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ERECTILE DYSFUNCTION AS A SENTINEL MARKER FOR CARDIOVASCULAR DISEASE

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INTRODUCTION

The incidence and severity of erectile dysfunction (ED) increase with age and factors of co-morbidity. ED is predominantly of vascular origin and shares common risk factors with cardiovascular disease. An association between ED and ischemic heart disease has been suggested due to the impairment of endothelium-dependent relaxation of the smooth muscle. There is accumulating evidence suggesting that ED could be a sentinel event for cardiovascular disease and not only for quality of life evaluation. Atherosclerotic lesions are variable in localisation with time. ED could represent a marker of sub-clinical vascular disease and a predictor of the progression of cardiovascular disease. It is important to adopt an appropriate approach to cardiac risk in patients with ED in order to decrease morbidity of cardiovascular disease.

EPIDEMIOLOGY

Erectile dysfunction (ED) is defined as the recurrent or persistent inability to achieve and/or maintain an erection appropriate for satisfactory intercourse[1].

In the general population ED affects an estimated 200 million men worldwide. The incidence and severity of ED increase with age and a man of 70 is three times more likely to have severe ED than a man of 40[2]. Its etiologies involve a range of different risk factors, among them many chronic diseases. ED is predominantly a vascular disease and shares common risk factors with cardiovascular diseases such as high blood pressure, diabetes mellitus, hyperlipidemia, smoking, excessive alcohol consumption and sedentary behaviour[3]. ED remains under-diagnosed and undertreated, and obviously medical problems commonly seen in the clinician's office are associated with ED.

ENDOTHELIUM DISEASE

Men suffering from ischemic heart disease have a high prevalence of ED. The main link between ED and cardiovascular disease is the vascular endothelium which plays a fundamental role in the regulation of the circulation. ED is likely to be caused by impairment of the endothelium-dependent relaxation of smooth muscle cells in the corpus cavernosum, which affects the cavernosal perfusion of the penis[4] (Fig.1)

The endothelin receptor binding sites mediate endothelin-induced vasorelaxation by stimulating nitric oxide (NO) formation. Decreased endothelin receptor sites in the corpus cavernosum could reduce NO production and could be one of the explanations for the development of ED. The same process contributes to the regulation of basal and stimulated coronary artery tone and may explain the apparent correlation between arterial dysfunction and ED[5]. All shared risk factors cause functional and structural abnormalities at the level of both vascular smooth muscle cells and endothelium (Fig. 2).

ED - "TIP OF THE ICEBERG"

Endothelial dysfunction has been shown to be a precursor of atherosclerotic lesions[6]. This could have implications for the patient's management; for example, it could imply a risk for heart disease. Prevention of arteriosclerosis should be a prime therapeutic target, especially in patients with age-related ED, as they often suffer from ischemic heart disease. Clinical manifestations of vascular diseases rarely appear simultaneously because arteries supplying various areas have different sizes. An obstruction causing significant obstruction of the blood flow in the penile artery would represent a minor abnormality if present in coronary or peripheral arteries due to their larger size.[7]

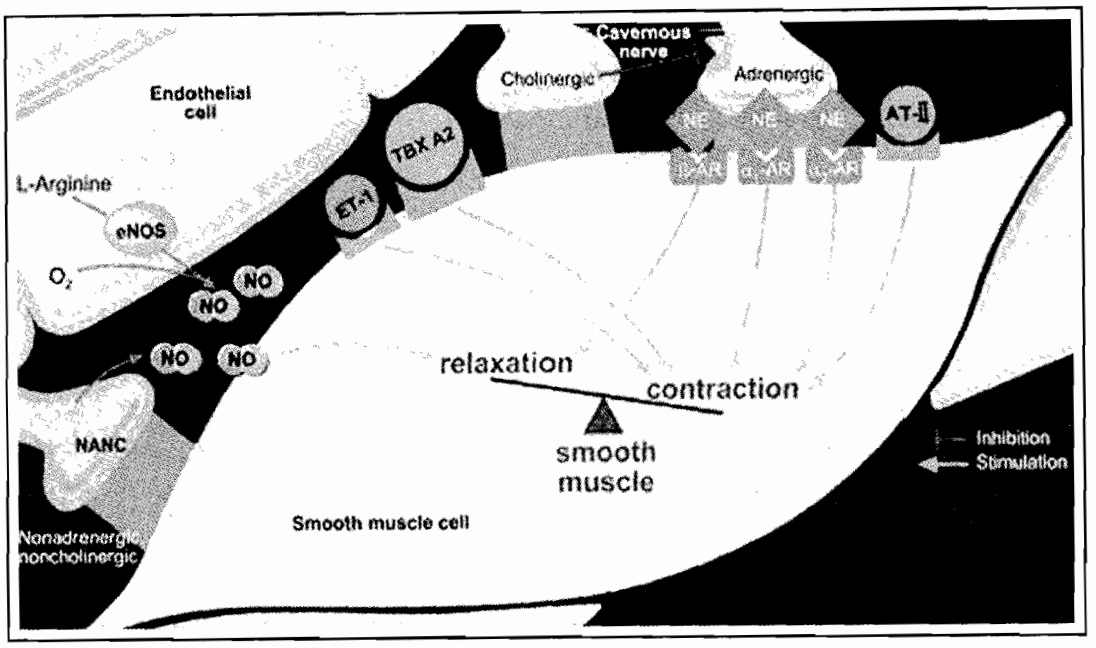

Fig. 1: Smooth muscle cell contraction/relaxation. From: Saenz de Tejada I et al. Anatomy, Physiology and Pathophysiology of ED.[8]

(Fig. 3). There is accumulating data supporting this explanation. An increased number of occluded coronary arteries is correlated to the severity of ED[9]. Montorsi showed that a significant proportion of patients with angiographically documented coronary artery disease have ED and that this latter condition may become evident prior to angina symptoms in almost 70% of cases[10].

Nevertheless, in 30-40% of patients acute myocardial infarction is the initial manifestation of coronary artery disease, and those patients do not necessarily have extensive arteriosclerosis when first diagnosed[11]. Progressive occlusive disease should be detected sooner in the micro vasculature than in larger vessels.

ED AS A SENTINEL ALARM FOR CARDIOVASCULAR DISEASE

There is accumulating evidence suggesting that ED could be a sentinel event for cardiovascular disease. This association should encourage the use of the presence and degree of ED as a screening test for such disorders, especially when they have not already been recognized. ED may provide a marker for the progression of the patient's cardiovascular disease by correlating the degree of ED with the severity of the cardiovascular disease[9]. Patients with ED often have hyperlipidemia and several teams have reported the relation between serum lipid and the risk of developing ED. The impact of high-density lipoprotein cholesterol (HDL-C) and the total cholesterol (TC) / HDL-C ratio is significantly related to the risk of ED[12]. Hyperlipidemia is often associated with impairment of the endothelium-dependent relaxation that once again could decrease the penile relaxation during the erectile process[13].

Nearly 70% of patients with high blood pressure have ED with much higher complication rates compared to ED patients without hypertension[14].

The Massachusetts Male Ageing Study (MMAS) showed that in each quartile of 10-year coronary heart disease risk, the rate of incident ED over a comparable period was 3 to 6 times greater, suggesting that ED is a sensitive (although not necessarily specific) indicator of wider arterial insufficiency[3]. An increased 10-year coronary heart disease risk was found in 56.6% of patients with ED compared to 32.6% of patients without ED (age-matched

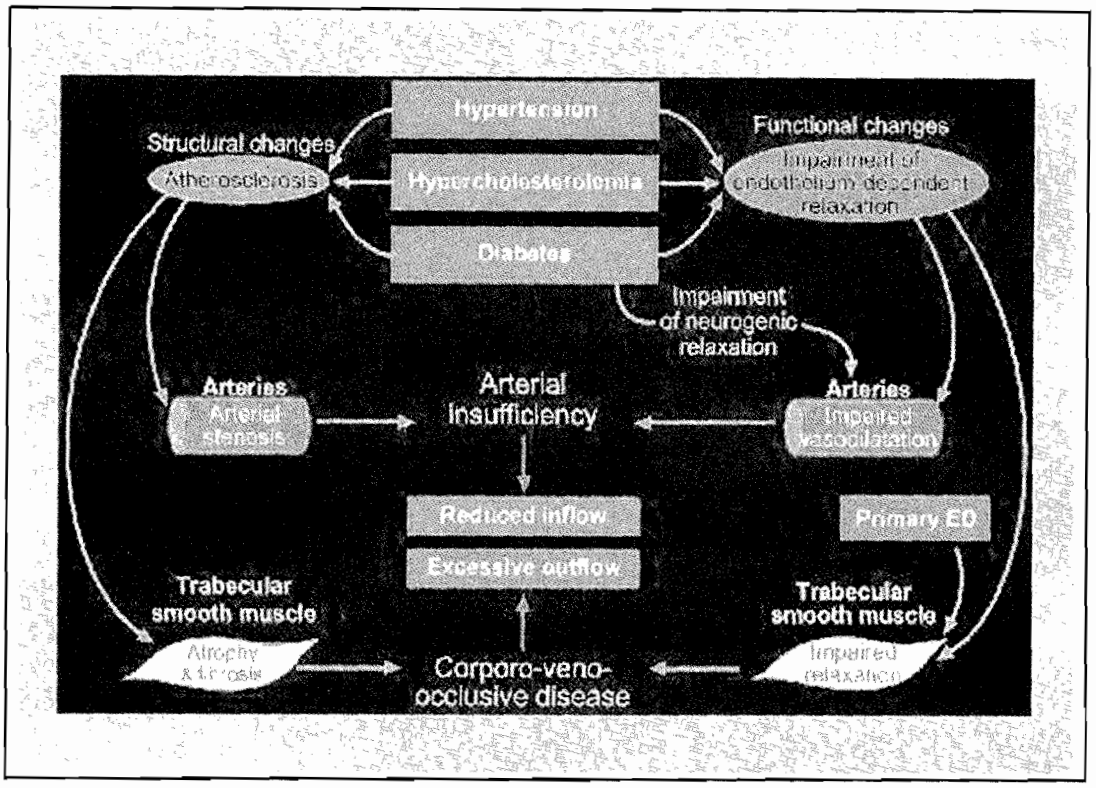

Fig. 2: Pathophysiology of vascular ED

40-70 years). Patients aged between 40 and 49 years as well as patients aged between 60 and 69 years were particularly at risk of increased coronary heart disease[12] (Fig. 4). The peak systolic velocity (PSV) in the cavernous arteries of patients with ED has been evaluated to help in selecting patients to undergo stress tests[15]. This remains debatable since the PSV has a good sensitivity (92.9%) but a low specificity (59.1%). Sairam found about 10% of undiagnosed diabetes in patients consulting for ED[16]. Erectile dysfunction could also represent an indicator of peripheral vascular disease with an increased age-dependence of 75%[17].

ED AND PREVENTION

ED often appears as a symptom of cardiovascular disease. The link between ED and cardiovascular disease is increasingly becoming clearer. Practitioners should be aware of this link during consultation. ED should be considered a significant medical condition and acquire the label of a true social disease that warrants the attention of practitioners in daily clinical practice[18].

It is of interest to take into account the whole patient management in men presenting with ED. An appropriate clinical and biological evaluation for cardiovascular risk factors should be considered[19]. Dietary reduction of serum lipids and physical activity are probably the first line treatment. An early adoption of a healthy life style may be the best approach to reduce the burden of erectile dysfunction on the health and well-being of men.

Oral treatment, for instance with PDE5 inhibitors (with nitric oxide modulating properties which may offer benefits to the patients because of their effects on the vascular endothelium[20]), is currently available for the vast majority of patients. These PDE5 inhibitors have good reliability and tolerability and restore more spontaneity. Offering such treatment may encourage men with erectile problems to consult and help practitioners to identify patients with ED with an opportunity for the diagnosis of other serious conditions, especially cardiovascular disease. This would allow an earlier intervention and improve treatment outcomes, thus reducing morbidity and mortality of cardiovascular disease.

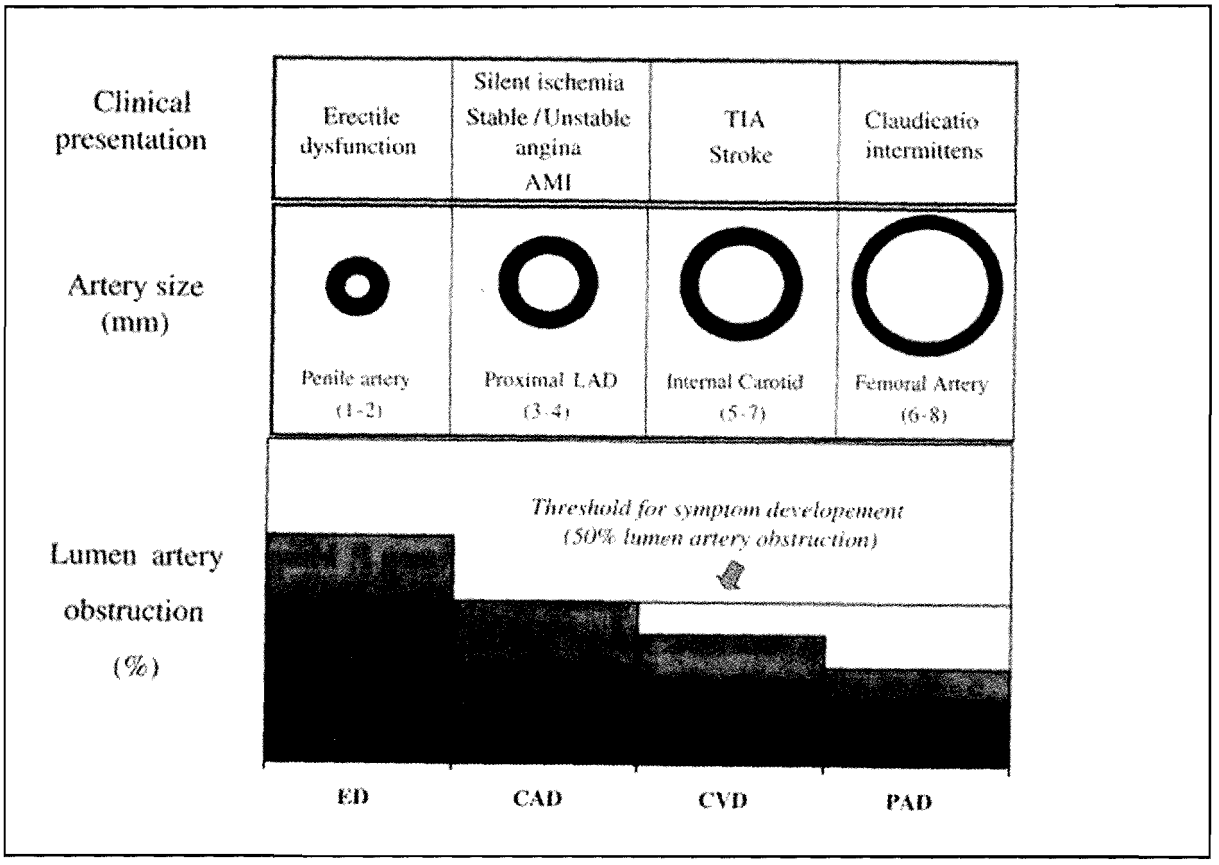

Fig. 3: Schematic drawing of atherosclerotic involvement of different vascular areas. The black part of the figure represents plaque burden in a patient with isolated ED. The red part represents a later step of the atherosclerotic disease with a greater plaque burden in a patient with clinically diagnosed coronary artery disease.
CAD = coronary artery disease; AMI = acute myocardial infarction; CVD = cerebrovascular disease; PAD = peripheral arterial disease; TIA = transient ischemic attack

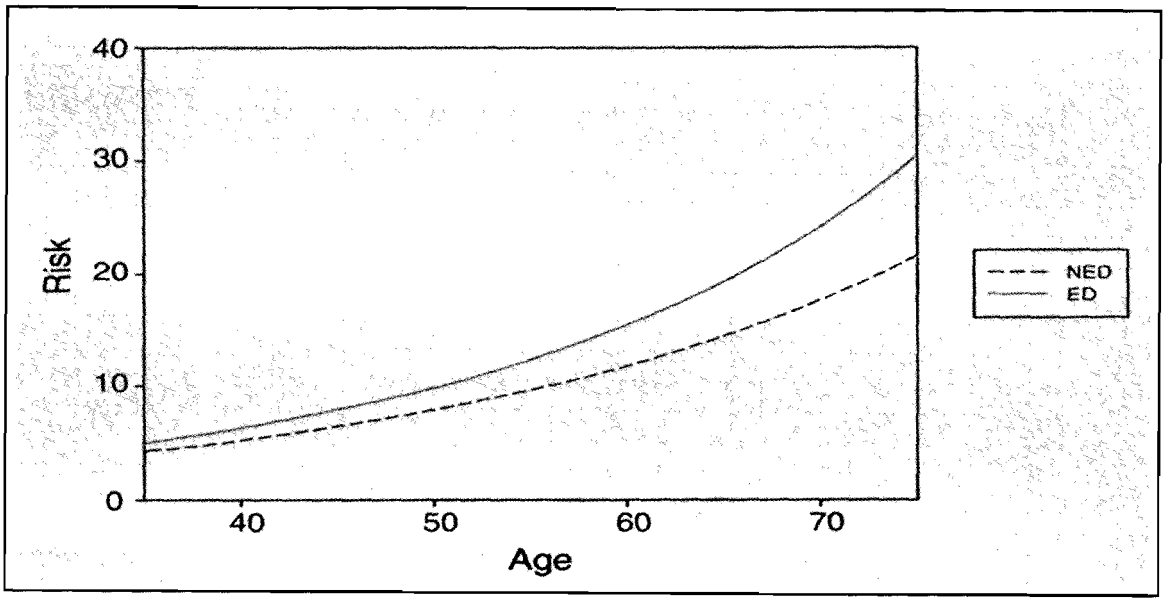

Fig. 4: Increased incidence of 10-year coronary heart disease in different age groups with and without ED

CONCLUSIONS

Patients with ED have a higher risk to develop cardiovascular diseases. ED is often of vascular origin and should be considered a sentinel symptom of cardiovascular pathology. For the patient it is of importance to evaluate and adopt a healthy life style.

As endothelial dysfunction is the feature of both ED and cardiovascular disease, inhibition of PDE5 as first-line therapy of ED may enhance endothelial function by amplifying the response of vascular smooth muscles to NO. This PDE5 inhibition may have a therapeutic potential for the management of cardiovascular disease as well as for ED which provides a window of opportuny for the diagnosis of cardiac disease.

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