Endothelial dysfunction in postmenopausal women and hypertension

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'Menopause is a cardiovascular risk factor for endothelial dysfunction … It also represents a unique opportunity to study the effect of endothelial dysfunction in healthy women and predicts the development of atherosclerosis and atherosclerosis-related disease.'

The endothelium is a major regulator of homeostasis and exerts a number of vasoprotective effects, such as vasodilation, inhibition of inflammatory responses and suppression of smooth muscle cell growth. Dysfunction of the endothelium thus causes reduction or abolition of these vasoprotective effects. Factors that lead to endothelial dysfunction (ED) include a reduction in nitric oxide (NO) production, increased oxidative stress and a decrease in NO bioavailability, whereas endothelium-derived contracting factors are increased. This imbalance leads to an impairment of endothelium-dependent vasodilation, which represents the functional characteristic of ED. Moreover, ED also comprises a specific state of 'endothelial activation', which is characterized by a proinflammatory, proliferative and procoagulatory milieu that favors all stages of atherogenesis [1,2].

Hence, ED it is considered a systemic disorder and a key variable in the pathogenesis of atherosclerosis and its complications. Current evidence suggests that endothelial status is not determined solely by the individual risk-factor burden but, rather, may be regarded as an integrated index of all atherogenic and atheroprotective factors present in an individual. ED reflects a vascular phenotype prone to atherogenesis, and may therefore serve as a marker of the inherent atherosclerotic risk in an individual. In line with this hypothesis, dysfunction of either the coronary or peripheral vascular endothelium was shown to constitute an independent predictor of cardiovascular events, providing valuable prognostic information additional to that derived from conventional risk-factor assessment [3]. The healthy endothelium, in fact, not only mediates endothelium-dependent vasodilation, but also actively suppresses thrombosis, vascular inflammation and hypertrophy. Nitric oxide is a particularly important mediator of both endothelium-dependent vasodilation and anti-inflammatory and antithrombotic effects of the endothelium, and endothelium-dependent vasomotion is therefore thought to represent a 'read-out' of other important functions of the endothelium.

It is now well recognized that high-resolution ultrasound study of endothelium-dependent brachial artery flow mediated dilation (FMD) is a useful tool for assessing the change in vasomotor response in relation to risk factors, aging and drug therapy [4]. This noninvasive technique is feasible and repeatable, and we have been performing it for a long time in our Women's Clinic. This 'imaging' technique is based on the fact that ED is not confined to the coronary arteries but, rather, represents a systemic disorder that also affects peripheral vascular beds, including both conduit arteries and small-resistance vessels in the extremities [5]. Several studies have confirmed that FMD of the brachial artery is impaired in patients with various atherosclerotic risk factors, including advanced age, hyperlipidemia, hypertension, diabetes mellitus, smoking and postmenopausal status [6–10]. Some studies indicated that the risk of developing ED increases with the number of risk factors present in an individual. In addition, assuming that the potential to alter endothelial function may vary between different risk factors, it may be speculated that certain clusters of risk factors, such as those observed in patients with metabolic syndrome, may have a greater impact on endothelial function than other risk-factor combinations. Furthermore, given its pivotal role in the atherogenic process, ED may be regarded as the 'ultimate risk of the risk factors', indicating the existence of a specific atherogenic vascular milieu (**Figure 1**) [3].

Our specific interest has been the study of ED in postmenopausal women. Menopause, in fact, is a cardiovascular risk factor for ED, independent from the presence of other risk factors. It also

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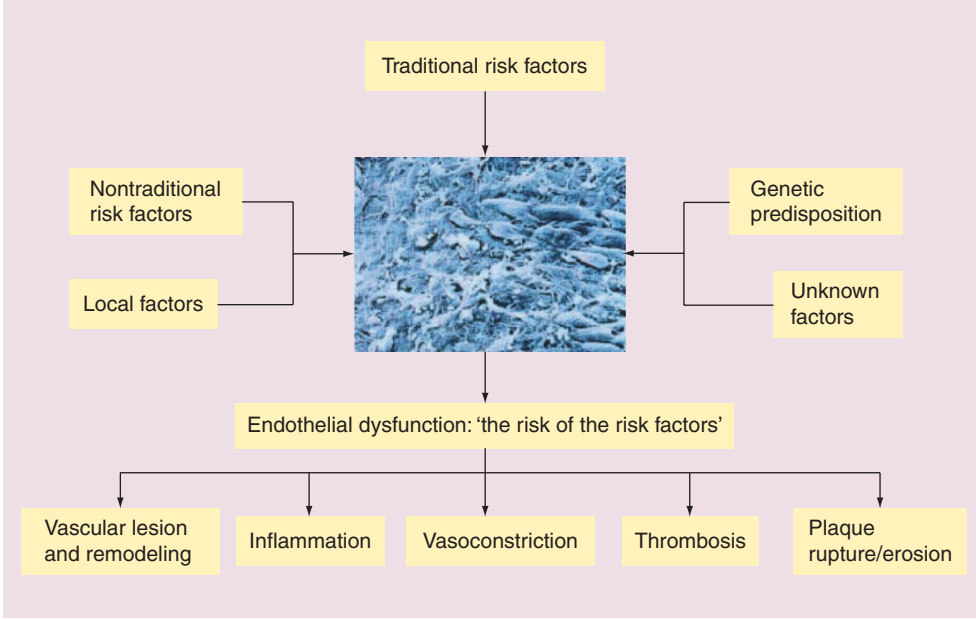
Figure 1. Endothelial dysfunction as the 'risk of the risk factors'.



Adapted from [3].

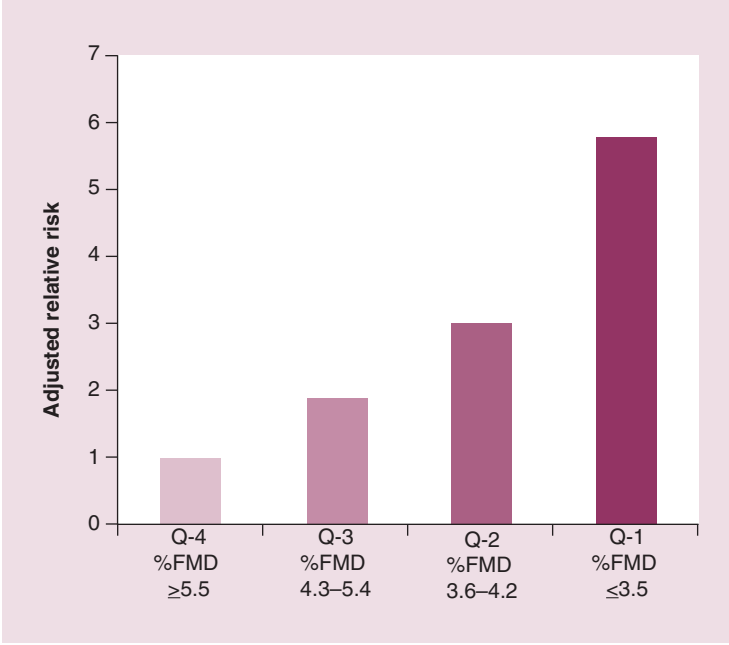
represents a unique opportunity to study the effect of ED in healthy women and predicts the development of atherosclerosis and atherosclerosis-related disease. For all these reasons it may be 'common' in postmenopausal women.

The evaluation of ED in postmenopausal women started in 1996 when the Women's Clinic was set up at our Institute. This is a clinic dedicated to the study, prevention and treatment of menopause-related disease.

The 'core' of our clinical research in the last 10 years has been to speculate on the fact that ED is common in postmenopausal, healthy women, but only in some women may predict the development of hypertension and/or diabetes and, finally, of atherosclerosis. Therefore it is not clear whether ED is actually a consequence or, rather, the cause of hypertension and/or diabetes.

Therefore our clinical research provided the first opportunity to assess relationship between endothelial vasomotor function and incidence of hypertension in a cohort of healthy postmenopausal women [11]. In this case, we conducted a prospective cohort study on 952 apparently healthy postmenopausal women with initially normal levels of blood pressure and no history of hypertension. All participants were followed up for a mean period of 3.6 ± 0.7 years. Endothelial function was measured as FMD of the brachial artery using high-resolution ultrasound. During follow-up, 112 women developed hypertension. The adjusted relative risk for women with FMD of 3.5 or less (lowest quartile) was 5.77 (95% confidence interval [CI]: 4.34–8.10) versus women with FMD of 5.5 or greater (highest quartile, referent). Each one-unit decrease of FMD was associated with a significant 16% (95% CI: 12–33%) increase in the multiple-adjusted relative risk of incident hypertension (**Figure 2**). Our study demonstrates that, in healthy, normotensive postmenopausal women, endothelial-dependent vasodilation is a parameter able to significantly predict the future development of hypertension, independently of numerous well-known risk factors and with a high correlation with the degree of impaired ED. The role of severely impaired endothelial function in predicting ED-related diseases was reconfirmed in a cohort of healthy, nonobese normoglycemic postmenopausal women of our Women's Clinic, followed-up for approximately 5 years [12]. In this population, each one-unit decrease in %FMD was associated with a significant 32% (95% CI: 22–48) increase in the multiple-adjusted relative risk of incident diabetes. This could suggest that an impaired endothelial function may also play a fundamental role in diabetogenesis in postmenopausal women. The fact that hypertension may predict the development of diabetes is well known, behaving to the subset of insulin-resistance,

Figure 2. Relative risk of developing hypertension in relation to the percentage of flow-mediated dilation quartiles.



Adapted from [11].
FMD: Flow-mediated dilation; Q: Quartile.

which is particularly relevant in postmenopausal women, who are, therefore, also at high risk of developing metabolic syndrome. No prospective data exist regarding the incidence rate of hypertension in postmenopausal women with Type 2 diabetes mellitus. In a recent study, we assessed the risk of developing hypertension in 102 diabetic (Type 2 diabetes mellitus) postmenopausal women, compared with 538 nondiabetic women. Compared with the nondiabetic group, women with Type 2 diabetes mellitus had a statistically significant higher risk of developing hypertension; in our prospective study on the incidence of hypertension, therefore the presence of Type 2 diabetes was found to be a potent independent risk determinant [13].

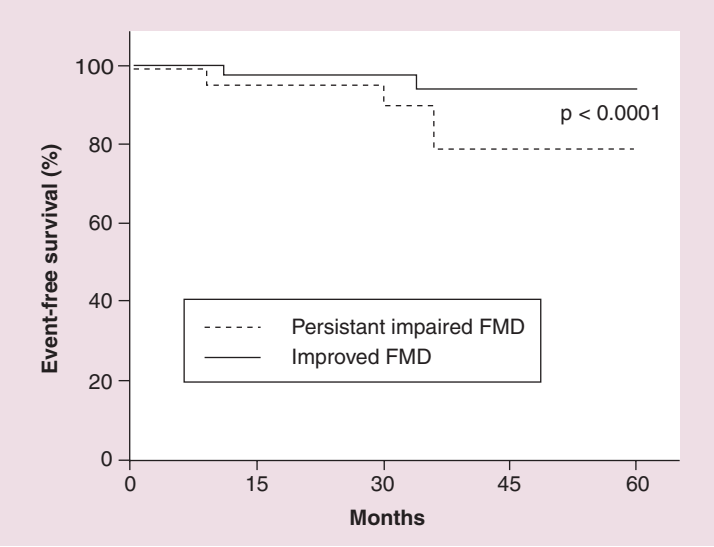
Therefore, hypertension, diabetes and atherosclerosis share common pathophysiology and etiopathogenesis suggesting that they spring from a common soil, which is represented by ED.

For this reason, we believe ED plays a pivotal role in postmenopause, either for risk factors and/or specific disease, or for prognosis. In fact we demonstrated its prognostic role in hypertension in a study where we assessed whether antihypertensive treatment was effective in modifying ED in postmenopausal women and whether an improvement of FMD in response to treatment, as an expression of a reversible ED, could provide a more favorable prognosis in the studied population [14]. A total of 400 consecutive postmenopausal women with mild-to-moderate hypertension and impaired FMD underwent ultrasonography of the brachial artery at baseline, and after 6 months, while optimal control of blood pressure was achieved using antihypertensive therapy. They were then followed up for a mean period of 67 months. After 6 months of treatment, FMD had not changed in 150 (37.5%) of 400 women (group 1), whereas it had significantly improved in the remaining 250 women (62.5%) (group 2). During follow-up, we noticed 32 events (3.50/100 person-years) in group 1 and 15 events (0.51/100 person-years) in group 2 ($p < 0.0001$). Moreover, 32 (21.3%) of 150 women experienced a nonfatal cardiovascular event in group 1 (persistent impaired FMD) (3.50 events/100 patient years) versus 15 (6.0%) of 250 women in group 2 (improved FMD) (0.51 events/100 patient-years) ($p < 0.0001$) (**Figure 3**). Our study demonstrated that in most hypertensive postmenopausal women, a significant improvement in FMD may be obtained after 6 months of optimized therapy in most, and it also clearly identifies patients with a more favorable prognosis. Conversely, a higher risk of nonfatal cardiovascular events can be predicted by a noninvasive variable: a lack of change in FMD.

> '…Hypertension, diabetes and atherosclerosis share common pathophysiology and etiopathogenesis, suggesting that they spring from a common soil, which is represented by endothelial dysfunction'.

This study has been included in two different meta-analyses both describing the strong association between coronary or peripheral ED and cardiovascular events [15,16], using different techniques (either invasive and noninvasive) in different populations, our study being the only one related to postmenopausal women. Finally, after the evidence showing that ED has a pivotal role in postmenopausal women, for both ethiopathogenesis and prognosis, we have demonstrated the importance of using endothelial active-drugs to treat ED-related disease, such as hypertension. In four groups of hypertensive postmenopausal women, we demonstrated that blood pressure could be reduced in monotherapy with four

Figure 3. Cumulative survival rates, free of hospital admission, for cardiovascular events in two study groups.



Cumulative survival rates, free of hospital admission, for cardiovascular events according to persistent impaired (group 1 = dashed line) or improved (group 2 = dotted line) endothelium-derived FMD.
FMD: Flow-mediated dilation.
Adapted from [14].

different classes of drug, but only with angiotensin-converting enzyme-(ACE) inhibitors was it possible to not only reduce blood pressure, but also improve endothelial function.

'…the most promising therapeutic objective in order to reduce the global cardiovascular risk in this specific population is to treat endothelial dysfunction.'

In conclusion, ED is common in postmenopausal women, but it may predict cardiovascular disease in only some of them and when particularly impaired. The strongest association is among ED, diabetes, hypertension and atherosclerosis. Currently, the most promising therapeutic objective in order to reduce the global cardiovascular risk in this specific population is to treat ED.

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