Vascular Ehlers–Danlos syndrome (vEDS) is an autosomal dominant disease that affects the arteries, bowels, uterus, and skin. Affected individuals can have spontaneous rupture of hollow organs, such as the bowels or gravid uterus, along with arterial dissections and ruptures that lead to premature death. The arterial disease seen in individuals with vEDS is diffuse, involving small to medium arteries and the aorta. The median lifespan of patients with vEDS is only 48 years with the majority of deaths attributed to vascular complications. Surgical treatment of vascular disease in patients with vEDS have been limited because of friable and fragile tissues. However, a human treatment trial using celiprolol, a cardioselective β-adrenergic blocking agent with β2 agonist properties, was shown to reduce the number of vascular events in patients with vEDS. Although there were limitations to the treatment trial, this study provided the first possible medical therapy for vEDS. While much of the morbidity and mortality of this condition is still due to spontaneous rupture of nondilated arteries, progressively enlarging arterial aneurysms have been reported, suggesting that there is a greater role for noninvasive imaging, elective surgery, and medical therapy than previously thought.

Type III collagen is composed of 3 α1(III) polypeptide chains coiled into a triple helix structure. Each polypeptide chain in the triple helix portion of the protein contains a domain of approximately 330 Gly-X-Y repeats. Disruption of this triple helical structure leads to abnormal protein folding, thereby resulting in pathogenicity. Missense mutations altering the glycine codons in the triple helical domain account for the majority of disease-causing mutations and lead to misfolding of type III collagen in the endoplasmic reticulum and retention of seven eighths of misfolded procollagen trimers in the cell. This type of mutation produces a dominant negative effect on the protein, thereby inhibiting extracellular accumulation of mature type III collagen. Unlike the dominant negative effect of missense mutations on type III collagen, nonsense and frameshift mutations in COL3A1 lead to premature termination of translation and nonsense-mediated decay, causing half the normal amount of type III collagen to be secreted, which typically produces a milder clinical phenotype.

Clinical manifestations observed in individuals with vEDS have historically been attributed to tissue fragility based on the fact that there are decreased amounts of type III collagen secreted by these cells. Questions were raised as to whether this tissue fragility was responsible for vascular manifestations observed in patients with vEDS after data emerged from a type III collagen−deficient mouse (Col3a−/−). When compared with their wild-type littermates, these mice developed spontaneous skin lesions and organ rupture, which limited their lifespan to 20% of their wild-type counterparts. Interestingly, the heterozygous Col3a1−/− mice did not demonstrate a predisposition to arterial or organ rupture and had a normal lifespan. Additionally, biomechanical manipulation of Col3a1−/− aortas showed that they could equally withstand rupture similar to wild-type tissues under extreme and supraphysiologic pressures (>800 mg Hg). Altogether, this suggests that the frank concept of tissue fragility caused by decreased levels of type III collagen may not fully explain the severe clinical manifestations observed in vEDS.

In this issue of *Circulation: Cardiovascular Genetics*, Morissette et al provide further support that vascular disease in patients with vEDS is not merely due to tissue fragility. They sought to quantify circulating biomarkers involved in vascular inflammation (transforming growth factor [TGF] β1, TGF-β2, monocyte chemoattractant protein-1 [MCP-1], C-reactive protein [CRP], intercellular adhesion molecule-1 [ICAM-1], and vascular cell adhesion protein-1 [VCAM-1], along with increased platelet turnover, in patients with vEDS. Study participants (n=41) were all confirmed to have disease-causing COL3A1 mutations; the control group (n=74) was age-, sex-, and body mass index–matched to vEDS participants. The majority of cases were the first family member diagnosed (n=28); 13 participants were family members of index cases. The markers of vascular inflammation were significantly elevated in patients with vEDS compared with matched controls. In addition, TGF-β1 and TGF-β2 levels were also increased. Platelets store TGF-β1, and therefore the increased turnover of platelets could be responsible for increased circulating levels of this growth factor. Interestingly, circulating interleukin-8 levels, a cytokine typically classified as proinflammatory, were decreased in patients with vEDS when compared with controls. Thus, many of the established biomarkers of vascular inflammation, including markers of endothelial dysfunction, such as VCAM-1, ICAM-1, and monocyte chemoattractant protein-1, and an acute phase reactant, CRP, are increased in patients with...
vEDS. The first and a critical question that these data evoke is whether these markers will have clinical utility. Specifically, will they aid in predicting life-threatening vascular complications in vEDS? CRP has proven to be a robust marker for predicting coronary artery disease, in part because it has a large dynamic range and long half-life. Although CRP is a marker for risk for atherosclerosis, the role of this protein in progression of the disease is not as clearly delineated. Interestingly, although VCAM-1 clearly plays a pathological role in atherosclerosis, plasma VCAM levels are not as predictive of coronary events as CRP.18

Therefore, can one or more of these inflammatory markers play a role in predicting vascular events in patients with vEDS? Although friable tissues hinder surgical repair, recent studies indicate that surgical repair of vEDS in an elective setting improves surgical outcomes.7 Therefore, a clinically useful biomarker would aid in the timing of elective repair of aneurysms and stable dissections. However, spontaneous dissection or rupture of a nondilated artery also occurs in patients with vEDS, and these vascular complications are difficult to prevent. Additionally, such biomarkers can be useful in treatment trials. Therefore, it would be advantageous to investigate if levels of inflammatory markers decreased in patients with vEDS treated with celiprolol.

These data also raise the question as to why these inflammatory markers are increased in patients with vEDS. Vascular inflammatory markers are increased in many conditions that predispose to vascular events. With atherosclerosis, circulating levels of inflammatory markers increase because of ongoing atherosclerotic pathology in the arterial wall.19,20 Levels of CRP, VCAM-1, and ICAM-1 are elevated in obstructive sleep apnea through a different mechanism. Hypoxia associated with sleep apnea leads to vascular oxidative stress, inflammation, endothelial dysfunction, thereby decreasing nitric oxide production and increasing platelet activation.21 VCAM-1, ICAM-1, and CRP are also elevated in patients with sickle cell disease at baseline.22

Microvascular occlusion and chronic inflammation are the hallmark of vaso-occlusive crises in these patients. Although the details of underlying pathophysiology remain unclear, it is thought to be the result of a complex and dynamic interplay between sickled red blood cells, endothelial cells, leukocytes, platelets, and various plasma proteins. Interestingly, evidence suggests that in patients with sickle cell disease, circulating platelets are chronically activated in the noncrisis steady state.23

Why would decreased production of type III collagen lead to increased markers of vascular inflammation and platelet turnover? Cutaneous manifestations of vEDS suggest that there is an aberrant wound healing response with loss of type III collagen. Thin, translucent skin with dehiscence of surgical wounds, fistulas, and wide atrophic or papyraceous scars raise the possibility that an aberrant response to tissue injury that may also occur when the arterial wall is injured. Tissue injury initiates the wound healing process, a well-described phenomenon involving 3 overlapping phases: acute hemostasis and early inflammation, subacute proliferative myofibroblasts and formation of highly vascularized granulation tissue, and prolonged remodeling and contraction of matrix scar.24,25

Injury of an artery may lead to increased levels of inflammatory markers if healing of the artery involves the same process. It is also interesting to note that recent investigations have drawn parallels between traditional cutaneous wound healing and resolution of intravascular thrombi. Similar to a wound, clot resolution involves: polymerized fibrin at the injury site, forming a nidus for recruitment of inflammatory cells; a wave of migrating fibromuscular cells entering the clot to synthesize, remodel, and contract provisional matrix into collagenous scar tissue; vascularization of the clot, and then the resolution into intimal lesions of smooth muscle cells.26–28

Because type III collagen is required for a proper wound healing response, it may play a similar role in thrombus resolution. Thus, decreased type III collagen could delay thrombus resolution, thereby leading to elevated markers of vascular inflammation and increased platelet turnover. In contrast to sickle cell disease and sleep apnea, vascular complications in patients with vEDS involve large to small vessels but not the microvascular bed. Therefore, it would be surprising if microvascularity is involved in this disease.

As is the rule in research, the current study showing increased markers of vascular inflammation and platelet turnover in vEDS raises further questions. Can these markers play a role in predicting arterial complications in patients with vEDS? Although the initial study provided some encouraging preliminary data suggesting that the markers could potentially correlate with severity of disease, further prospective studies are needed. Additionally, exploring why these markers are increased at baseline in patients with vEDS may provide novel insight into the molecular pathology driving the vascular disease, another step to improving medical treatment to prevent vascular disease and premature death in these patients.

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References
Milewicz et al Inflammatory Markers in vEDS


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