androgens) are not restricted to females.

In young women, levels of androgens and estrogens can influence vascular physiology. Polycystic ovarian syndrome (PCOS) and hyperandrogenism are among the most common endocrine disorders in reproductive-age women. Insulin and androgens have complex relationships: a significant number of hyperandrogenic young women have insulin resistance and, conversely, women with diabetes are at greater risk of developing PCOS.[100] From a cardiovascular standpoint, PCOS, hyperandrogenism, and obesity are all associated with a more atherogenic lipid profile.[100] At the time of menopause, women with PCOS have both increased androgen production and increased risk of developing metabolic syndrome compared to their healthy counterparts.[101]

Despite the previously described studies suggesting a link between hypoandrogenemia and CVD, some researchers have suggested that development of CVD in perimenopausal and postmenopausal with PCOS is related to protracted hyperandrogenism.[102] This assertion is obviously confounded by the multiple other CVR factors present in women with PCOS. In a cohort from the WISE study, a total of 104 postmenopausal women with a history of premenopausal PCOS had more frequent CVD risk factors than women without clinical features of the syndrome, including diabetes, obesity, metabolic syndrome, angiographic coronary disease, and cardiovascular events.[102] Young women with PCOS may benefit from traditional methods of reducing CVD such as calorie restriction, weight loss, and control of blood sugar, pharmacologic methods such as use of sibutramine (an appetite suppressant), or improved control of hyperandrogenism. However, it remains to be determined whether these therapeutic measures may reduce CVR later during postmenopausal years and whether hyperandrogenism in itself is a cause of CVD in PCOS women.

While overall levels of androgens may remain stable in the perimenopausal period, the fall in estrogen levels leads to a decrease in the estradiol/T ratio. This shift seems to be more pronounced in women with increased waist circumference (a surrogate marker of abdominal obesity). This gradual increase in androgenic status may also be implicated in the development of insulin resistance, and a more atherogenic lipoprotein profile, with subsequent increase in CVR after the menopausal transition.[105] In nondiabetic, postmenopausal women who were not using HT, those with CVD displayed lower SHBG levels and free androgen index (FAI) and HbA1c values as compared to controls. Glycosylated hemoglobin values were inversely associated with SHBG, and positively associated with FAI, even after adjusting for age, CVD case control status, and body mass index (BMI). In multivariate models, a significant inverse association between SHBG and HbA1c persisted, as well as a significant positive association between FAI and HbA1c.[103,104,106]

As previously mentioned, however, other studies have not detected age-adjusted overall differences in androgen levels in postmenopausal women.[107] In a Swedish cohort of perimenopausal women, those with CVD (especially women taking HT) had lower serum androgen levels as compared to matched controls, even when controlled for lipids and other potential risk factors.[108] In addition, in women, there is an inverse relationship between DHEAS, androstenedione, and androgen concentrations and carotid wall thickness as well as between T and SHBG concentrations and carotid atherosclerosis.[109,110] Endogenous sex hormone levels have also been studied in postmenopausal women undergoing carotid artery endarterectomy. In several studies, an association has been reported between low serum androgen levels and severe internal carotid artery atherosclerosis, suggesting that higher physiological levels have an atherogenic protective role.[111]

Dehydroepiandrosterone (DHEA), in particular, has effects on endothelial proliferation and angiogenesis.[112] A specific plasma membrane DHEA receptor has been demonstrated in endothelial cells, and DHEA is metabolized intracellularly to other biologically active steroids, including estradiol (which also induces vascular endothelial proliferation).[112] However, T, another DHEA metabolite, does not increase vascular proliferation.[113] In vitro studies indicate that DHEA affects vessels by increasing endothelial NO production. In an acute (and likely non-genomic) fashion, DHEA also increases insulin sensitivity.[114] These observations may help explain DHEA's cardioprotective effects. Interestingly, endothelial cells treated with DHEA also increase ET-1 secretion by 2-fold, suggesting that DHEA has both vasodilatory and vasoconstrictive effects on the vasculature.[114]

ENDOTHELIAL FUNCTION AND THE REGULATION OF VASOMOTOR TONE

The endothelium participates in the control of hemostasis, blood coagulation and fibrinolysis, platelet and leukocyte interactions with the vessel wall and the regulation of vascular tone and blood pressure.[115] Endothelial cells produce many compounds aimed at controlling functions of VSMCs and circulating blood cells. In the same individual, endothelial cells from different locations in the vascular system display marked phenotypic variation, expressing different antigens, receptors, and responses to the same stimulus.[116] Responses of in vitro cultured endothelial cell may not correspond to those found among the same cells in vivo.[115,116] Endothelium produces, and is influenced by, a number of vasodilating and vasoconstricting substances that regulate vasomotor tone. Among these mediators are NO, PGI_2, and endothelin. These factors are involved in angiogenesis but may also contribute to atherosclerotic plaque development.[116] The biological function of the endothelium is to maintain the vascular network in optimal condition for blood flow.[115]

The development of atherosclerosis is related, in part, to vascular endothelial dysfunction. The endothelial cell surface maintains a nonthrombogenic blood-tissue interface due to the presence of antithrombin III, thrombomodulin, protein C anticoagulant, plasminogen activator, and PGI_2, and NO (which inhibit platelet activation) and the production of clotting factors.[117] A carefully regulated equilibrium between pro- and anticoagulant factors maintains normal blood flow and allows platelet adherence, thrombosis, and thrombolysis.[117]

Oxidative Stress and NO

Nitric oxide was originally named endothelium-derived relaxing factor.[118] It is produced in response to various stimuli, including fluid shear, stress, and exposure to neurohumoral factors such as acetylcholine, bradykinin, serotonin, and substance P. Nitric oxide is formed from the amino acid L-arginine by a 2-step oxidation process involving conversion of L-arginine to L-citrulline, which is catalyzed by eNOS. After its synthesis in the endothelial cell, NO diffuses to the subadjacent VSMCs, where it activates guanylyl cyclase (sGC) and leads to the production of cyclic guanosine monophosphate (cGMP). Although short lived, NO is a potent vasodilator that contributes to the maintenance of basal vascular tone and blood flow and thus to the physiological regulation of blood pressure.[118] It also has important antiplatelet, antioxidant, antiadhesive, and antiproliferative properties.[119,120]

Estrogens can produce rapid vasodilatation by increasing NO synthesis and decreasing ET-1 and angiotensin II production. Estrogen also causes vessel relaxation via acetylcholine- and serotonin-dependent mechanisms, mediated by its effects on PGI_2 secretion and calcium channel inhibition.[121] 17β estradiol, but not 17α estradiol, causes rapid endothelial NOS activation. This acute vasodilatory effect occurs via nongenomic pathways involving membrane-associated estrogen binding sites that are independent of nuclear ERs.[122] In vitro studies have been performed to investigate the effects of progesterone and 17β estradiol on eNOS in endothelium intact aortic rings. The rapid stimulatory action of progesterone and 17β estradiol on eNOS (leading to production of NO and ultimately to decreased platelet aggregation) was specific to these 2 hormones; neither T nor 17α estradiol was effective.[123] It seems that nongenomic pathways are important in maintaining normal vasodilatory mechanisms. Transcription of another form of NOS, inducible NOS (iNOS), is positively regulated by ESR2 and negatively regulated by ESR1, suggesting that both receptors are involved in the genomic regulation of vasodilatory mechanisms in VSMC.[124] ER-β gene knockout mice—deficient in the ER β gene—demonstrate vascular dysfunction and hypertension as a result of iNOS dysregulation.[125]

In response to vasorelaxants, such as acetylcholine, NO acts on underlying VSMCs to induce vascular relaxation. In addition, VSMCs themselves express eNOS and contribute to vascular relaxation.[126] Endothelial cell incubation with oxidized LDL results in translocation of eNOS to an internal membrane compartment and renders it insensitive to stimulation by acetylcholine.[127] In addition, elevated HDL is associated with normalization of the endothelium-dependent relaxation response triggered by acetylcholine (via prevention of eNOS translocation).[128] High-density lipoprotein acts as an atheroprotective substance via direct stimulatory effects on various endothelial kinases that modulate eNOS.[129,130] Oxidized LDL and HDL thus appear to have opposing effects on endothelial cell NO bioavailability.

Vascular Endothelial Growth Factor

Vascular endothelial growth factor (VEGF) is a broad term that includes a number of proteins from 2 families that result from alternate messenger RNA (mRNA) splicing of a single VEGF gene.[131] They can be proangiogenic (proximal splice site, expressed during

angiogenesis) or antiangiogenic (distal splice site, expressed in normal tissues). The inclusion or exclusion of exons 6 and 7 can modulate VEGF's ability to bind and activate VEGF signaling receptors.[131-133]

Vascular endothelial growth factor promotes angiogenesis and endothelial cell migration and proliferation via its actions on intracellular mediators.[134] Although VEGF, as its name implies, acts mainly on vascular endothelial cells, it also affects other cell types (for example, monocytes, macrophages, neurons, and kidney epithelial cells). In vitro, VEGF stimulates endothelial cell mitogenesis and migration. It also enhances vascular permeability —VEGF is 50 000 times more potent than histamine in this regard—and modulates endothelial cell surface adhesion molecule expression.[135] In regions of increased angiogenesis, VEGF (along with TNF-a and other inflammatory cytokines) is produced by aggregating macrophages.[136-139]

The VEGF receptor Flt-1 is expressed in human monocytes, which induces chemotactic responses among monocytes.[140,141] In a strain of ApoE-deficient cholesterol-fed mice, a single dose recombinant human (rh) VEGF treatment significantly increased the number of potentially atherogenic macrophage/monocytes.[142] Therefore, VEGF seems to enhance atherosclerotic plaque progression. However, in patients with ischemic syndromes, intra-arterial rh VEGF administration also markedly increases collateral vessel development.[143] Thus, VEGF seems to have a potential therapeutic role for coronary and peripheral occlusive vascular disease. Despite this, experimental treatments have failed due to the appearance of endothelial cell angiomatoid proliferation and intima thickening upon treatment with VEGF.[144]

Finally, some cardiovascular benefits of the Mediterranean diet have been related to the moderate consumption of red wine, and VEGF may play a role here as well.[145] In cultured VSMCs, short- and long-term exposure to red wine polyphenolic compounds inhibited VEGF expression via inhibition of a specific protein kinase pathway.[146]

Prostanoids

Prostanoids, including prostaglandins (PGs) and thromboxanes (TXs), are synthesized from arachidonic acid by the combined action of cyclooxygenases (COXs) and PG and TX synthases.[147] After their synthesis, prostanoids are immediately released into the extracellular space, where they interact with prostanoid receptors on neighboring cells. Prostanoids have potent, although sometimes opposing, biological effects. Prostacyclin is a vasodilator and platelet aggregation inhibitor, whereas TXA_2 acts as a vasoconstrictor and inducer of platelet aggregation.[148] A balance between the 2 is important to maintain cardiovascular health.[147-150]

Prostacyclin is the main product of COX (the rate-limiting enzyme in PG biosynthesis) at the vascular endothelium. It is a 20-carbon oxygenated fatty acid, derived from arachidonic acid, which acts as a vasodilator, platelet aggregation inhibitor, and VSMC proliferation inducer.[151,152] Prostacyclin acts on smooth muscle receptors to activate adenylate cyclase and inhibit vasoconstriction.[152] The PGI_2 pathway, as a vasodilatory system, has some redundancy with the NO system: PGI_2 increases endothelial cell NO production, and NO increases PGI_2 activity on smooth muscle relaxation.[153] In this capacity, it may function in a compensatory role when other vasorelaxation mechanisms are not functioning (for example, in eNOS-deficient mice who cannot produce NO).[153] In addition, PGI_2 also inhibits platelet aggregation via inhibition of the platelet-activating factor (PAF), which is synthesized by activated endothelial cells.[154] Interestingly, HDL also has inhibitory effects on endothelial cell PAF in vitro, and HDL particles modulate platelet function in vivo.[155]

Thromboxane A_2 is also produced by endothelial cells and serves as a potent vasoconstrictor and platelet activator.[156] It is involved in a wide range of CVDs including hypertension, MI, cerebral vasospasm, preeclampsia, and several thrombotic disorders.[156] In females, it increases vascular tone and blood pressure to compensate for estrogen-sensitive local vasodilating mechanisms and maintain vascular homeostasis.[156] Prostaglandin H synthase (PGHS), an enzyme involved in both PG and TX production, is a target of common nonsteroidal anti-inflammatory drugs (NSAIDs), including aspirin and ibuprofen and has been proposed as a possible therapy to prevent plaque formation.[157,158]

Estrogen interacts with this system at multiple levels. Prostaglandin H synthase–mediated vasodilatation predominates when estrogens are elevated, and estradiol treatment in castrated rats neutralizes PGHS-related vasoconstriction.[159] This finding could be considered a new approach for estrogenic treatment with the potential for further research in human participants.

The link between vascular tone (as regulated by the prostanoid system) and HDL is interesting as well. Prostanoid synthesis is induced by HDL via several mechanisms. Exposure of endothelial cells to HDL in vitro stimulates calcium-sensitive phospholipase A_2, an enzyme required for production of PGI_2.[160] High-density lipoprotein's effect on PGI_2 synthesis can be blocked by incubation of endothelial cells with HDL and calcium chelator.[159] High-density lipoprotein can also act synergistically with the inflammatory cytokines TNF-α and interleukin (IL)-1β to produce a large increase in COX-2 expression.[160]

CARDIOVASCULAR FUNCTION AND THE RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM

Vascular hemostasis does not occur only at the level of the endothelium. Renin-secreting cells at the level of the renal glomerulus are sensitive to changes in blood flow and blood pressure. Renin catalyzes the conversion of the angiotensinogen protein into the decapeptide angiotensin I. Serum angiotensin-converting enzyme (ACE) then converts angiotensin I into the octapeptide angiotensin II that acts via adrenal gland receptors to enhance aldosterone secretion. Aldosterone then stimulates kidney salt and water reabsorption and arteriolar constriction, causing an elevation in blood pressure. Enhanced renin angiotensin aldosterone system (RAAS) activation contributes to the evolution of hypertension.[161]

Angiogenesis, Endothelial Function, and the RAAS

Angiotensin II acts as an atherogenic agent; it is involved in blood coagulation and the pathogenesis of acute thrombosis via multiple mechanisms. It promotes vascular inflammation, stimulating human endothelial cells to release the inflammatory chemokine interferon inducible protein 10 (IP-10) and potentially promoting atherosclerosis.[162,163] It also acts on specific membrane receptors to activate intracellular signaling pathways that converge upon the transcription factor nuclear factor (NF)-κB, resulting in expression of procoagulant tissue factor.[164] Within the atherosclerotic plaque and inflamed vascular endothelium, monocytes and macrophages may synthesize additional angiotensin II, continuing the cycle of coagulation. Angiotensin II has also been shown to induce cellular senescence via a mitogen-activated protein kinase (MAPK) signal pathway.[165]

Interestingly, other angiotensin peptide fragments, such as angiotensin IV, may counteract this development of endothelial dysfunction. In ApoE–/– mice fed with a high-fat diet and displaying endothelial dysfunction and impaired vasodilatation, angiotensin IV produced a significant improvement in endothelial function, which seems to be mediated by increased NO bioavailability.[166] Another anti-atherogenic compound, ACE2, is a homologue of ACE

that inactivates the proatherogenic angiotensin II and has been proposed as an atheroprotective substance. In situ hybridization and immunochemistry studies, ACE2 mRNA is expressed in early and advanced human carotid atherosclerotic lesions. During atherosclerosis development, ACE2 levels were lower in stable advanced lesions as compared to early and ruptured atherosclerotic ones.[167]

The RAAS appears to cross talk with circulating lipoproteins. For example, some of the protective effects of HDL seem to be mediated by angiotensin II type 1 receptor (AT1R) downregulation, at least under diabetic conditions created by streptozotocin injection. In vivo, 6 weeks after apolipoprotein A-I gene transfer, HDL increase was associated with a 4.7-fold reduction in diabetes mellitus–induced aortic AT1R expression and improvement of NO bioavailability. In vitro, HDL reduced the hyperglycemia-induced upregulation of the AT1R in human aortic endothelial cells.[168] In addition, in fat-fed LDL receptor-deficient (LDLr (–/–)) mice, the renin inhibitor aliskiren reduces atherosclerotic lesion size in both the aortic arch and the root. When renin-deficient bone marrow is transplanted to irradiated LDLr(–/–) mice, a profound reduction in the size of atherosclerotic lesions is obtained. Thus, renin inhibition reduces atherosclerotic lesion development.[169]

Estrogen's Effects on the RAAS

The RAAS has been implicated in menopause-associated hypertension. In an estrogen-deficient follitropin-receptor knockout mouse model (FORKO), angiotensin II-induced vasoconstriction was enhanced, acetylcholine-induced vasodilatation was suppressed, and blood pressure was elevated. Indices of inflammation (nitrotyrosine formation and superoxide production) and cardiac collagen content were also increased in the FORKO animals.[170]

The vasodilator responses of the aortic ring in response to estrogen deprivation have been studied in rats. Animals were assigned to 1 of 3 groups: ovariectomized (OVX) non-OVX (sham) and OVX plus subcutaneous 17β estradiol (15 μg/kg per day, OVX + estradiol). Ovariectomized rats had a significant higher blood pressure than the other 2 groups at weeks 9 and 13. A significant decrease in NO levels with increased renin activity was observed in OVX rats as compared to sham operated ones. Estradiol treatment reversed these effects.[171] Plasma atrial natriuretic peptide (ANP) levels were also lower in castrated rats and could be restored by estradiol treatment. Acetylcholine-dependent endothelial relaxation was reduced in the isolated thoracic aortic rings of OVX animals, and estradiol treatment restored this response as well. These data supports the conclusion that estradiol is protective to the endothelium, preventing hypertension through modulation of the RAAS.[171]

Interestingly, however, estrogen treatment increases hepatic renin substrate production in some situations.[172,173] Hormone therapy increases angiotensin II plasma levels in postmenopausal hypertensive women whose blood pressures were well controlled with antihypertensive agents (excluding diuretics, ACE inhibitors, and angiotensin II receptor antagonists). Angiotensin I, angiotensin II, bradykinin, and renin plasmatic activity manifested a significant increase after HT in hypertensive (but not normotensive) women.[174] However, although angiotensin II levels were increased, blood pressure was unaltered. Serum ACE was significantly decreased in both groups (although aldosterone levels were unchanged), and bradykinin levels were increased (possibly to maintain homeostasis in the setting of elevated angiotensin II).[174] The overall effect of decreased ACE serum activity with increased levels of bradykinin induced by HT may have a cardioprotective effect. In pathological states such as hypertension and congestive cardiac failure, and despite its upregulatory effects on angiotensin II, estrogen may ultimately protect high-risk populations against the potentially deleterious effects of angiotensin II.[172] Hypertension is not considered a contraindication to estrogen treatment.[175]

In women with premature ovarian failure, 24-hour systolic and diastolic blood pressures were studied under different HT regimens. In an open-label randomized crossover trial, women with premature ovarian failure were treated with transdermal estradiol and vaginal progesterone or oral standard ethinyl estradiol and norethisterone acetate therapy for 12 months. Both regimens produced the same hormonal response and clinical symptom relief. Combined treatment with transdermal estradiol and vaginal progesterone was associated with lower systolic and diastolic blood pressures than the standard oral regimen at 12 months. In addition, the parenteral/vaginal combination produced a significant reduction in plasma angiotensin II and serum creatinine without altering aldosterone levels.[175,176]

In a separate study, transdermal HT (estradiol plus medroxyprogesterone acetate or MPA) significantly decreased diastolic and mean blood pressure and bradykinin levels in a group of normotensive postmenopausal women as compared to oral combination HT (continuous oral CEEs plus cyclic oral MPA). There were no significant changes in plasma renin and ACE activity and angiotensin I or angiotensin II levels. In the group of women taking oral HT, after 1 year, blood pressure remained unchanged, renin activity, and angiotensin I, angiotensin II, and bradykinin levels were significantly increased, and ACE activity significantly decreased.[173] Proper randomized trials are needed to determine whether transdermal HT may be preferable to oral administration of HT with respect to blood pressure and angiotensin II levels.

Aldosteronism is a well-recognized cause of hypertension and also plays a major role in progression and outcome of IHD.[177] Aldosterone is regulated by the pituitary-adrenal axis and the RAAS and itself regulates extracellular fluid content and electrolyte balance. Some new progestins, such as drospirenone, may also have a benefit on perimenopausal women with mild hypertension secondary to hyperaldosteronism.[178]

VITAMIN D AND CVR

Vitamin D is a hormone involved in regulating calcium and phosphorus levels that has important autocrine and paracrine roles. It is involved in the maintenance of normal cardiovascular function.[179] The American Heart Association recommends that healthy individuals obtain adequate amounts of vitamin D by consuming a variety of foods in moderation. Such sources include milk, salmon, mackerel, sardines, cod liver oil, and some fortified cereals.[180] A small dose of sunlight may also increase endogenous vitamin D levels without significant skin risks.[180] Vitamin or mineral supplements are not a substitute for a balanced, nutritious diet that limits excessive calories, saturated fat, trans fat, sodium, and dietary cholesterol.[145]

Epidemiological, clinical, and experimental data suggest that low serum vitamin D levels are associated with negative cardiovascular outcomes including hypertension, obesity, diabetes mellitus, and the metabolic syndrome.[181,182] Interestingly, the pleiotropic effects of statins include a stimulatory effect on the vitamin D endocrine system.[12] Vitamin D receptors (VDRs) have a wide tissue distribution that includes VSMCs, endothelium, and cardiomyocytes.[179]

The active form of vitamin D, 1,25-dihydroxyvitamin D ($1,25(OH)_{2D}$), increases VEGF expression (via a vitamin D response element in the VEGF promoter) and release in aortic VSMCs, an effect which, in vitro, is mediated by p38 MAPK activation.[183] In vitro studies also suggest that vitamin D suppresses proinflammatory cytokines and increases anti-inflammatory cytokines. In patients with congestive heart failure (CHF), vitamin D supplementation increased IL-10 (an anti-inflammatory cytokine) levels after 9 months, while the proinflammatory cytokine TNF-α remained constant. However, survival did not

differ significantly between the individuals who received vitamin D as compared to a control group.[184]

A cross-sectional study performed in 257 individuals assessed the relationships between serum 25(OH) D and CVD markers (including HDL levels and prevalence of the metabolic syndrome). Total vitamin D intake, including dietary supplement intake, was directly associated with increased serum vitamin D and HDL-C levels: for each 10 ng/mL serum vitamin D increase, there was a 4.2 mg/dL increase in HDL. Prevalence of the metabolic syndrome decreased significantly as serum vitamin D levels increased.[185] Conversely, low levels of vitamin D also appear to put an individual at risk of CVD. In an analysis of 1739 individuals included in the Framingham Heart Study, those with vitamin D blood levels below 15 ng/mL had twice the risk of a cardiovascular event such as a heart attack, heart failure, or stroke in the next 5.4 years as compared to individuals with higher vitamin D levels. The risk remained significant after adjustments for traditional CVR factors such as high cholesterol, diabetes, and high blood pressure.[179] Endogenous vitamin D levels have also been studied in individuals undergoing coronary angiography. During a median follow-up of 7.7 years, during which 22.6% patients died, patients in the lower two 25-hydroxyvitamin D (25(OH)D) quartiles displayed a higher mortality rate (all-cause and cardiovascular) than those in the highest 25(OH)D serum quartile.[185] Low vitamin D levels also appear to be associated with a higher risk of MI in men aged 40 to 75. Men with blood vitamin D levels <15 ng/mL had a higher risk of infarction than those with higher vitamin D levels (>30 ng/mL). This relationship remained significant even after adjustment for BMI, alcohol consumption, physical activity, history of diabetes mellitus and hypertension, ethnicity, region, omega 3 intake, and lipoprotein levels.[181]

Finally, in another study, individuals were classified by serum 25(OH)D sex-specific quartile levels. After a mean follow-up period of 6.2 years, 51 participants died, including 20 deaths due to cardiovascular causes. After adjustments for confounding variables such as age, sex, tobacco use, and comorbidities, low 25(OH)D levels were significantly predictive for all-cause (1.97, 1.08-3.58, $P = .027$) and cardiovascular (5.38, 2.02-14.34, $P = .0001$) mortality.[182] However, it remains unclear whether low vitamin D levels are a cause or a consequence of poor cardiovascular health, and more studies are required to confirm the relationship between vitamin D supplementation and reduced mortality.

THE ROLE OF ADIPOCYTE HORMONES

Obesity is associated with increased cardiovascular mortality and morbidity.[186] Obese individuals exhibit vascular endothelial dysfunction, which predicts CVR and is central to the pathogenesis of atherosclerosis.[186] Increased amounts of centrally distributed adipose tissue are associated with increased insulin resistance, type 2 diabetes mellitus, lipid disorders, and CVD.[187,188] Adipose tissue can be thought of not simply as an energy storage organ but also a secretory organ that produces a variety of bioactive substances capable of influencing the cardiovascular system.[187] There is considerable evidence linking adipocyte hormones and growth factors with cardiovascular complications.[188] Adipose tissue also participates in immunological functions through the production of a number of cytokines that may be involved in the pathogenesis of atherosclerosis, the most important of these adipokines being leptin, adiponectin, visfatin, TNF-α, VEGF, IL-6, resistin, plasminogen activator inhibitor 1 (PAI-1), and angiotensinogen, several of which will be discussed here.[189]

Leptin

Leptin is an adipocyte-derived hormone that is released into the blood in direct proportion to the amount of adipose tissue present. It promotes weight loss by decreasing food intake and

increasing metabolic rate. It is also involved in glucose metabolism, as well as in normal sexual maturation and reproduction. Leptin gene expression and secretion are increased by overfeeding, high-fat diet, insulin, glucocorticoids, endotoxins, and cytokines and decreased by fasting, T, thyroid hormone, and exposure to cold.[186,190]

Leptin interacts with the cardiovascular system in multiple ways. It may play an important role in regulating vascular tone, as evidenced by the widespread distribution of functional leptin receptors in vascular cells.[190] There are also several studies reporting an independent interaction between high leptin levels and atherosclerosis, MI, stroke, and coronary artery intima-media thickness, suggesting that high leptin levels are associated with increased CVR.[191-193] Activation of the sympathetic nervous system by leptin produces a slow but progressive increase in mean arterial blood pressure. In rats, intravenous leptin infusion increased arterial blood pressure and heart rate.[194] Leptin-induced increases in arterial blood pressure is probably mediated by effects on the central nervous system, because intracerebro-ventricular leptin administration is equivalent to systemic administration in terms of its vascular effects.[195]

Leptin receptors are also present in endothelial cells, and leptin treatment in rats has been reported to cause dose-dependent increases in NO levels.[196,197] In vitro studies have also shown that leptin produces endothelium-dependent relaxation of arterial rings.[198,199] It has been argued that these vasodilatory effects might oppose leptin's neurogenic pressor action. However, these results are controversial; other researchers have not documented leptin-induced increased blood flow in vascular beds.[200] Finally, high leptin levels also stimulate superoxide free radical production, which reacts with NO to create peroxynitrite, a toxic molecule that can interfere with DNA replication and damage vascular endothelial cells.[201] Thus, increased leptin levels can cause long-term cardiovascular damage and possibly contribute to hypertension, atherosclerosis, diabetes and other disorders.

Additionally, in women, circulating leptin levels are associated with stress-induced changes in heart rate, heart rate variability, and cardiac pre-ejection period, independent of age, adiposity, and smoking.[202] Plasma leptin levels in women also correlated with stress-induced increased IL-6 levels.[202] It has been postulated that leptin may mediate the adverse effects of stress and obesity on female cardiovascular health.

Adiponectin

Adiponectin is an abundant adipocyte-derived plasma protein with anti-atherosclerotic effects.[203] It is a unique adipokine, produced in lower amounts in obese than in lean individuals. Its receptors are present on endothelial cells, and it acts predominantly in a beneficial manner by increasing insulin sensitivity, stimulating fatty acid oxidation, inhibiting inflammatory reactions (including stimulation of the proinflammatory cytokine TNF-α), and inducing endothelium-dependent NO-mediated vasorelaxation.[203-205] It is also a negative regulator of angiogenesis: in vitro, addition of adiponectin at physiologic concentrations inhibits endothelial cell proliferation and migration and prevents new vessel growth. It also inhibits nonendothelial cell growth although the concentration needed is higher than for endothelial cells, suggesting a selective action on endothelial cells at low concentrations.[206]

Adiponectin is an important lipid and glucose metabolism regulator.[207] However, in mice, deletion of adiponectin does not cause any differences in body weight, suggesting that, under physiologic conditions, adiponectin may be redundant.[208] Similarly, in mice, adiponectin over-expression did not produce a significant increase in body weight or adiposity.[205] In humans, high adiponectin concentration has been associated with lower occurrence of diabetes and cholesterol abnormalities. Adiponectin's anti-angiogenic activity

seems to be especially pronounced under pathological conditions and could be related to suppression of angiogenesis that prevents atherosclerotic plaque growth.[209] However, despite these metabolic changes, elevated adiponectin levels may lead to increased risk of MI in older adults. In a cohort of 1386 older participants in the population-based Cardiovascular Health Study, 604 suffered a heart disease event, and those with the highest adiponectin levels were the most likely to be affected.[210] These results would seem to contradict the effects of adiponectin on lipid and glucose regulation, and further research is necessary to clarify adiponectin's role on the cardiovascular system.[210]

Resistin

Resistin is a hormone produced by fat cells that is associated with inflammation and insulin resistance. In a prospective case-control study nested in the Women's Health Study and the Physician's Health Study II, serum resistin levels were significantly higher in postmenopausal women than in men. Elevated baseline resistin levels were associated with an increased risk of type 2 diabetes. Positive correlations have previously been reported between BMI and resistin levels. These findings further suggest a complex interaction between gender, metabolic disease, and inflammatory markers.[211]

Resistin exerts a direct effect on myocardial cells, decreasing their ability to contract. In the Health Aging and Body Composition Study, 3000 elderly individuals were followed over 7 years. The risk of new onset heart failure increased 38% for every 10 ng/mL increase in resistin blood levels. This hormone appears to be an even stronger predictor of heart failure risk than other inflammatory markers linked to heart disease, such as C-reactive protein (CRP).[212] The association of resistin and adiponectin with heart failure has also been studied in 2739 individuals from the Framingham Offspring cohort. The hazard ratio for individuals in the top third of resistin distribution was 4.01 (95% CI: 1.52-10.57) compared to 2.89 (95% CI: 1.05-7.92) in the middle third during 6 years of follow-up. This association remained strong even after adjusting for presence of coronary heart disease, obesity, insulin resistance, and other markers of inflammation.[213]

Finally, significantly higher resistin levels have been found in individuals with masked hypertension compared to normotensive ones.[214] These results may be prognostic for future cardiovascular events. Hyperesistinemia may contribute to insulin resistance, endothelial dysfunction, chronic inflammation, and ultimately accelerated atherogenesis.[215-217] Therefore, resistin should be included as a novel variable and marker of CVD, although its precise clinical significance remains to be defined.

ADDITIONAL INFLAMMATORY MARKERS

Insulin

Studies of insulin resistance in young populations showed higher fasting insulin concentrations in girls, a difference that has remained despite adjustments for adiposity and pubertal stage.[218,219] Wilkin and Murphy postulated that females, who are born lighter than males despite higher insulin concentrations at birth, are intrinsically more insulin resistant than males.[220] In women, insulin resistance and diabetes are associated with greater CVR, including up to a 6-fold increase in MI risk, as compared to men (who have a 4-fold increased risk of MI in the setting of diabetes).[221,222] These observations has been confirmed in multiple studies including the Framingham Heart Project, the Chicago Heart Association Detection Project in Industry, and the Minnesota Heart Survey.[221,223]

C-Reactive Protein

C-reactive protein is an acute-phase reactant that was originally described in 1930 in the sera of patients acutely ill with pneumococcal pneumonia.[224] The Physicians' Health Study described CRP as a CVD risk factor in men, noting that high plasma concentrations were associated with a 2-fold increased risk of stroke and a 3-fold increased risk of MI.[108] Subsequent studies confirmed its utility as a prognostic factor for CVD in women: an increase in CRP levels above 3.0 mg/L was associated with elevated age-adjusted incidence rates of future cardiovascular events (from 3.4 to 5.9 per thousand person-years of exposure).[225] C-reactive protein does not, however, appear to differ between men and women.[225]

Ferritin

Serum ferritin is a biomarker of body iron stores.[226] Sullivan first noted an increased risk of MI in patients with high serum ferritin levels, hypothesizing that elevated iron stores contribute to CVD risk via increased free radical production, which promotes the development of atherosclerosis.[226,227] While men exhibit higher serum ferritin levels at baseline than both pre- and postmenopausal women, women also appear to be at risk from elevated ferritin levels.[228] In 1 case-cohort study, postmenopausal women with serum ferritin levels in the highest tertile had a 2-fold higher risk of ischemic stroke compared to women in the lowest tertile.[228] These findings are complicated by the fact that other authors have noted a U-shaped association between serrum ferritin and CVD, with levels in the extreme low range also representing a CVR factor.[229] In addition, clinical trials testing the impact of phlebotomy on cardiovascular events have not found decreased mortality after reduction of body iron stores.[229] Many of the available studies linking ferritin to CVD risk are small, comprised of varying ethnic groups, and include multiple confounding variables, suggesting that further work needs to be done to clarify the role of ferritin.

Homocysteine

Homocysteine (Hcy) is a sulfur-containing amino acid formed as an intermediate metabolite during the catabolism of the essential amino acid methionine. Some 80% of plasma Hcy is bound to proteins.[230] Its involvement in atherogenesis was elucidated by observing individuals with homozygous homocystinuria (who characteristically present with premature vascular disease).[230] Hyperhomocysteinemia is presently considered an independent risk factor for the development of atherosclerosis, as well as for arterial and venous thrombosis. More than 80 clinical and epidemiological studies support the fact that hyperhomocysteinemia is an atherosclerotic disease risk factor, even among individuals who have normal cholesterol levels.[231]

Although the precise etiological mechanisms are unknown, hyperhomocysteinemia likely leads to endothelial injury and dysfunction via generation of free radicals.[232] Circulating reactive oxygen species initiate cell membrane and circulating lipoprotein peroxidation. Subsequently, oxidized LDL is taken up by intima macrophages to form foam cells and begin the process of atheromatous plaque formation. The atherogenic effect of Hcy has been confirmed using experimental models; hyperhomocysteinemia can accelerate atherosclerosis development in susceptible models such as the apolipoprotein E-deficient mouse.[233] Interestingly, however, reduction in Hcy levels does not improve prognosis if disease is already present, as suggested by research studies involving a cohort of nearly 5000 Norwegian heart attack survivors with severe heart disease.[234] No preventive study has yet been conducted among participants who are in a relatively good state of health. In addition, reduction in Hcy levels does not quickly repair existing arterial structural damage.[234]

Homocysteine also stimulates VSMC proliferation and collagen deposition in the atheromatous plaque and inhibits vascular endothelial cell growth. Elevated Hcy levels may also promote thrombosis by increased thrombin generation and endothelial cell sensitization to the effect of inflammatory mediators.[235] Other possible mechanisms for Hcy-mediated atherogenesis include decreased NO bioavailability and excessive endothelial monocyte/neutrophil adhesion.[236] Evidence from animal models has demonstrated that hyperhomocysteinemia stimulates vascular cell proinflammatory pathways, resulting in vessel wall leukocyte recruitment and infiltration with increased chemokine secretion, and monocyte differentiation into cholesterol scavenging macrophages.[235] Finally, accumulation of adenosylhomocysteine (a by-product of hyperhomocysteinemia) leads to inhibition of methyltransferases and ultimately prevents repair of aged and damaged cells.[237]

In vitro experimental results indicate that Hcy can lead to ESR1 hypermethylation. This process is correlated with more severe atherosclerotic lesions; patients with atherosclerosis have a high rate of ERS1 promoter region hypermethylation.[237] Interestingly, menopausal women who took micronized estradiol (2 mg/d) for 6 months, with or without the addition of norethisterone acetate (1 mg/d), had a significant reduction in Hcy levels. However, there was no correlation between Hcy levels and measurements of carotid vascular resistance following HT.[238] In men, there were no associations between Hcy and T, DHEAS, and estradiol levels, even after adjustments for smoking, alcohol intake, daily physical activity, diabetes mellitus, and hypertension.[239]

FINAL REMARKS

Cardiovascular disease is a complex process that includes genetic, inflammatory, and immune factors as well as endocrine components. During the last decades, much emphasis has been given to blood cholesterol and lipids as the primary determinants of CVR. However, many endocrine factors (including androgens and estrogens) and biochemical factors are involved in the atherosclerosis process as well, both systemically and at the level of the vascular endothelium. Much research remains to be done regarding the interaction between these various factors and their role in gender-related cardiovascular differences.

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