

Getting to the Heart of the Matter: Lupus and Heart Disease

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Dr. Manzi was the keynote speaker at this year's Symposium. This edited transcript is printed with Dr. Manzi's permission.

Systemic lupus erythematosus is an autoimmune disease that more commonly affects women than men. An autoimmune disease is one in which the body's immune system goes awry. The immune system can be likened to the fortress of a castle, built to protect against external invaders. For the body, these external invaders include viruses and bacteria. In an autoimmune disease such as lupus, the immune system, which is supposed to protect against these invaders, turns on the body and attacks various organ systems. There are several different autoimmune diseases. For example, insulin dependent diabetes is actually an autoimmune disease in which the immune system attacks the islet cells of the pancreas, preventing them from producing insulin. Some types of thyroid disease can be autoimmune diseases. Rheumatoid arthritis primarily attacks the joints, and multiple sclerosis attacks the nervous system. In many of these autoimmune diseases, the attack is limited to a certain organ. Unfortunately, in lupus, many different organs can be affected, including the heart.

The impact that lupus has on heart disease has become more apparent as improvements in disease treatments over the last 50 years have allowed patients to live longer. In the early 1970s, there were reports of strokes and coronary disease occurring commonly in lupus patients at young ages, particularly in women. However, the magnitude of the problem was not appreciated until more recently.

To understand heart disease in women with lupus, we must first consider heart disease in the general population. Are women's hearts different from men's hearts? Is cardiovascular disease different in women and men? The answer is yes. There are clear differences. A fact that is often not appreciated is that heart disease is a tremendous problem in women. In fact, it is the number one cause of death and disability in women in the United States. Furthermore, in the US, women incur more than 50% of the annual health care costs associated with heart disease. However, women are traditionally much more concerned about cancer, specifically breast cancer, when in fact women die from cardiovascular disease at much higher rates than from all cancers combined.

This situation was recently reviewed in an article in Time Magazine. Women were asked what they perceived to be their risk of dying from cardiovascular disease. Only 8% of the women felt they had a high risk. More frightening, only 11% of their physicians viewed cardiovascular disease as their primary health care risk. These findings underline the tremendous

misconception that women are somehow protected against heart disease. To the contrary, men are keenly aware of this risk and often worry about having a heart attack. This misconception may arise from an inherent difference in men and women regarding heart disease. Premenopausal women rarely have heart attacks. In fact, before the age of 55, men are 10 times more likely than women to have a heart attack. However, after the age of 55, women's risks begin to equal those of men. It appears that being premenopausal offers a protective effect. Unfortunately, premenopausal protection is lost in women with lupus.

In 1997, my colleagues and I decided to determine the extent of the increased risk for heart disease faced by women with lupus. We examined the rates of heart attacks in 500 women with lupus and compared them with 2000 women without lupus. We divided the women, aged 15-65, into five 10-year age groups. We couldn't even make a comparison in the women under 34 because so few of the non-lupus women had had heart attacks. In the premenopausal age range of 35 to 44, the lupus women were 50 times more likely than the non-lupus women to have had a heart attack, a substantially increased risk. However, in women older than 45, the lupus women were only 2 to 4 times as likely to have a heart attack. This decrease in relative risk occurs as the normal population starts having heart attacks— after they go through menopause. It is the premenopausal risk that is of great concern in lupus. Our findings have since been confirmed by several other reports.

The question now becomes, “Why do young women with lupus have heart disease?” The answer may lie in the inflammatory nature of the autoimmune disease. It is now known that inflammation of the blood vessels is an underlying cause of atherosclerotic plaques. It is intriguing to speculate that the inflammation so characteristic of lupus may be related to the coronary problems affecting these patients.

According to the latest theory on the role of inflammation in atherosclerosis, one of the initial triggers to plaque formation involves injury to the blood vessel wall. Potential sources of injury include smoking, certain viruses, and high levels of homocysteine in the blood (which can occur in B-vitamin deficiencies). In lupus patients, immune complexes are an additional source of injury. In lupus, the immune system makes antibodies against self-antigens, substances made naturally by the body. When the antibodies bind to these self-antigens, they do so in the blood vessel and they can deposit in tissues and cause damage. As a result, in lupus there is a low level of damage to the vessel wall from these immune complexes on a regular basis. Thus, injury to the wall by other sources such as smoking can be accelerated by immune complexes in a patient with lupus.

Once the vessel is injured, it is susceptible to trapping LDL-cholesterol (bad cholesterol), which is the culprit for forming plaque in the blood vessel. It is important to keep LDL levels in the blood low because the higher the levels, the more likely it is to get trapped on the blood vessel. Once the LDL-cholesterol goes through the vessel wall, it becomes chemically altered through a process called oxidation. The oxidation of LDL sets off the destructive process of plaque formation. Oxidized LDL stimulates an immune response in which antibodies are formed against it. In addition, it stimulates an inflammatory response. Inflammatory cells migrate to the site of injury, enter the vessel wall, and ingest the lipids (fats and cholesterol) that are trapped there, initiating the formation of the atherosclerotic plaque. Once the inflammatory cells engulf

the lipids, they are called foam cells. Once foam cells form, other T cells and smooth muscle cells begin to proliferate and a fatty streak forms. If this process continues unchecked, a plaque forms. There are several steps in this process that may be more likely to occur in patients with lupus. First, as we discussed previously, lupus patients likely have more initial injury to the blood vessels. Second, lupus patients may be more likely to oxidize LDL, thus accelerating plaque formation. Third, when lupus patients are experiencing a skin rash, or joint pain, that is a manifestation of inflammation. It is likely that inflammatory cells are also migrating to the site of the blood vessel injury, thus increasing the ingestion and engulfment of oxidized LDL. As a result, lupus patients likely have more plaque.

However, having plaque is not enough to have a heart attack. It was previously thought that the plaques clogged the blood vessels restricting blood flow, which ultimately caused a heart attack. It is now known that to have a heart attack or stroke, the plaque must first rupture (break open) and a blood clot form at the site of the ruptured plaque. It is possible to have plaques that never rupture, thus no heart attack. So what makes a plaque likely to rupture? Three conditions have been identified as making a plaque more vulnerable: the more fat in the plaque, the thinner the cap on the plaque, and the more inflammation at the site of the plaque. We are theorizing that because of the inflammatory nature of the disease, perhaps lupus patients have more inflammation in their plaques, making the plaques more likely to rupture.

Clot formation is the ultimate step necessary to have a heart attack or stroke. Therefore, clotting risk is important. Up to 50% of lupus patients have antibodies to antiphospholipids, referred to as antiphospholipid antibodies, anticardiolipin antibodies, and lupus anticoagulant. Having these antibodies means the blood of these patients is more likely to clot. Furthermore, these antiphospholipid antibodies are able to recognize oxidized LDL and increase its uptake into the inflammatory cells at the site of injury inside the blood vessel wall. In addition to their role in heart disease, antiphospholipid antibodies are related to miscarriage during pregnancy.

Research studies have attempted to identify risk factors for heart disease in lupus. Some of the factors are the traditional cardiovascular risk factors found in the general population. The modifiable factors include tobacco use, obesity, low physical activity (because of lupus), and high blood pressure. Those that are not modifiable include aging, a family history of heart disease, and diabetes. However, even when all of these risk factors are taken into consideration, having lupus, the disease itself, is an added risk for coronary disease.

We have speculated on the possible reasons why patients with lupus are more likely to have a heart attack. As physicians and patients, what can we do about it? Physician awareness should be increased. Physicians rarely suspect heart disease when a young woman with lupus experiences chest pain, and they are not always aggressive in checking blood cholesterol and blood pressure for routine care. Physicians should approach lupus patients as they would patients with diabetes. Just as they are tuned in to the risk in diabetes, they should be tuned into lupus the same way. Lupus patients need to be aware of the risk and act as their own advocate. They should change the risk factors that can be changed and make sure they are monitored well by their physicians. According to the American Heart Association, blood pressure should be 120/70 mm Hg. Some patients may need to take cholesterol-lowering agents. Two clinical trials are now underway examining the role of statins. One trial, being conducted in Baltimore, is

monitoring and comparing the progression of heart disease in patients receiving a statin with those receiving a placebo. In the second trial, being conducted at Duke University, statins are being administered to children diagnosed with lupus. We believe that heart disease starts early in lupus, therefore these children are being given statins to determine whether taking agents to lower lipid levels will prevent the progression of heart disease. Lupus patients who are diabetic should take every effort to control that disease. Patients who smoke should quit since smoking is a huge risk. Lupus patients are often sedentary because of their disease; the fatigue can be overwhelming. However, even low levels of exercise such as 10 minutes of easy walking each day can be beneficial. Exercise increases the good cholesterol, HDL, and lowers the bad cholesterol, LDL. Controlling weight is a very important issue. Obesity is an epidemic in the United States and has a considerable impact on heart disease as well as many other health-related issues.

What else can you do? At this point, we are undecided about prednisone. For many years physicians blamed heart disease on the prednisone since at high doses it can increase blood pressure and can raise cholesterol and triglyceride levels. On the other hand, it is the most effective treatment for inflammation. The compromise is to limit the time on prednisone and to try to lower the dose. Many lupus patients are also taking 81 milligrams of aspirin each day, which may also reduce the clotting risk. There are many other treatments now under investigation. For example, there are trials being conducted that are examining whether anti-oxidants such as vitamin E and beta-carotene can reduce heart disease. Although we don't know the results yet, taking anti-oxidants is easy and something lupus patients should consider. It won't hurt to take B-complex vitamins as well.

Pharmaceutical companies have recently become highly interested in lupus. There are five new drugs being tested in clinical trials in Pittsburgh. These drugs are targeted therapies, meaning they are intended to target the specific problem in lupus and not simply suppress the entire immune system. If these drugs are effective in treating the underlying inflammation, they may also prevent cardiovascular disease. Another treatment under question is estrogen. To take estrogen or not take estrogen is the million-dollar question. This dilemma is also true for birth control pills and hormone replacement therapy. Some of the larger women's health initiatives and trials have found that heart disease is more common in women taking estrogen. The truth probably lies somewhere between there being no risk at all and the risk being so great that all treatment must stop immediately. Hormone replacement therapy has been very beneficial to women who have been incapacitated by conditions such as hot flashes. On the other hand, these women are also concerned about the risk of heart disease and breast cancer. Women need to have individual discussions with their physicians. There is no blanket statement that a lupus patient cannot be on estrogen replacement. But there are risks. Estrogen can increase the risk of clotting. So if a lupus patient has antiphospholipid antibodies, the clotting risk may be elevated by the addition of estrogen. However, there are low-dose products that may be right for some patients. Similarly, we prescribe Depo-provera as a birth control agent for many young women with lupus since this agent does not contain estrogen. The bottom line is that the decision about estrogen is very individual and patients should discuss this issue with their physicians.

One closing point: although this discussion has focused on how lupus affects coronary disease, lupus can affect the heart in many other ways that were not discussed herein.