Editorial

The Measurement of the Endothelial Glycocalyx as a New Biomarker of Endothelial Derangement in Systemic Sclerosis: A Challenge for the Future

In systemic sclerosis (SSc), the involvement of the vascular system dictates the fate of the patient[1,2]. In recent decades, significant attention has been devoted to understanding the mechanisms involved in the derangement of the endothelium of the microvascular system in SSc. In this perspective, many papers have investigated the consistency of endothelial markers to disclose the ongoing endothelial derangement during the progression of the disease. To date, no endothelial marker has been shown to be useful in a real-world setting, and the search for new methodologies to shed light on this important clinical need is still ongoing.

The endothelial layer is the interface between the bloodstream and the vessel wall. It is well known that any modification of the endothelial function is of pivotal importance in SSc pathogenesis[3,4]. In fact, endothelial cells (EC) react to any humoral, neural, hemodynamic, and oxidative stress. Moreover, the endothelium affects platelet function, vessel wall inflammation, proliferation and migration of smooth muscle cells, and vascular tone control[5]. Therefore, endothelial derangement is of paramount importance in SSc pathogenesis.

In this issue of *The Journal*, Machin, *et al* provide interesting data disclosing that microvascular structural and functional abnormalities in SSc could be due to a dysfunctional endothelial glycocalyx (EG)[6]. They have evaluated sublingual microvessels with an automated capture and analysis system, showing that microvascular functional abnormalities precede structural modifications. In SSc, this method may provide a new target to assess even the earliest microvascular changes[6], which might result in a tool better than nailfold videocapillaroscopy, which can examine only morphological abnormalities[7]. The use of the capture and analysis technique has previously shown that the capillary density and the percentage of perfused vessels were significantly reduced together with the EG thickness in patients with SSc compared to healthy controls[8]. This observation triggered the interest for the EG as a key to visualize an unknown endothelial "world" that could not be clinically investigated to date.

It is notable that in SSc the first "fight" in the disease pathogenesis evolution takes place very early, specifically on EC. The immune system participates in this process and contributes eventually to the derangement of the endothelium[5], which is present before the detection of fibrosis, being usually clinically evident with a microvascular dysfunction such as Raynaud phenomenon (RP). RP precedes other disease manifestations and has been identified as one of the red flags that raises suspicion of very early SSc[9]. It has also been suggested that reactive oxygen species, generated during ischemia/reperfusion, may be the trigger of EC activation, dysfunction, and injury, thus also involving the capillaries downstream[10].

The EG is a layer covering the surface of the EC and is made by a mesh of endothelial membrane–bound molecules, including proteoglycans and glycoproteins, that are the basis for plasma–EC interaction. Therefore, the EG plays a crucial role in the protection of EC, acts as a mediator of shear stress, and helps the associated production of nitric oxide as well as the housing of vascular protective enzymes and a wide range of anticoagulant factors. Moreover, the EG modulates the inflammatory response controlling leukocyte adhesion and the binding of inflammatory mediators, such as chemokines, cytokines, and growth factors[11]. These activities may explain the pivotal position of the EG in the maintenance of the endothelial integrity. In fact, it serves also as a passive barrier to the efflux of proteins and fluid from the capillary lumen, preventing capillary fluid leakage and edema formation. Further, EG is a dynamic structure

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functionally linked to the cell membrane and cytoskeleton[12]. The damage of the EG has been shown after ischemia/reperfusion injury[13] due to EG-bound proteins such as xanthine oxidoreductase and superoxide dismutase.

The modification of EG dimensions and function has been reported in sepsis, diabetes, obesity, cardiovascular disease, endstage renal disease, and hypercholesterolemia[13,14,15,16]. Few data are reported regarding SSc where the failure of the EG might significantly impair the endothelial barrier function, the capacity to inhibit coagulation and leukocyte adhesion, and also the shear stress–induced nitric oxide release, with a significant deterioration of the vascular tone control[12,17]. Therefore, the innovative value of the method used by Machin, *et al*[6] essentially consists of overcoming the limits of intravital videomicroscopy previously used by Miranda, *et al,* which is largely dependent on manual analysis[8]; the Machin method provides improved insight into EG loss. This may allow assessment of markers of perfusion and then of function [number and longitudinal fraction of microvessel segments filled with red blood cells (RBC)], measuring the modification of the EG barrier on the endothelial surface[6] in an early disease stage[18]. In SSc, the sublingual microvessel segments exhibited a lower total and perfused microvascular density, a lower RBC fraction (indicating an impairment in microvascular tissue perfusion), a higher perfused boundary region (PBR; suggestive of a dysfunctional EG), a reduced EG thickness, and an inverse relationship of PBR to EG thickness[6]. It is interesting to note that EG abnormalities involving reduced penetrability require conformational changes in RBC to pass through small microvessels, and are accompanied by impaired endothelium-dependent dilation. Indeed, the analysis of microvessel segments by lumen diameter revealed that perfused microvascular density and RBC fraction were lower in small, medium, and large diameter microvessel segments[6].

These results suggest a significant relationship between different factors such as microvascular density and perfusion and the EG barrier function. Because the EG is an important determinant in vascular homeostasis and permeability, these elements may be clinically relevant in the early phase of SSc when finger edema and capillary leakage are prominent[19].

It is exciting to measure such a tiny detail on the endothelial surface and make of it a precious biomarker disclosing the disease activity. For this reason, the proposal of a new technique to investigate the thickness of EG as a relevant clinical measure is a fascinating clinical challenge for the future. In fact, the measurement of the EG merits further investigation to evaluate its "weight" as an instrument to disclose the activity of the disease at the endothelial level[20], thus potentially contributing to the treatment used to block SSc evolution, in particular in early and very early disease.

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