Blood Hyperviscosity / Plasmapheresis

In 1979, a research paper authored by Kahaleh, Sherer, and LeRoy titled *Endothelial Injury in Scleroderma* included the following passage:

> Many theories exist regarding the etiology and pathogenesis of scleroderma: endocrine dysfunction, nervous disorder, infection, physical trauma of various types, and immune factors. Many, if not all, of the manifestations of scleroderma can be explained on the basis of functional and structural vascular compromise after repeated vascular insults, subsequent healing of vascular walls with proliferative vascular response, and luminal narrowing. The coagulation cascade may be triggered by the intimal lesion, leading to fibrin deposition, reduced blood flow, and local ischemia.

This disease model for Scleroderma is consistent with findings that show abnormally elevated blood viscosity (increased blood “thickness”) strongly associated with Scleroderma, as will be explained below. More importantly, it leads to an alternative approach to Scleroderma treatment that is not widely known and may be an option for some Scleroderma patients. It also suggests specific research directions that may provide a way to control the development and progression of Scleroderma related symptoms without the potential harmful side effects that often accompany the drugs that are now used to delay the progression of Scleroderma symptoms.

**Background**

A series of research studies beginning with a paper in 1977 (McGrath, et. al.) have consistently showed abnormally elevated blood viscosity (hyperviscosity) in the majority of systemic Scleroderma patients. This finding has been replicated in a number of studies with one of the more recent findings documented in 2006 (Volkov, et al.). The specific type of blood hyperviscosity documented in these research articles (when reported) is red blood cell hyperaggregation (red blood cells clump together). These studies have used a number of different ways to measure the type of and degree of blood hyperviscosity, both in vivo (actually monitoring the red blood cells circulating in the patients’ bodies) and in vitro (blood samples withdrawn from the patient and measured separately).

Why is this significant? The average size of a micro-capillary is about 8 microns in diameter, with an estimated range of 5 to 10 microns in diameter. A normal blood cell is 6 to 8 microns in diameter. This means that some red blood cells have to fold in order to fit through the smallest capillaries. As red blood cells start to clump together, it becomes increasingly difficult for the “clump” of red blood cells to make it through the smallest micro-capillaries. Normal blood pressure is very strong, and at least for a while, the pressure will be strong enough to force the clump through the micro-capillaries. However, at some point, this will start to cause damage to the single layer of endothelial cells that line the micro-capillaries. The research literature on the effects of hyperviscosity on micro-capillaries documents most of the early symptoms seen in SD, including tortuous capillaries that are seen in nail beds and glomerular damage (kidneys) caused by hemodynamic mechanisms.
Although entirely speculative, since there is no research that has yet addressed this issue, a reasonable and testable hypothesis would be that with limited Scleroderma, either the degree of RBC hyperaggregation or the “stickiness” of the aggregated cells may be lower than in the more rapidly progressing forms of the disease. Even if the degree of clumping is low, and the overall hyperviscosity of the blood is only slightly elevated, over a long period of time damage to the endothelial lining could still occur resulting in the development and progression of Scleroderma symptoms.

**Treatment Implications**

In the late 1980s and early 1990s a series of research studies was done in the Netherlands that looked first at the difference in blood hyperviscosity between patients with primary Raynaud’s (not related to an underlying autoimmune condition) and secondary Raynaud’s specific to Scleroderma. This research showed that red blood cells were highly aggregated in secondary Raynaud’s patients but not in primary Raynaud’s patients, suggesting that different mechanisms were potentially involved in the two different forms of Raynaud’s.

The researchers then tried using plasmapheresis on both the primary and secondary Raynaud’s patients. Plasmapheresis is considered the “gold standard” in treating blood hyperviscosity disorders. Basically, plasmapheresis mechanically replaces most of the plasma while preserving the red and white blood cells. Specifically, the procedure involves removing blood from one arm, running it through a machine that centrifuges out and keeps the red and white blood cells, discards the plasma (the liquid part of the blood), and replaces it with either new plasma or, more commonly, sterilized albumin. The combined albumin and the original red and white cells are remixed and returned to the other arm. Typically this takes about 1½ hours and is done in an outpatient hospital environment. The effect of a single plasmapheresis treatment is to remove 80 to 85% of blood components except for the red and white blood cells. This includes beneficial things like clotting factors but also potentially harmful things such as antibodies.

The treatment protocol in these early studies mostly involved doing four plasmapheresis treatments – one per week for four weeks – and then studying the results of this intervention. What they found was that it had little effect on primary Raynauds (non-Scleroderma) patients, but typically eliminated all of the Raynaud’s symptoms in Scleroderma patients for a number of months. The studies also indicated significant improvement in other Scleroderma related symptoms, including healing of digital ulcers. Patients were monitored for up to three years following this single course of treatments. After a varying number of months, red blood cell aggregation returned to pre-treatment levels and Raynaud’s symptoms redeveloped, but none of the patients developed skin ulcers during the follow up period.

Since all of these studies were open label without control groups, any overall conclusion about the potential for treating Scleroderma symptoms using plasmapheresis needs to be tempered by the need to do well controlled research. However, these preliminary findings are completely consistent with the Scleroderma disease model that suggests that Scleroderma symptoms develop as a direct result of
repeated endothelial cell damage to the walls of the micro-capillaries from clumped red blood cells.

In a private communication between the author of this Scleroderma FAQ and one of the lead researchers on this series of studies, it was learned that a number of Scleroderma patients in the Netherlands were treated with long-term regular plasmapheresis treatments based on the results of these research studies. The researcher, who was also a clinician, indicated that a treatment protocol of one treatment per week for four weeks followed by a resting period of two months before repeating the treatment cycle (16 treatments per year) yielded significant improvement of existing clinical symptoms and no additional symptom progression when used with limited Scleroderma patients. There were no side effects experienced other than localized to the immediate treatment period. However, they found that this treatment protocol was not aggressive enough to completely stop symptom progression in rapidly progressing diffuse Scleroderma patients. By switching to a weekly plasmapheresis treatment schedule with these patients, they were able to stop symptom progression entirely. However, after an average of about 1½ years of weekly treatments, these patients began to develop major complications from the plasmapheresis treatments themselves, including infections and other complications resulting from the immunosuppressive effects of constant weekly plasmapheresis treatments. Notably, the less-frequent treatment protocol used for the limited Scleroderma patients showed none of these side effects.

There are only a few studies that have looked at the effects of plasmapheresis on systemic Scleroderma patients. In several of these studies the treatment protocol was a combination of a limited number of plasmapheresis treatments plus a standard drug, d-penicillamine versus d-penicillamine alone. In all cases, the group that added plasmapheresis to the treatment regimen showed significantly better outcomes than the drug group alone. Again, any interpretation of these results needs to be tempered by the limited design of the studies. It is also worth noting that in a couple of studies where plasmapheresis was tried with patients who had severe symptoms, there was no improvement in symptoms.

The logic behind using plasmapheresis to treat Scleroderma is straightforward: assuming that the “cause” of Scleroderma symptom development is damage to the endothelial cells lining the micro-capillaries caused by trauma from clumped red blood cells being forced through the blood vessels by blood pressure, then eliminating the clumping of the red blood cells through plasmapheresis (or potentially any other method) should prevent symptom progression and potentially allow existing symptoms to be improved as well, assuming that pre-treatment organ damage is reversible. For example, since skin cells and cells in the intestinal track divide frequently (this accounts for the hair loss and nausea in typical cancer treatments), it is possible that skin and GI symptoms would improve more quickly if red blood cell clumping is interrupted than would be the case for internal organs which regenerate more slowly. Assuming the hyperviscosity/plasmapheresis treatment model is valid, plasmapheresis treatments ideally need to be started early before there is major, non-reversible organ damage and these treatments need to be continued on a permanent basis since the research clearly shows that once
treatments are stopped, the red blood cell hyperviscosity will return over time. While cost is a consideration (a plasmapheresis treatment is roughly the same cost as a dialysis treatment), since Medicare covers plasmapheresis treatments for Scleroderma, many private insurance plans should cover the cost as well.

**Research Implications**

One of the major unanswered questions in Scleroderma research is whether the antibodies associated with systemic Scleroderma actually cause the development of Scleroderma related symptoms (pathogenic theory) or instead are merely a marker of the underlying disease (epiphenomena theory). The above-mentioned research on hyperviscosity and plasmapheresis is consistent with the pathogenic theory but is not definitive. A single plasmapheresis treatment removes 80% to 85% of everything in the blood except for red blood cells and white blood cells. This includes Scleroderma related antibodies but also might include co-factors also circulating in the blood that are actually the direct cause of the red blood cell hyperaggregation. However, what these research results do suggest is that there is a blood circulating factor, for example, Scleroderma specific antibodies, that is causing endothelial cell damage to the micro-capillaries.

Basic initial research needs to be done to look at the hyperviscosity characteristics, including the degree of red blood cell clumping (if abnormal) as well as the “stickiness” of the aggregated cells. It is theoretically possible that different antibody subtypes might have different aggregation characteristics. For example, one subtype might tend to show more clumping when the heart is resting (diastolic blood pressure) than another subtype but be more sticky so when the heart is pumping (systolic blood pressure), the clumps are less likely to break apart potentially causing more damage to the endothelial cells.

A number of studies should look specifically at changes to hyperviscosity levels following a series of plasmapheresis treatments. It will be important to do this research focusing on the differences, if any, for different Scleroderma subtypes based on antibody type. This would make it easier to develop optimum plasmapheresis treatment strategies for different subtypes of systemic Scleroderma.

If the theory that red blood cell hyperaggregation causing damage to the cell walls is correct, then this suggests that Scleroderma might be controllable in the same way that insulin can help prevent diabetes symptoms from developing and antiretroviral drugs can help HIV from progressing into AIDS. Plasmapheresis is one interim treatment approach that may be effective, especially in slower-progressing limited Scleroderma. However, because of the cost of plasmapheresis and the high probability that this treatment approach may not be adequate to control the rapidly progressing forms of Scleroderma without immune suppression from too frequent plasmapheresis treatments, research should be done to look at other ways of reducing red blood cell aggregation that are lower cost and have fewer potential side effects, for example:
• There is some research that indicates that Intravenous Laser Blood Irradiation Therapy can temporarily reduce red blood cell aggregation.

• A study on nattokinase, a pro-fibrinolytic enzyme, showed dose dependent decrease in red blood cell aggregation and overall plasma viscosity. Nattokinase is generally considered safe but can interact with anticoagulant drugs.

• Purified poloxamer 188 is a highly purified form of the nonionic block copolymer poloxamer 188. It lowers blood viscosity, decreases red blood cell (RBC) aggregation, and decreases friction between RBCs and vessel walls to increase microvascular blood flow and decrease cell injury. While it has mostly been used to treat sickle cell disease, it may have potential to treat Scleroderma by reducing RBC aggregation.