SCLERODERMA ASSOCIATION OF B.C.

The Bulletin

SPRING-SUMMER 2023 | VOLUME 5 NUMBER 1

Scleroderma Association B.C.

Scleroderma in children

Autoantibodies in Scleroderma

The Joan Kelly Memorial Research Fund

Summary

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A Word from Our President

JUNE AWARENESS

In 2012 SABC reached out to the community to raise public awareness of scleroderma by organizing the inaugural **"Scleroderma Ride for Research"**. From that humble beginning the *June Awareness Event*s have occurred across the province and contributed over $500,000 to the St. Paul's Foundation for scleroderma research. Organizers and participants have had events in Vancouver, Victoria, Kamloops, Surrey, Valemount, Smithers and virtually across the province. We are making a difference!

This year there will be **"Moving to Cure Scleroderma"** events in Victoria, Surrey, Vancouver and Virtually across the province. Come out and join an event near you or do your part virtually. Look for more information on the SABC website.

RESEARCH FUNDING

SABC continues to support scleroderma research in British Columbia and Canada, primarily the Scleroderma Association of B.C. Research Program through St. Paul's Foundation. Traditionally this has occurred by individual donations directed to research and specific events with the purpose of raising awareness and collecting donations for research.

We have recently taken steps to create the means of supporting long-term research funding with the creation of an endowment. The initial capital for the endowment was donated from the estate of a long-time scleroderma patient and from generous donors like you and provides a starting point of almost $400,000. We anticipate the value of the endowment to continually increase as specific donations to support this goal are received. To honour one of the co-founders of SABC, the endowment is called the **"Joan Kelly Memorial Research Fund"**. Further information regarding this endowment can be found in this spring publication.

RESEARCH ARTICLE

Research wouldn't happen without the dedication of people like Dr. Senecal who is one of the many champions of research that gives people living with scleroderma hope. The article within entitled Autoantibodies in Scleroderma describes the autoantibodies commonly involved in scleroderma. Which types do you have? **The goal for using the results generated from this study:** ***the faster doctors can diagnose scleroderma with each patient's specific autoantibodies present, the faster patients can get on an individualized treatment plan to help live a better quality of life***.

CONNECTING WITH OTHERS

SABC's board and volunteers have been steadily working to stay connected with our members and to expand our existing ways of sharing information.

Virtual support group meetings have been happening almost monthly. Some are directed at specific topics, with specialists joining the call in that area of expertise. Other times it is an open discussion to share individuals' experiences and how others have worked through different situations and challenges.

Kenny's sharing his story about his journey of his recent lung transplant, confirms this **"scleroderma warrior"** has not let this disease define who he is.

Speaking of our sharing information, we are in the process of updating the SABC website, primarily targeting improvements in how we find our way around the site. We know that the content we present is beneficial to patients, their families, health care professionals and the community, so now our aim is to create an easier way for visitors to find what they are looking for. Our website helps those newly diagnosed to find the info they need, but we need to also provide continuing educational content all the while spreading scleroderma awareness. Any comments on helping us keep the website user-friendly are always appreciated!

This fall we will be running a hybrid in-person and virtual AGM & Conference on Saturday October 21st. Put this date in your calendar and watch for more information regarding guest speaker topics, registration, etc., on our website.

ROSANNE QUEEN
President
Scleroderma Association
of B.C.

Moving to Cure SCLERODERMA

JUNE IS SCLERODERMA AWARENESS MONTH!

And it's time again for Moving to Cure Scleroderma!

We look forward to these annual raising scleroderma awareness events during the month of June and are excited to see one and all in Surrey, Victoria, Vancouver and virtually from Anywhere in B.C.

Patients, their families and friends come together with their sea of blue t-shirts showcasing their enduring 'warrior' spirit while raising funds to support scleroderma-specific research in B.C. and Canada.

We are excited to see each other again this June!

SURREY

SUNDAY, JUNE 4TH / WALK

TYNEHEAD PARK - Surrey, V4N 2E2

We are excited to welcome everyone to our second "Moving to Cure Scleroderma" 5 km walk in Surrey on June 4th! Our goals are to create awareness for scleroderma and raise money for critical research.

Please join us at 9 am on June 4th at Tynehead Park, Serpentine Fields Entrance. Let's get moving for the cure for scleroderma!

WALK COORDINATORS:
CHELSEA FITZPATRICK-LINDSAY, COQUITLAM & KELLY GRANT, CHILLIWACK

VICTORIA

SUNDAY, JUNE 11TH / WALK

SHORE PARK - 1767 Island Hwy, Victoria, V9B 1J1

We are excited to host the 6th Annual Scleroderma Walk in Victoria on June 11th, 2023. We are looking forward to more friends and family joining in to raise awareness and funds for research for this little understood disease. There will be a choice of a 2 or 5 km walk as well as refreshments and a silent auction of exciting prizes. Please save the date and we would love to see your smiling faces at 9 am at West Shore Parks and Recreation Picnic Shelter

WALK COORDINATOR:
LINDA BARNES, VICTORIA

For more details on the schedule of the walks and to register on-line, please visit

Moving to Cure SCLERODERMA

sclerodermabc.ca

A big thank-you to the walk coordinators who welcome you to join them and support us all this June.

Not able to make any of June's organized walks? No problem!

Wherever you are in B.C. please visit sclerodermabc.ca and help raise funds for research.

100% of funds raised supports scleroderma research here in B.C. and across Canada!

VANCOUVER

SUNDAY, JUNE 18TH / BIKE RIDE/WALK

STANLEY PARK - Vancouver V6G 1Z4

David and I are now hosting our 12th ***"Scleroderma Bike Ride/ Walk for Research"*** Each year we are amazed at the continued support we receive from people joining us and helping raise research dollars. The SABC Research Project team is deeply committed to helping those living with scleroderma research and we are deeply committed to supporting them.

RIDE/WALK COORDINATORS: ROSANNE & DAVID QUEEN, NORTH VANCOUVER

ANYWHERE IN B.C.

ALL OF JUNE, VIRTUAL MOVING

Hey British Columbia, June is Scleroderma awareness month. Come on out and participate in SABC's virtual ***"Moving to Cure Scleroderma"*** No matter where you live in BC, pick a day in June, wear your blue and show us your favorite activity.

What is a virtual event? Engage in an activity of your choice, in a location of your choice! You can walk, bike, run or run a marathon, do yoga, kayak or any activity you enjoy. It's your choice so be as energetic, adventurous or creative as you can be!! Let's get our family, friends, co-workers and even your community involved in spreading awareness and most of all having fun.

VIRTUAL COORDINATOR: TERESSA COLOSIMO, VALEMOUNT & NORTHERN RURAL COMMUNITIES

DON'T FORGET TO EMAIL YOUR "MOVING TO CURE SCLERODERMA" PHOTOS TO CHELSEA AT:

chelsea@sclerodermabc.ca

My name is Kenny Reid

I am now 56 years old, and I live in Tsawwassen, BC and this is my short story, so far, on living with what Scleroderma has done to my body.

It all started in January 2020. I had finished playing a gig (as a hobby I'm a singer in an 80's cover band) and could not believe how tired I was feeling after playing our setlist and how out of breath I felt. The skin on my hands was tight and causing me grief (not being able to make a fist) and not allowing me to play my guitar well at all. My hands were also constantly cold which I had noticed for a few months earlier. These feelings continued for the next three months and I developed a persistent cough.

My wife Alison forced me in May to the ER in VGH to see if they could give any insight. I have never been one to bother medical folks. Lo and behold, following tests and a CT scan it was determined that I had Interstitial Lung Disease (ILD). My first thought was how the hell did I catch this? I have been a runner most of my life and always kept myself fit, and a non smoker.

»»»»

I was sent for a pulmonary breathing test. The results determined that my lung capacity was 76% of a normal person, so not too bad I thought, trying to remain positive. Over the course of the next month and multiple tests it was determined that I had Scleroderma which had ultimately caused the (ILD). I had no idea what Scleroderma was, let alone that there was no cure. My breathing was getting steadily worse with me getting out of breath just walking from the bedroom to the living room. My breathing capacity during this year had further reduced to 44% which caused some real concern with my Respirologist..

I was recommended to speak to the Lung Transplant Team. I started the testing as a precaution and the number of tests was exhaustive, taking over 7 months to complete. Over the course of the tests I met all the transplant doctors, who went about their own individual assessments to determine whether I was a viable candidate. These meetings eventually accumulated in a final meeting in April 2022 with the main surgeon Dr. John Yee, who told me that unfortunately a double lung transplant was my only option for survival. I was officially put on the Lung Transplant List in June 2022, with the strictest instruction that I am always accessible to my phone.

I received a call from Pre-Transplant at 8am on Aug 7, 2022. They potentially had new lungs for me, and I had to make my way to VGH's 12th floor immediately. My head was in a spin and the emotional rollercoaster was to begin. My wife and son Lewis were scared but knew we had no choice. I gathered my bag and we made our way to the hospital with our trusted friend Clive driving, who kept us positive for what lay ahead. I was told that there was a chance that the procedure could be a false alarm should the lungs not be perfect enough. I arrived at the hospital for them to prepare getting me ready for the procedure. Everything was now becoming a blur with nurses being a hive of activity around me. My operation was booked for 6:30 am the next morning should everything go according to plan.

Fortunately, the new lungs were deemed a go. At 6 am that morning, and I was whisked off into the Operating Room. I vaguely remember waking up in the ICU (apparently telling all sorts of weird stories) and being transferred to the recovery floor.

So now I have new lungs but let's deal with the Scleroderma - which can cause esophageal reflux affecting the transfer of food through the stomach tract. To prevent any aspiration of food or drink back into the new lungs, as this can permanently damage the new lungs beyond repair, I had another procedure of getting a feeding tube attached to the lower intestine and a medication tube attached to my stomach. This allows for all food and medications to be added externally and not via mouth. In all honesty, not being able to drink or eat food for 3 months was the hardest part of the whole process. But now that I have my feeding tube and medicine tube in, I can BREATHE which made the whole process worthwhile - what a feeling that was!

My recovery was unfortunately not straightforward due to complications and bumps in the road. I spent the next 3 1/2 months in hospital. But on the positive side I got to meet so many lovely nurses and managed to share my love of music with some nurses and doctors by making them playlists on Spotify. My recovery has been slow and steady since getting home. It was reassuring to know the transplant team was, and still is, available to me virtually at home at the end of a phone line. This made the scary transition from hospital to home a more comfortable experience for my family and me.

It has been a journey, one of which I am eternally grateful to have been part of. The journey will also be part of my and my family's life for the rest of our lives. My wife Alison has connected with wives of other lung transplant patients with scleroderma at the same time as myself, have swapped emails and they now have a constant stream of contact and have become great friends (I'm sure they just moan about us guys!!). This, trust me is a great part of the whole journey, actual people who know what the care-giver is going through, which we as transplant patients really cannot understand because it's all about us (well that's what the spouses say…ha, ha!)

Forward to Spring 2023 and I have new Lungs and a new life. I am walking daily and getting stronger- - looking forward to my first game of golf in 3 years and it's all thanks to one wonderful Donor who saved my life. I cannot thank the nurses and doctors enough (not forgetting my nurse niece Katie who kept me calm) and the whole Transplant Team, for their care and attention during my recovery. They are part of our family now – Alison has already got the Christmas list going!! They are all very special people indeed. Lastly, I was also so grateful to have my 80-year-old mother Sheena here from Scotland while I was going through the recovery. She made my first meal of homemade lentil soup once I was allowed to take food by mouth, which was delicious. I would also like to thank our amazing family and friends both here in Canada and around the world for their constant support which was invaluable throughout this journey.

I am now looking forward to fronting my band again. Thank you for reading my story.

Kenny

THE GIFT THAT KEEPS ON GIVING

Over the last 30 years, the Scleroderma Association of B.C. has supported research across Canada with contributions from donors like you. Although there is limited financial support from governments and institutions, SABC donors have contributed more than $1,000,000 to fund Scleroderma research.

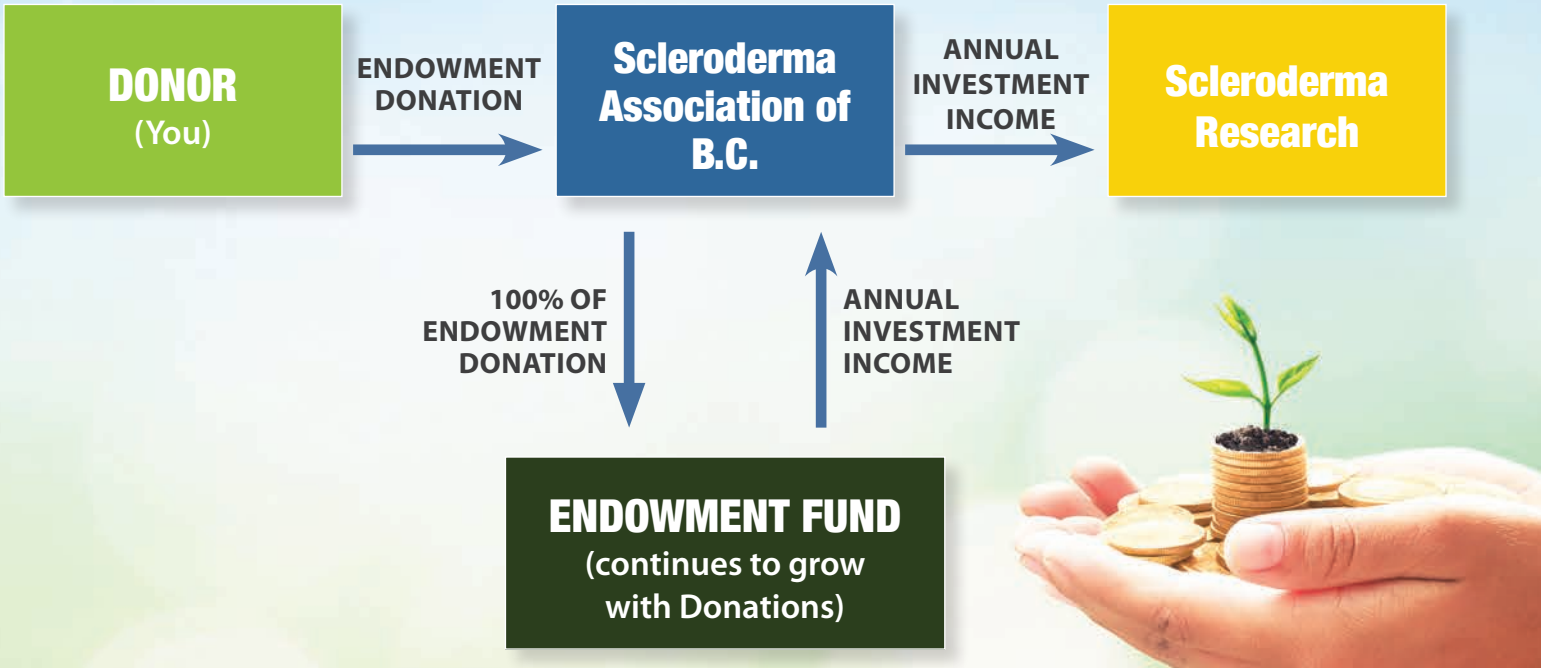
SABC feels now is the time to take our support for Scleroderma research to the next level by setting up an endowment to fund future research. The way the endowment will work is that any contributions to the endowment will be invested and the earnings from the investments will be used to fund future research. In this way, our contributions will be put to work, earning money to fund Scleroderma research. This will truly be the gift that keeps giving. This also helps make the funding more predictable as we will have a good sense of how much the endowment will earn every year and so can better plan for multi-year research endeavours.

The endowment is named after Joan Kelly who was a true Scleroderma warrior who cofounded SABC. The ***Joan Kelly Memorial Research Fund*** has been generously initiated by a few Scleroderma warriors who have kicked it off with $370,000 worth of contributions from an estate or donations. Gifts of assets and other contributions to SABC can be directed to the Joan Kelly Memorial Research Fund, where the capital is invested and the annual income earned is used to provide a source of funding for the long-term financial support of scleroderma research.

SABC has established a Terms of Reference describing use of the funds to be consistent with SABC's strategic vision regarding scleroderma research and patient care. Funding can only be provided for research purposes where the research is intended to improve the treatment, care or support of patients coping with scleroderma. The Fund will not be used for SABC operating costs. The Terms of Reference is available for review for all donors or potential donors.

Annual disbursement of income from the Fund will be limited to the income earned in the previous SABC fiscal year and be determined based on assessment of research proposals.

ENDOWMENT PROCESS



Our Spring-Summer 2020 Vol 2 No. 1 Bulletin has some financial articles, ***"Maximizing Charitable Dollars"*** and ***"Wills and Representation Agreements"***, that are of interest for those that may consider donating to the Fund. The Bulletin can be found on the SABC website under the "Contact Us" tab and selecting Become a member.

The ***"Maximizing Charitable Dollars"*** article illustrates how individuals can make a larger impact on the future of research by contributing non-registered investment accounts directly to SABC. **Some extracts from the article:**

> **"This strategy is mutually beneficial to you, and your chosen charity – you receive no tax liability, and your charity receives more money."**

AN EXAMPLE, BASED ON INFORMATION AT THE TIME OF PUBLICATION, IS SHOWN BELOW.

	SELL SECURITIES FOR CASH. DONATE AFTER-TAX PROCEEDS	DONATE SECURITIES DIRECTLY TO CHARITY
Original Cost of Securities	$10,000.00	$10,000.00
Current Market Value	$50,000.00	$50,000.00
Capital Gain	$40,000.00	$40,000.00
Tax on Capital Gains @ 49.8%	$9,960.00	$0.00
Donation Amount After-Tax	$40,040.00	$50,000.00

> **"In BC for 2019, if you donated $50,000 of securities in kind, you could have received a charitable tax credit for $22,848.52 versus $18,634.92 by selling the securities first, then donating the cash. You could therefore increase your charitable tax credit by $4,213.60 donating the securities in kind and not selling them first."**

The **"Wills and Representation Agreements"** article discusses some options for providing donations to charities of your choice from your estate. One option is to include the charity as a beneficiary in your will. A second option is to name the charity as a beneficiary of a financial asset, such as TFSA, RRIF, RRSP or Life Insurance, that will be automatically passed to the charity. In the development of any estate plan, it is always good to discuss your intentions and desires with your family.

SCLERODERMA IN CHILDREN

Jayne MacMahon, MD
Childhood Myositis Fellow, Paediatric Rheumatology
PGY6, Universiy of Toronto
Division of Rheumatology | The Hospital for Sick Children

WHAT IS SCLERODERMA?

Scleroderma is a rare condition in children. It often affects the skin. It can cause the skin to become hard and tight. In some children, it can affect other organs (e.g., lungs, kidneys, joints, stomach, and intestines).

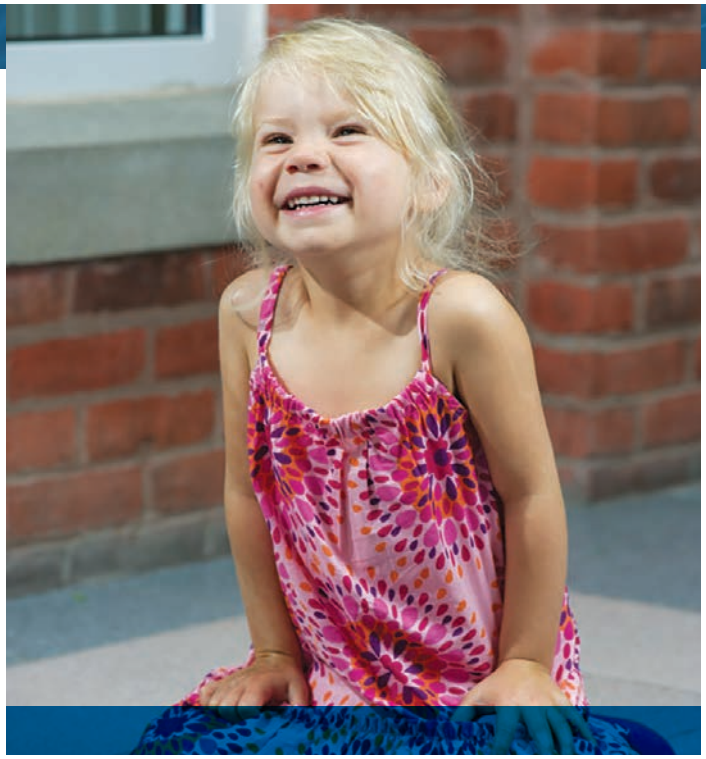
Scleroderma is an autoimmune disease. It happens when the body attacks its own skin, and sometimes organs, by mistake. In autoimmune diseases, our immune system (the chemicals and blood cells that are supposed to fight off germs) is overactive. Extra chemicals and blood cells get trapped in the blood vessels of the skin (and sometimes organs). This causes inflammation and damage there. It is a chronic (ongoing) condition. It may get worse over time.

THERE ARE TWO TYPES OF SCLERODERMA IN CHILDREN.

The first is called 'localized scleroderma'. This is the most common in children. It affects the skin in one area of the body only.

The other type is called 'systemic scleroderma'. This can affect many areas of the skin, as well as the organs of the body. It is rare in children.

SCLERODERMA IN CHILDREN



WHAT ARE THE SYMPTOMS?

It is important to remember that scleroderma can affect every child differently. The most common things that happen are:

- Tightness and swelling of the skin, sometimes the skin changes colour.
- Pain or swelling in the joints.
- Pale, tingling or numb fingers, often in cold weather or when stressed. (This is called Raynaud's Phenomenon).
- Hard bumps (calcium) under the skin.
- Sores on the fingertips or knuckles.
- Spider veins.
- Heartburn and trouble swallowing.
- Shortness of breath.

HOW IS IT DIAGNOSED?

If you or your doctor thinks your child has scleroderma, the first step is to be seen by a specialist doctor (called a 'pediatric rheumatologist'). The specialist will ask about your child's illness and give your child a check-up. They may ask for extra blood tests or X-rays. Depending on how your child is feeling, this may include:

- Blood and urine (pee) tests to look at blood counts, antibodies (chemicals found in the blood that may contribute to causing scleroderma), how well the liver is working, and how well the kidney is working.
- Imaging tests (such as X-rays, CTs, and MRIs). These look for any changes in the body's organs.
- Breathing tests (called Pulmonary Function Tests) to look at how well the lungs are working.
- Ultrasound of the heart (called an echocardiogram) to look at how well the heart and blood vessels are working.
- Biopsy of the skin to look at the skin more closely under a microscope.

SCLERODERMA IN CHILDREN

HOW IS IT MANAGED?

Scleroderma cannot be cured. The goal is to improve the skin and stop the organs from becoming damaged. Every child's treatment will be different.

IT MAY INCLUDE:

- Medicines (such as ibuprofen) to help with pain and reduce inflammation.
- Skin creams to work directly on softening the skin.
- Medicines to reduce the strength of the overactive immune system and stop inflammation. These are called 'immunosuppressive'. They can be given by mouth, by needle under the skin or through the vein.
- Treating symptoms such as heartburn or Raynaud's Phenomenon.
- Physical therapy and exercise to keep muscles strong, and the joints from tightening up.
- Regular visits with your child's rheumatology specialist.

Localised scleroderma treatment often must last for several years. It is very rare for localised scleroderma to change and become systemic scleroderma.

Children with systemic scleroderma are at a higher risk of getting damage to the skin and organs. With the proper treatment, patients may have little or no symptoms (i.e., remission) for years at a time.

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AUTOANTIBODIES IN SCLERODERMA

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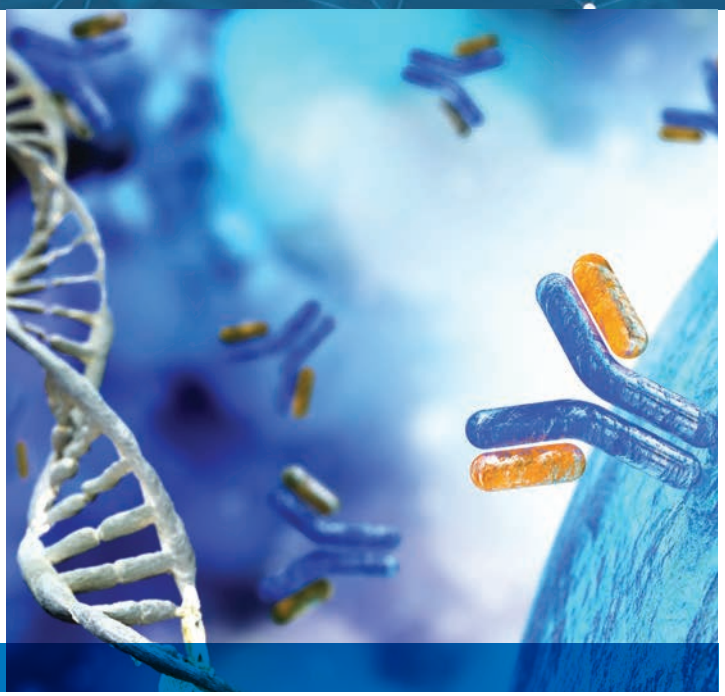
Division of Rheumatology, CHUM
Montreal, QC, Canada



Scleroderma, also known as systemic sclerosis (abbreviated hereafter as SSc), remains to this day a disease of unknown cause. However, research has made considerable progress in understanding the mechanisms involved in the lesions caused by the disease, both in the skin and in the internal organs. The study of the mechanisms of a disease is called "pathophysiology".
The mechanisms that contribute to pathophysiology are referred to as "pathogenic".

FOUR MAJOR MECHANISMS OF SCLERODERMA

Four major pathogenic mechanisms are recognized in the pathophysiology of SSc.

1. First, there is a dysfunction of the immune system that causes it to attack the individual's own body. This explains why SSc is considered an "autoimmune" disease.
2. There is also microvascular damage, meaning that it targets the small blood vessels. Raynaud's phenomenon (fingers changing colour when exposed to cold temperatures) present in almost all SSc patients, and which is so often both the first symptom and the first sign of the disease, is the typical manifestation of this vascular damage.
3. There is also inflammation. Although it is often underestimated in SSc, research has shown its crucial importance, to the point that "without inflammation, there is no fibrosis".
4. Finally, fibrosis (or sclerosis, which gives its name to SSc) is the ultimate result of the previous intertwined mechanisms, both in the skin and in the internal organs.

AUTOANTIBODIES IN SCLERODERMA

As we can see, the pathophysiology of SSc is complicated. These pathogenic mechanisms have been the subject of intensive research in order to understand their interrelationships and to find "weak points" in the pathophysiological cascades that may become new therapeutic targets. In this article, we will focus on the dysregulation of the immune system and, in particular, on the specific antibodies that are typically found in the blood of SSc patients. Other important and complex aspects of immune system dysfunction in SSc (such as cellular immunity, innate immunity and signaling) will not be discussed here.

IMMUNE SYSTEM DYSFUNCTION IN SCLERODERMA

One of the primary functions of the immune system is to *protect* the individual from infection. Normally, the immune system does this job extraordinarily well, even though every day each individual is exposed to countless potentially dangerous microbes both in the human body itself and in the environment.

However, there are times when the immune system goes haywire and produces antibodies that *attack* the individual instead of protecting them. This is what happens in several autoimmune diseases, and the antibodies produced are called "autoantibodies".

Indeed, SSc is characterized by highly specific autoantibodies in the blood of affected individuals. By "specific" we mean that these autoantibodies are not seen in other diseases.

AUTOANTIBODIES CONTRIBUTE TO THE DIAGNOSIS OF SCLERODERMA

There are four main autoantibodies, referred to as "classic", which are named as follows:

- anti-centromere
- anti-topoisomerase I
- anti-RNA polymerase III
- anti-Th/To

These autoantibodies, their synonyms, and the molecules against which they are directed (antigens) are listed in ***Table 1***. In general, the SSc autoantibodies are mutually exclusive: in a given individual, only one of the four autoantibodies will be present. Several other less common autoantibodies have been described in recent years that are also associated with SSc, but because of their rarity and the fact that their significance still needs to be better defined, they will not be discussed here.

In fact, the four classic autoantibodies are so specific to SSc that there are now laboratory tests for their detection. In an individual with certain signs of SSc, such as Raynaud's phenomenon and skin thickening, the presence of a high titer (a significant amount) of any of these autoantibodies in the blood helps to support the diagnosis of the disease.

Thus, after a detailed questionnaire and physical examination, the rheumatologist or other medical specialist will request a blood test for these autoantibodies if they suspect a diagnosis of SSc. The diagnostic workup is usually completed by a capillaroscopy (microscopic examination of the small blood vessels around the nails) and also by tests to evaluate the internal organs, such as a CT scan of the lungs and lung function tests to look for pulmonary fibrosis.

It should be noted that the mere presence of one of the four autoantibodies in the blood does not definitively establish a diagnosis of SSc: there must be other clinical manifestations to support this diagnosis.

AUTOANTIBODIES IN SCLERODERMA

TABLE 1

CLASSIC SCLERODERMA (SYSTEMIC SCLEROSIS) AUTOANTIBODIES

NAME OF THE AUTOANTIBODY	SYNONYM	TARGETED ANTIGEN	SCERODERMA SUBSET	ASSOCIATED PHENOTYPES
Anti-centromere	Anti-CENP-B	Centromere protein B (CENP-B)	limited	- digital ulcers - pulmonary arterial hypertension - primary biliary cirrhosis - decreased risk of renal crisis and pulmonary fibrosis
Anti-topoisomerase I	Anti-topo I Anti-Scl70	DNA topoisomerase I	limited, diffuse	- pulmonary fibrosis - cardiac involvement - increased mortality
Anti-RNA polymerase III	Anti-RNApol III	RNA polymerases	diffuse	- renal crisis - cancer
Anti-Th/To		Macromolecular complex	limited	- pulmonary arterial hypertension - pulmonary fibrosis

EACH AUTOANTIBODY IS ASSOCIATED WITH SPECIFIC CLINICAL MANIFESTATIONS

A striking feature of the four autoantibodies is that each is associated with particular clinical manifestations, called "phenotypes," as shown in ***Table 1***.

For instance, anti-centromere autoantibodies are associated with the limited cutaneous form of SSc, in which skin thickening is typically limited to the fingers and forearms and life expectancy is longer. Patients with these autoantibodies appear to be at lower risk of some potentially serious manifestations of SSc, such as renal crisis (sudden cessation of kidney function accompanied by extremely high blood pressure that can lead to death) or lung fibrosis (pulmonary fibrosis).

On the other hand, anti-centromere autoantibodies are associated with the eventual occurrence (often after a long evolution) of increased pressure in the arteries of the lungs (pulmonary hypertension) which can be become life-threatening over time.

Anti-centromere autoantibodies are common in the Quebec scleroderma population of French-Canadian origin. In fact, in our study of SSc in French Canada involving 309 affected individuals, more than 40% of the patients were anti-centromere carriers [1].

In comparison, anti-topoisomerase I autoantibodies are less common, occurring in about 15% of our population with SSc. However, their detection is important because they are associated with a higher risk of potentially severe pulmonary fibrosis and also heart (myocardial) damage.

In a study comparing the life expectancy of our patients separated according to the four autoantibodies, the survival ten years after diagnosis was worse in patients with anti-topoisomerase I (67% survival rate) or anti-RNA polymerase III (85%) autoantibodies, and better in those with anti-centromere (90%) or anti-Th/To (100% autoantibodies).

Thus, testing for SSc autoantibodies is not only useful for diagnosing SSc but also provides important clinical information for predicting the associated phenotype and potential disease course. The physician can then individually tailor the follow-up and intensity of treatments according to the risks identified by the autoantibody present.

AUTOANTIBODIES IN SCLERODERMA

PRESENCE OF AUTOANTIBODIES FROM THE ONSET OF SCLERODERMA - PRESCLERODERMA

Another characteristic of the four autoantibodies is that they are present in the blood early in SSc, at the onset of the first signs of the disease. This concept was derived from a small number of observations made in the 20th century involving individuals with Raynaud's phenomenon only and carrying anti-centromere or anti-topoisomerase I autoantibodies who subsequently developed SSc. However, this concept had never been validated in a large number of subjects with long-term follow-up. Our research team, therefore, undertook a 20-year prospective study of 586 adult individuals with isolated Raynaud's phenomenon (without any other manifestation of SSc or other autoimmune diseases) to see who would develop SSc over time[2]. These individuals all had capillaroscopy at baseline and also had blood drawn for the four SSc autoantibodies.

Of course, given that isolated Raynaud's phenomenon is common in the adult female population in Quebec, most of these individuals did not develop SSc. However, 74 individuals, or 12.6% of the 586 participants, developed SSc at follow-up.

At follow-up, 80% of individuals who had one of the four SSc autoantibodies at baseline and an abnormal capillaroscopy developed SSc[2]. These individuals were 60 times more likely to develop SSc than those who tested negative. The time interval for developing SSc ranged from a few months to a few years.

This study, therefore, identified factors that predict a high risk of progression to SSc in individuals with isolated Raynaud's phenomenon[2]. In addition, the study demonstrated the existence of an early phase of SSc, now referred to as *prescleroderma*, during which the disease appears to be incubating but cannot be formally diagnosed by physicians.

This novel concept opens the door to research projects aimed at better understanding the pathophysiology of this incubation period and the mechanisms leading to the progression to definitive SSc, with the hope of identifying new preventive therapeutic targets.

DO AUTOANTIBODIES CONTRIBUTE TO SCLERODERMA LESIONS?

As we have seen, the presence of highly specific autoantibodies is compelling evidence of immune system involvement in SSc. Moreover, each autoantibody is associated with a specific SSc phenotype ***(Table 1)***. Finally, SSc autoantibodies are present as far back as possible, presumably from the onset of Raynaud's phenomenon[2].

These data inevitably raise the question: is there evidence that these autoantibodies themselves contribute to the pathophysiology of SSc lesions? In other words, are SSc autoantibodies pathogenic?

In 2019, our research team was approached by the editors of the *Journal of Scleroderma and Related Disorders*, the only medical journal dedicated to scientific research in SSc. Drs. M. Matucci-Cerinic (University of Florence) and M. Kuwana (Nippon Medical School, Tokyo) asked us to prepare an article aimed at answering this very thorny question. The question is not theoretical: if evidence were to show a pathogenic role of SSc autoantibodies, would it not be of great interest to develop new treatments targeting these autoantibodies to block their deleterious effects?

Our team at the Centre hospitalier de l'Université de Montréal, composed of Sabrina Hoa, MD, Roger Yang, MD, Martial Koenig, MD, and the undersigned, set out to review all the data accumulated over the past 40 years. The result was a 27-page article, with 182 references, published in 2020[3]. Here are the two main conclusions.

The first conclusion is that in order to assert the pathogenic role of an autoantibody in SSc (or in any systemic autoimmune disease), one must first establish rigorous scientific criteria for pathogenicity. We have therefore proposed 7 rigorous criteria that should ideally be present to state without any doubt that an autoantibody is pathogenic. These criteria are presented in ***Table 2***.

TABLE 2

Pathogenicity criteria for the definition of pathogenic autoantibodies in scleroderma (systemic sclerosis) and other systemic autoimmune diseases

CLINICAL PATHOGENICITY CRITERIA	
CRITERION 1	The autoantibody should be specific to the disease. An even greater pathogenic value is suggested when the autoantibody is phenotype specific, that is, within the disease spectrum, it associates with a particular set of clinical and laboratory manifestations.
CRITERION 2	The autoantibody is serologically present before the onset of clinical manifestations.
CRITERION 3	Autoantibody levels and disease activity/severity should, in general, correlate
CRITERION 4	Removal of the autoantibody, or blocking its functional effects, should ameliorate the disease process (e.g. by immunosuppression, plasma exchange, biological agent, immunotherapy, or other means).
EXPERIMENTAL PATHOGENICITY CRITERIA	
CRITERION 5	The autoantibody should be capable of causing in experimental systems the lesions attributed to it (e.g. in living cells or in an experimental animal model).
CRITERION 6	A suitable immunization that leads to the production of similar autoantibodies should lead to a similar disease process.
CRITERION 7	The autoantibody should be found along with a plausible target antigen at the site of tissue damage.

AS WE CAN SEE IN TABLE 2, THE SCIENTIFIC BAR HAS BEEN SET HIGH!

In a second phase, the team screened all published articles on the pathogenic role of autoantibodies in SSc and catalogued them for each of the 7 criteria according to the following grading scale:

— **No evidence;**

? **Contradictory, inconclusive data;**

\+ **Weak evidence;**

++ **Some evidence;**

+++ **Strong, definitive evidence.**

Finally, using these assessments, a verdict was reached as to whether the pathogenic role of autoantibodies was definitive, probable, possible, or whether the data were insufficient. ***Table 3*** shows the results.

Of the four classic SSc autoantibodies, only anti-centromere and anti-topoisomerase I autoantibodies have been extensively studied for their pathogenic role. The second conclusion was that there is indeed some evidence of pathogenicity for these two autoantibodies and therefore their pathogenic role is possible[3]. As shown in ***Table 3***, the evidence for a pathogenic role is strongest for anti-topoisomerase I.

Thus, further research is needed to better understand how these autoantibodies contribute to SSc lesions.

TABLE 3

Scientific evidence of a pathogenic role for autoantibodies in scleroderma (systemic sclerosis)

Classic autoantibodies	Strength of scientific evidence according to seven pathogenicity criteria*							Pathogenic role**
	1	2	3	4	5	6	7	
ANTI-TOPOISOMERASE I	+++	+++	+++	++	++	++	—	Possible
ANTI-CENP-B (ANTICENTROMERES)	+++	+++	++	—	++	—	—	Possible

Legend

* Criteria as described in Table 2.
Grading: —, no evidence; ?, contradictory, inconclusive evidence;
+ , Weak evidence; ++, Some evidence; +++, Strong definitive evidence;
** Grading: definitive, probable, possible, and insufficient data.

CONCLUSION

As we have seen, the four classic SSc autoantibodies are essential for the diagnosis of the disease and are useful in predicting its manifestations, course and associated life expectancy. The high specificity of these autoantibodies for SSc, their association with a particular phenotype and their presence from the onset of the disease suggest that they play a pathogenic role, the demonstration of which according to rigorous scientific criteria is well underway and needs to be completed.

Moreover, the remarkable association of these autoantibodies with SSc suggests that they are directly and intimately linked to the cause of the disease, the identity of which remains a mystery to this day.

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HOW SCLERODERMA CAN AFFECT THE HUMAN BODY

The symptoms of scleroderma vary greatly from person to person, so that patients will not necessarily develop all the complications of the disease.

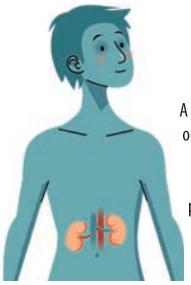
The symptoms of the disease may be visible, as is the case when the skin is affected, or the symptoms may be invisible, as when internal organs are affected.

SYMPTOMS AND MANIFESTATIONS OF SCLERODERMA

SKIN HARDENING
Thickening and loss of elasticity of the skin on different parts of the body. Hence the name «scleroderma», which means hard skin.

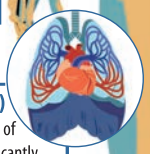
PULMONARY FIBROSIS
A potentially serious complication where normal lung tissue is gradually replaced by scarred fibrotic tissue, making it difficult to breathe and deliver needed oxygen to the body.

Pulmonary fibrosis causes shortness of breath and also sometimes a dry cough.



RENAL CRISIS
A renal crisis, which is due to an acute obstruction of arterioles and capillaries in the kidneys, leads to a sudden and sharp increase in arterial blood pressure. The symptoms are those of a hypertensive crisis: new and severe headaches, marked shortness of breath (left heart failure), and even epileptic seizures (convulsions). This is a very serious complication which requires urgent medical attention. Often during a scleroderma renal crisis, the kidneys stop functioning and dialysis (filtering the blood to avoid uremia) is then needed.

BLOOD VESSELS
The narrowing of the arteries, small blood vessels, and capillaries, can lead to many complications, including the development of pulmonary arterial hypertension (PAH), digital ulcers, and other conditions.



PULMONARY ARTERIAL HYPERTENSION (PAH)
Increased pressure in the pulmonary arteries due to the narrowing of small arteries in the lungs. Blood flow to the lungs is significantly restricted, making the heart work harder to pump blood through the lungs.

As arterial blood pressure rises in the pulmonary arteries, small pulmonary vessels slowly become clogged (a process which may take several years). This occurs through fibrosis of the small vessels, eventually leading to thrombosis, and the blood can no longer reach all parts of the lungs. Thus, it becomes more difficult for the lungs to supply enough oxygen to the body.

Sustained high blood pressure in the arteries of the lungs puts a strain on the heart, making it more difficult to circulate the blood through the lungs. Over time, this can eventually lead to congestive heart failure, particularly the right side, what is referred to as right heart failure (RHF). Right heart failure is indicative of significant PAH and is a serious complication of scleroderma.

PAH results in one or more of the following symptoms:

- Shortness of breath on exertion and at rest
- Palpitations (heart rhythm disorder)
- Fatigue
- Chest pain
- Dizziness
- Temporary loss of consciousness (syncope)
- Swelling of the ankles and legs

SCLERODERMA FACES
Hollow eyes, pinched nose, thin pursed lips, mask-like face, small puckered mouth (microstomia), and peri-oral folds.

Thinning lips and facial muscle atrophy can make the teeth appear more prominent.

EYES
Dry eyes caused by a decrease in tear production.

TELANGIECTASIA
Small dilated capillaries visible on the face and hands, sometimes referred to as «spider veins».

RAYNAUD'S PHENOMENON
Raynaud's is present in up to 95% of people with scleroderma. Whitening of fingers and/or toes triggered by cold or severe stress. The whiteness phase can be followed by a blue phase and then a red phase.

SCLERODACTYLY
The skin of the fingers, which have become infiltrated with collagen (fibrosis), may look full and sausage-like. Functional loss or decreased range of motion.

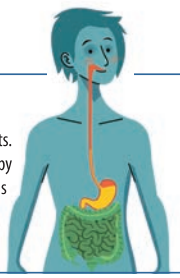
CALCINOSIS
Calcium deposits under the skin that may require antibiotics to cure occasional infections and sometimes surgery to drain calcium deposits and relieve pain.

DIGITAL ULCERS
Ulcers occur on the fingertips or on the top of the fingers. They are painful and difficult to heal.

In the most severe cases, it can lead to necrosis and amputation may be needed.

SKIN PIGMENTATION
Dark or pale spots occurring in one-third of patients.

DIGESTIVE SYSTEM
Gastrointestinal disorders affect the vast majority of patients. Gastric reflux is a common symptom that manifests itself by a burning sensation radiating up to the throat after meals and may cause inflammation of the lining of the esophagus (esophagitis reflux) if left untreated.



MUSCLE AND JOINT PAINS
Joint pain is common. It is caused by inflammation of the joints and tendons, which quite often leads to joint swelling and stiffness that can become quite debilitating.

Muscular pain (myalgia) can be intermittent or continuous. It can also be associated with muscle weakness (myositis). Symptoms include difficulty in climbing stairs, lifting objects and getting up, and also difficulty swallowing.

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Scleroderma Association B.C.

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Give us a call, send us an email, and meet other people living with scleroderma.

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