by genetic, metabolic and hormonal factors. During the early stage of the atherosclerotic process, the subepithelial trapping of oxidised LDL molecules that trigger the local reaction of inflammation play a major role. The result is the accumulation of macrophages, monocytes and T cells, the production of matrix and various enzymes such as metalloproteinases (MMPs) and the production of proinflammatory cytokines, such as tumor necrosis factor (TNF) and interleukin 1 & 6 (IL-1 & 6), which mediate a Th1 response; the final result is a rupture in the atherosclerotic plaque. Another important step is the calcification of the coronary vessels, which has a genetic element but is also influenced by hormonal factors.

It seems that estrogens protect the vasculature at different levels. Through their direct actions, estrogens influence the evolution of the atherosclerotic lesions, whereas by their indirect actions they modulate various vasoactive, pro-inflammatory and metabolic factors as well as factors of the coagulation system (Table 2).

There is evidence that the administration of estrogens is protective for the formation of the atherosclerotic plaque when administered to either healthy or hypercholesterolemic rats. Hodgin et al have shown that this protective action of estrogens is mediated by ERα in hypercholesterolemic transgenic Apo E knockout mice, whereas when these rats were double knockout for the Apo E and for the ERα gene, this protective effect was diminished.

Estrogen deficiency also induces the calcification of atherosclerotic plaques. Postmenopausal women not receiving hormone replacement therapy (HRT) have more calcified atherosclerotic plaques in their coronaries than premenopausal or postmenopausal HRT users. Aortic calcification increases when the time elapsed since menopause is longer. Men have twice as many calcifications on their vessels as women until the age of 60, but after this age this gender difference attenuates, indicating the role that estrogen deficiency may play in vascular health. It is interesting that the mechanism of vessel calcification is similar to that of bone formation. Paradoxically, the vessel calcification during menopause occurs inversely to the bone demineralization and postmenopausal osteoporosis.

It seems that in these two processes, various molecules such as metalloproteinases (MMPs) and osteoprotegerin may play an important role. In their very recent study in autopsies of arteries of pre- and postmenopausal women, Christian et al reported the critical role of ERβ in the atherosclerotic and calcification process; these receptors were found to a greater extent in atherosclerotic coronary vessels and were correlated with more severe lesions, independently of the chronological age of these women. One other point that should be mentioned is that estrogen receptor gene expression may be affected by DNA methylation, which occurs with aging thus contributing to the atherogenic process in the cardiovascular system.

Estrogens also modulate the response to vessel injury with the mediation of both ERs. Both ERs expression increases after vessel injury. In animal models, ERβ appear to be important for the differences in the response to vascular ischemic injury between the two sexes. Experiments in ERβ...