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Mini Review

"Endothelial Protector Drugs" and Diabetes: Is there a Role for these Drugs?

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Review

Diabetic vasculopathy, including macro and micro vascular disorders, is the leading cause of morbidity and mortality in patients with type 1 (T1) and type 2 (T2) diabetes mellitus (DM) [1].

A lot of researches pointed out that endothelial dysfunction, characterized by an imbalance between Endothelium-Derived Relaxing Factors (EDRFs) and endothelium-derived contracting factors (EDCFs) play a central role on the development and progression of diabetic vasculopathy [2-5].

Endothelial dysfunction and inflammation, as indicated by abnormal flow-dependent vasodilatation and by increased circulating levels of adhesion molecules (ICAM-1 and E-selectin) are known to occur in T2DM and seems to be an important predictor in systemic atherogenesis [6].

Both hyperglycemia and insulin administration increasing circulating levels of endothelin-1 (ET-1), an endothelial cell (EC)-derived potent vasoconstrictor peptide with mitogenic, pro-oxidative and pro-inflammatory properties that have shown to be extremely relevant to the pathophysiology of diabetic vasculopathy [7-10].

Circulating and local levels of ET-1 are increased in diabetic animal models and diabetic patients [1,11,12].

Considering the global epidemic of diabetes, it seems to be critical to update our understanding of the pathogenesis of diabetes and related vascular complications in order to "clearly understand" if an "endothelial protector drug", able to modulate endothelial adhesion molecules and ET-1 could represent a novel treatment options for prevention and delaying the progression of diabetic complications [6].

The mechanism regulating endothelial cells and vascular smooth muscle cells function to become an important therapeutic targets in diabetic vascular complications and especially, the modulation of the vasoconstrictor, mitogenic, pro-oxidative and pro-inflammatory properties of ET-1 is undoubtedly important in diabetic complications.

As everybody knows the small vessels (microcirculation comprises arterioles, capillaries, venules and lymphatics, all <100 mm in diameter) are crucial for maintaining tissue metabolism and structural and functional changes in the microcirculation are present in diabetes mellitus irrespective of the organ studied (retina, kidney, CNS and skin) [6]. The pathophysiology of diabetic microangiopathy is complex because it involves not only metabolic but also genetic factors [6]. For example has been shown that subjects with diabetes heredity have impaired microvascular responses to both endothelium and nonendothelium-dependent stimuli in the skin microcirculation in spite of normal body dimension, normal glucose tolerance and normal insulin sensitivity [13-15]. Early on in the course of the disease, microvascular perfusion occurs in the limbs, but most of the blood flow under normal thermal conditions passes through arteriovenous shunts, bypassing the nutritive capillary bed and leading the "so-called capillary ischemia" [16,17].

Endothelial dysfunction, characterized by an imbalance between endothelium-derived vasodilatator and vasoconstrictor substances, plays an important role in the pathogenesis of vascular complications in diabetes, including microangiopathy. Almost two different steps seem to be involved in the microcirculation

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imbalance: "leukocyte recruitment cascade" and "Endothelin-1 overexpression" [16,18,19].

The recruitment of leukocytes from circulating blood into tissues is crucial for the inflammatory response: during this process a number of well-studied adhesion molecules on the endothelium sequentially interact with their ligands expressed on the cell surface of leukocytes. The interaction between adhesion molecules and ligands occurs in a cascade-like fashion, driving leukocytes from the circulation to the extravascular space, that is, through the steps of leukocyte rolling, firm adhesion and transmigration (Figure 1) [20].

The selectin family of adhesion molecules mediates the capture and rolling steps of leukocytes along the endothelial cells. The selectin consists of three members of C-type lectins (P, E and L-selectin).

After the selectins have initiated leukocyte rolling along the surface of endothelium, a different set of adhesion molecules comes into play to reduce the leukocyte rolling velocity and allow to leukocyte to firmly adhere to the endothelial surface. This firm adhesion step is largely mediated by molecules of immunoglobulin superfamily such as intercellular adhesion molecule (ICAM – 1) and vascular cell adhesion molecule (VCAM-1) expressed by endothelial cells and by those expressed constitutively by leukocyte or by many other types of cells. Upon achievement of stable adhesion to the endothelial surface, the leukocyte extravasate between endothelial cells along the intercellular junctions. PECAM-1 (Platelet Endothelial Cell Adhesion Molecule) and VAP (Vascular Adhesion Protein) mediated leukocytes transmigration [20]. Various lines of evidence indicate that the shedding of selectins is enhanced on the endothelium during the progression of diabetes and that the soluble form of selectin proteins has the potential to be a clinically useful biomarker of the severity of Diabetic Rethinopathy: E-Selectin, in particular, may also serve as a proangiogenic factor [20].

Once that the leukocytes have transmigrated from endothelial junctions a hyperproduction of ET-1 (Endothelin 1) have been released by the endotheliam. ET-1 is one of the most potent vasoconstrictor described and has been suggested to be involved in the development of cardiovascular disease. It possess pro-inflammatory and profibrotic effects [6]. Enhanced of endogenous ET-1 has been demonstrated in hypertension, coronary artery disease and heart failure [6].

In diabetic microangiopathy one important feature of endothelial dysfunction is an increased in production and

biological activity of the vasoactive and proinflammatory peptide ET-1. Elevated levels of ET-1 are found in patients with type 2 diabete. Furthermore ET-1 may contribute to the development of endothelial dysfunction, and consequently insulin resistance, by increasing the production of Reactive Oxigen species, mainly superoxide anion, in the vasculature [6].

Taking into account the role of endothelial adhesion molecules (specifically E-Selectin) and ET-1 in the pathogenesis of diabetic microangiopathy and that mostly of the diabetic complications such as retinopathy, nephropathy and neuropathy have their basis in disturbed microvascular function, we hypotized that added to standard therapy an endothelial protector drug, able to counteract hyperespression of endothelial adhesion molecules and ET-1 could be a new promising idea to postpone diabetic microvascular complication.

Recent published and not published studies shown that an "endothelial protecting drug", such as aminaphtone (2-hydroxy-3-methyl-1,4-napthohydroquinone-2-p-aminobenzoate), a synthetic molecules derived from four aminobenzoic acid which is currently employed for "capillary disorders" could be useful in reverse microalbuminuria and in control nailfold periungueal videocapillaroscopy and retinal impairment (OCT and fluoroangiography) in diabetic patients [21,22].

Considering that recently aminapthone shown a very interesting direct pharmacodinamic profile on endothelial cells (improvement of E-selectin and ET-1 hyperespression) and that other drugs like avosentan (a new potent, non peptidergic and selective Et-a receptor antagonist) demonstrated to decrease proteinuria after 3 – 6 months of treatment, it seems encouraging to study if this new "endothelial therapeutic approach" could be useful for diabetic patients when added to standard therapy [23-29].

Since the typical approach with anti- ET-a selective antagonist avosertan, atrasentan and sitaxsertan seems to be encouraging in term of efficacy (proteinuria control in diabetic patients) but not in term of safety (increased of morbidity and mortality associated with anti-ET-a selective antagonists induced fluid retention) an old and safe endothelial protector approach with aminapthone could represents a "new/old" way to postpone diabetic microangiopathy complications [27-29].

Figure 1: Leucocyte recruitment to the vessel wall.

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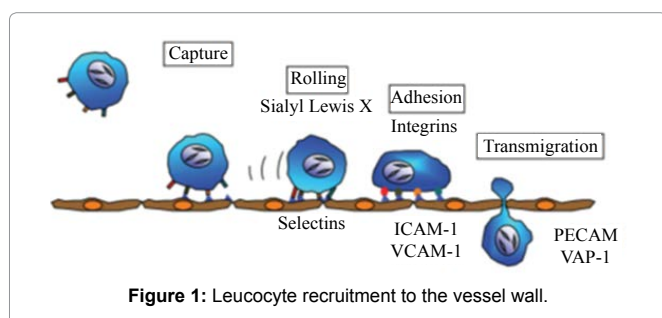
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