Editorial Commentary

Arterial erectile dysfunction is an early sign of vascular damage: the importance for the prevention of cardiovascular health

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The article by Nakahara and colleagues (1), entitled "*^{18}F-Fluoride Positron Emission Tomographic Imaging of Penile Arteries and Erectile Dysfunction*" focus on the role of fluorine-18 sodium fluoride (NaF) positron emission tomography (PET) of penile arteries in patients with erectile dysfunction (ED). In particular, NaF is known to localize in areas of active microcalcification in atherosclerosis plaques. In a cohort of 437 prostate cancer patients undergone to NaF-PET for detection of bone-metastasis, the authors found a higher NaF uptake in penile vessels of patients with ED compared to potent ones, suggesting that atherosclerosis is associated with ED in prostate cancer patients (1).

ED is a common male sexual dysfunction (2). Basing on the underlying causes, it can be classified as psychogenic or organic, with the latter being further divided into non-endocrine and endocrine. Among the non-endocrine causes, the vasculogenic mechanism is by far the most common one and can be divided into arterial inflow disorders and venous outflow disorders (defects in the veno-occlusive mechanism). Atherosclerosis, a sign of endothelial dysfunction, results in decreased perfusion/ischemia of penile arteries and is one of the main causes of arterial ED (3).

A large body of evidence address to endothelial dysfunction a role in the pathogenesis of ED (3). Currently, endothelial dysfunction is evaluated by different and complementary tools, such as flow-mediated dilation, penile nitric oxide release test, peripheral arterial tonometry or several serum markers (e.g., c-reactive protein, vascular cell adhesion molecule-1, endothelin 1 and others) (4). We have focused on the role of endothelial microparticles (EMPs) and endothelial progenitor cells (EPCs) in the pathogenesis of endothelial dysfunction in patients with ED for long (4-15).

EMP are membrane vesicles derived from the plasma membrane of endothelial cells, carrying cytokines, proteins and microRNA. They are thought to be early markers of endothelial damage, triggering the endothelial repair in an EPC-mediated way. In particular, CD144pos and CD146pos EMPs are the most specific markers of endothelial damage and have been suggested to enhance the EPC release (11). However, by the release of some kinds of microRNA, they might directly stimulate vascular repair by genetically reprogramming the endothelial cells. Accordingly, the microRNA-133a has been demonstrated to enhance the expression of insulin-like growth factor receptor 1 (IGF1R), whose deficiency accelerate atherosclerosis (16) in vascular smooth muscle cells (17).

EPCs are bone-marrow derived cells able to differentiate into mature endothelial cells, facilitating vascular repair in different ischemic tissues. EPC population consist of two different cell subtypes, the early and the late ones (18). Circulating late phenotype of EPCs (CD45neg/CD34pos/CD144pos) raises in case of classical cardiovascular risk factors, such as metabolic syndrome (8,13), hypogonadism (9,10), atherosclerosis (5) and decreases after pharmacological intervention with androgens (9),

PDE5 inhibitors (4,12) and physical activity (18). Their serum concentration reflects the quality of endothelial function (flow-mediated dilation) and also vascular penile parameters (dynamic penile Doppler) in patients with ED (19). Therefore, EPCs have been regarded as a potential diagnostic marker for the early detection of vascular dysfunction. In fact, their change in serum concentration precede the structural alterations resulting from vascular damage, such as carotid atherosclerosis (5,12). Decreased EPC mobilization from the bone marrow, decreased homing capacity of late EPC or lower ability to positively modulating the function of late EPCs have been all addressed as possible pathogenetic moments in the endothelial dysfunction (11). *In vitro* data show promising results on the treatment of diabetes mellitus-induced ED with genetically modified EPCs, since a marked increase of the erectile function was observed after treatment, consistent with a reduction of the degree of apoptosis and collagen/smooth muscle ratio and an increase of endothelial nitric oxide synthase (eNOS) expression in penile tissues of treated versus not-treated mice (20). Nevertheless, the possible therapeutic applications of EPCs humans deserve investigation (11).

Taken together, this evidence confirms the central role of endothelial dysfunction and atherosclerosis in the pathogenesis of arterial ED, as already recognized by the scientific community and further confirmed by Nakahara and colleagues (1).

The main pitfall on the study (1) is the suggestion of extending NaF-PET evaluation to noncancer patients with ED, whit no reference to ultrasonography assessment. On the diagnostic point of view, after proper initial framework, second-line evaluation requires penile Doppler ultrasonography when a vascular etiology is suspected. Commonly, ultrasound scan is performed statically (during penile flaccidity) and dynamically (following drug-stimulated erection), allowing dorsal and cavernosal penile arteries examination. A few minutes after drug injection, the cavernosal artery inflow becomes well detectable with increasing peak systolic velocity (PSV). The PSV cutoff is 35 cm/s. Lower values suggest an arterial sub-obstruction. Also, media-intima thickness can be measured by penile ultrasound, allowing the detection of atherosclerotic plaques (3). The importance of penile Doppler ultrasound is not restricted to the diagnosis of ED. By providing information on the peripheral vascular status, it is useful for the early detection of vascular damage. Subclinical atherosclerosis has been shown to precede arterial ED by a decade, with the latter in turn preceding cardiovascular events (e.g., myocardial infarction, stroke) by 2–5 years (21). On these premises, penile Doppler ultrasound can intercept cardiovascular disease in patients with arterial ED, thus allowing cardiovascular risk stratification and the establishment of secondary prevention measures (e.g., life style change, treatment of risk factors).

In conclusion, patients with arterial ED show endothelial dysfunction and dysfunctional mechanism of endothelial repair, which lead to endothelial damage, platelet aggregation and atherosclerosis (14). Penile Doppler ultrasound allows the detection of arterial ED, which is important for the prevention of cardiovascular event (3).

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None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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