Werner Syndrome Handbook

A Guide for People with Werner Syndrome, Their Family and Healthcare Professionals

1st Edition

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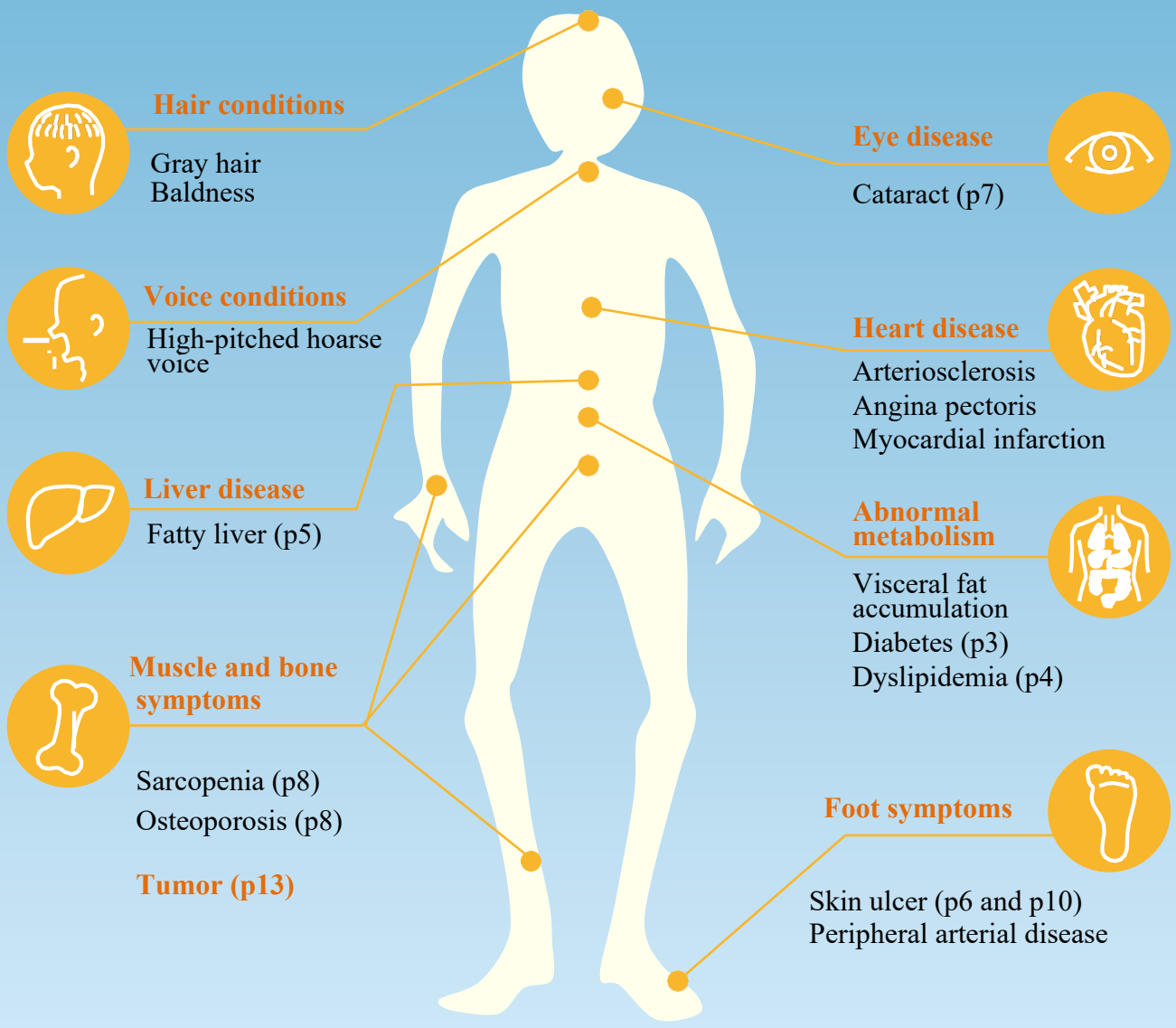
Clinical manifestations of Werner syndrome

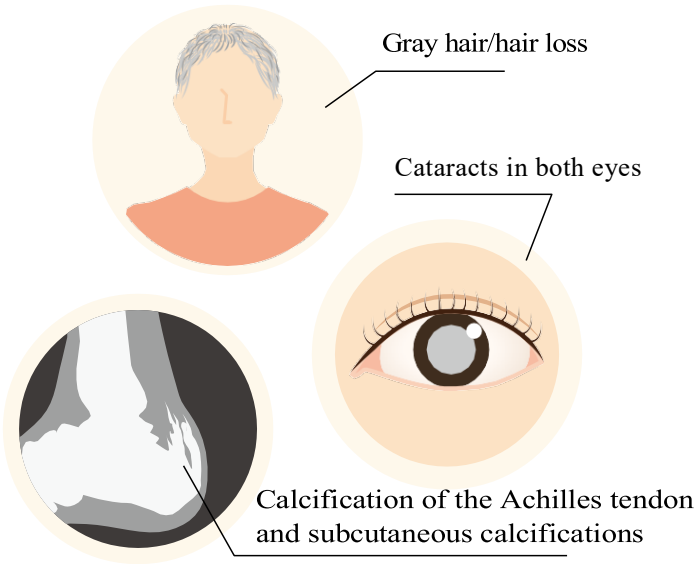


1 What is Werner syndrome?

Werner syndrome is said to be a disease of "premature aging" = a progeroid syndrome because aging seems to progress rapidly after puberty. The patient looks older than their actual age.

People with Werner syndrome starts to develop symptoms such as gray hair/hair loss, cataracts in both eyes, and a high-pitched hoarse voice in their 30s. In addition, muscle atrophy in the arms and legs, formation of calluses due to skin hardening, and hard-to-heal foot/elbow wounds (intractable skin ulcers) may be observed. Patients usually have short stature, and X-rays may reveal subcutaneous calcification (accumulation of calcium components) of the Achilles tendons and subcutaneous tissue.

Main Symptomms



Diabetes and dyslipidemia (abnormal cholesterol and triglyceride levels) are also common among these patients. Therefore, they are at risk of developing arteriosclerosis and cancer; hence, careful follow-up is required. Skin care is necessary as repeated infections from ulcers can cause bacteria to enter the bone marrow.

The number of Werner syndrome patients in Japan is estimated to be 700~2,000. The disease is prevalent in Japan, with 60% of the patients reported worldwide being Japanese. In the past, most of the reported cases were from areas with many consanguineous marriages, which leads to closely related kinship; in recent years, the number of patients whose disease is not related to consanguinity is dramatically increasing. Lifestyle habits such as daily diet and exercise are unrelated to the onset of this disease.

Werner syndrome is caused by an abnormality in the WRN gene. The disease only occurs when both WRN genes are defective. Each of the patient's parents only has one causative gene and does not develop the disease. About 1 in 4 of the patient's siblings will develop the disease; however, the probability that the patient's children or their children will develop the disease like their parent or grandparent is extremely low.

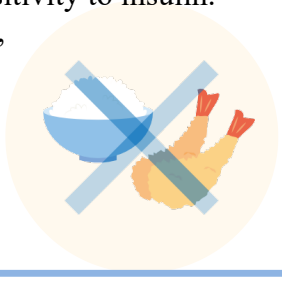
There is no fundamental cure for Werner syndrome. However, early detection and treatment are important for diseases such as cancer, cataracts, diabetes, dyslipidemia, etc., because surgery and medications are effective and they improve the patients' prognosis.

In the past, many patients died from cancer and arteriosclerotic diseases such as myocardial infarction in their mid-40s. However, a recent study shows that the average life expectancy has increased by more than 10 years, and the number of Werner syndrome patients in their 60s is significantly increasing: the oldest patient was aged 77 years.

2 Things to be aware of in life

Prevention and treatment of visceral fat obesity, diabetes, and dyslipidemia

Excessive carbohydrate and fat intake should be avoided as fat tends to accumulate in the abdomen (visceral obesity), thus increasing the susceptibility to diabetes and dyslipidemia. Exercise should be performed regularly. Treatment for general type 2 diabetes is recommended to manage diabetes; medications that improve the sensitivity to insulin, a hormone that lowers the blood sugar levels, are also used in many cases as the primary cause of Werner syndrome is decreased sensitivity to insulin. Dyslipidemia is managed based on the treatment used for general dyslipidemia, and low-density lipoprotein (LDL) cholesterol-lowering drugs called statins are often used. Hypertension is treated by avoiding excessive salt intake and using general antihypertensive drugs as needed. Good control of these risk factors suppresses the progression of arteriosclerosis and prevents myocardial infarction.



Prevention of sarcopenia (muscle wasting)

Protein-rich foods such as soy products, fish, and meat should be consumed. Amino acid supplements for leucine are said to be effective in preventing general sarcopenia and may also be effective for Werner syndrome patient.

Prevention of Osteoporosis

Consumption of foods containing vitamin D, calcium intake are recommended to prevent osteoporosis.

Calcium intake

Foods containing vitamin D

Prevention/treatment of skin wounds (intractable ulcers)

It is important to prevent foot blisters by choosing well-fitting shoes as foot wounds take long to heal and greatly interfere with daily life. Thin and tough skin can break or tear easily due to the pressure applied by the underlying bones. Such wounds are at risk of developing into deep ulcers. Special shoes (orthoses) may be used to protect areas with high pressure or that will likely develop into wounds. Areas prone to ulcers such as the Achilles tendon, heels, feet, and elbows should be protected and assessed on a daily basis. If ulcers form, symptomatic treatment such as cleaning, disinfection, protection, and moisture retention is the primary treatment. However, surgery to graft skin from other areas of the body may be effective in some cases.

Early Detection of Cancer

Early detection and treatment are important because cancer develops more often than usual. Therefore, undergoing regular cancer screening is recommended.

3 Diabetes

What is diabetes?

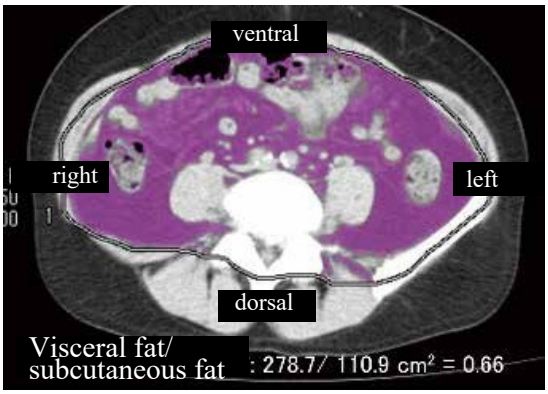
Diabetes is a disease that occurs when the insulin levels are low or the insulin is ineffective, resulting in high blood sugar levels (glucose concentration in the blood).

Symptoms including “recently, my mouth is dry”; “I go to the bathroom more often and pee more”; and “I get tired easily” may appear. Meanwhile, other patients may remain asymptomatic.
What is alarming about diabetes is that other diseases may develop if it is left untreated.
In addition to problems such as “blindness,” “accumulation of waste products in the body due to the inability to urinate properly (uremia),”and “rotting of the foot,” it increases the risk of heart disease, stroke, and even cancer and dementia.

Main symptoms

Diabetes and Werner syndrome

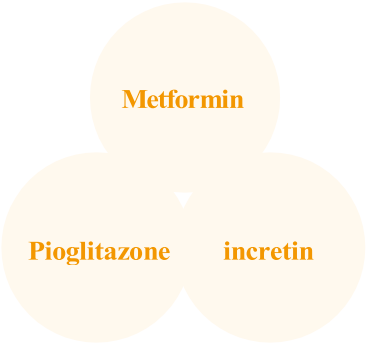
According to a previous survey conducted in Japan, 60% of patients with Werner syndrome, regardless of gender, develop diabetes as a complication. One of the causes is fat accumulation around the abdomen, which contributes to the patient’s metabolic syndrome appearance. As a result, sensitivity to insulin decreases.



Computed tomography scan: the purple-colored area indicates visceral fat.

Treatment for diabetes

The intake of snacks and juice drinks should be limited. Eating until 70%–80% full is highly encouraged. Performing various exercises as tolerated (exercises using plastic bottles, etc.) are effective. Metformin and pioglitazone are known to be effective. Recently, incretin-related drugs have also been shown to be effective.

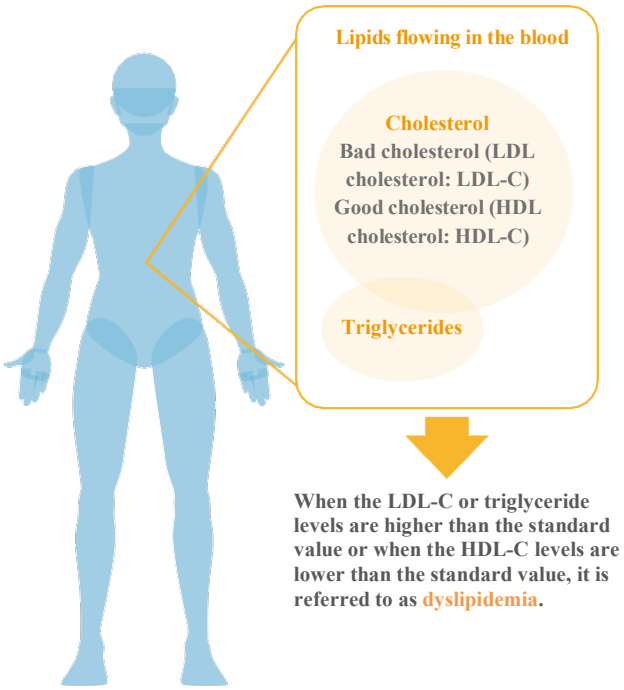


4 Dyslipidemia

Dyslipidemia and arteriosclerosis

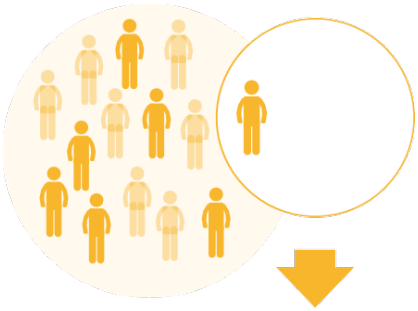
Fats (lipids) such as cholesterol and triglycerides circulate freely in the blood.

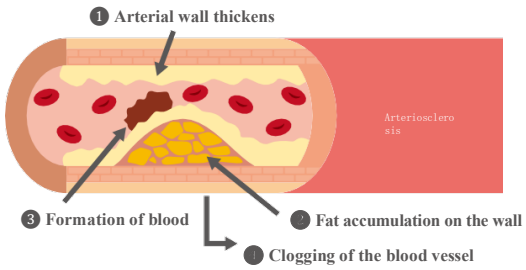
Cholesterol is further divided into bad cholesterol (LDL-C) and good cholesterol (high-density lipoprotein cholesterol [HDL-C]). When the LDL-C or triglyceride levels are higher than the standard value or when the HDL-C levels are lower than the standard value, it is referred to as dyslipidemia. Dyslipidemia increases the likelihood of developing arteriosclerosis and is a risk factor for heart diseases, such as angina pectoris and myocardial infarction, and stroke.



Dyslipidemia, arteriosclerosis, and Werner syndrome

According to a previous survey conducted in Japan, half of Werner syndrome patients develop dyslipidemia (70% with high LDL-C levels, 80% with hypertriglyceridemia, and 30% with low HDL-C levels).
Similar to diabetes, patients develop a metabolic syndrome appearance, leading to insensitivity to insulin, which is believed to be one of the causes of dyslipidemia. Although angina pectoris and myocardial infarction commonly develop in people with Werner syndrome compared with that in the general population, the incidence of stroke is relatively low.





Treatment for dyslipidemia

Lifestyle modification, limited animal fat intake, and standard treatment such as the administration of statin drugs are used to prevent arteriosclerosis.

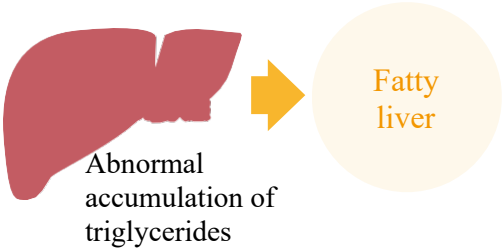
5 Fatty liver

About fatty liver

Fatty liver is defined as an abnormal accumulation of triglycerides, a type of lipid, in the liver.

Alcoholic fatty liver due to alcohol consumption is well known; recently, non-alcoholic fatty liver, in which fat accumulates in the liver even with low alcohol consumption, is drawing attention.

Both may progress to diseases such as cirrhosis and liver cancer.

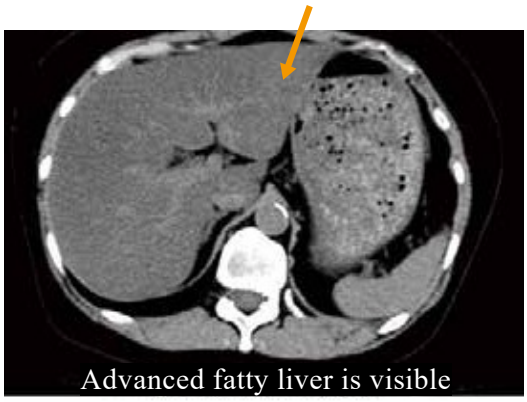


Fatty liver and Werner syndrome

Approximately 30% of patients with Werner syndrome develop fatty liver.

In general, non-alcoholic fatty liver is more common in obese people, whereas Werner syndrome patients develop fatty liver even if their body weight is significantly below normal.

No study has reported that cirrhosis or liver cancer is common in Werner syndrome patients with fatty liver.



Abdominal computed tomography scan

Treatment for dyslipidemia

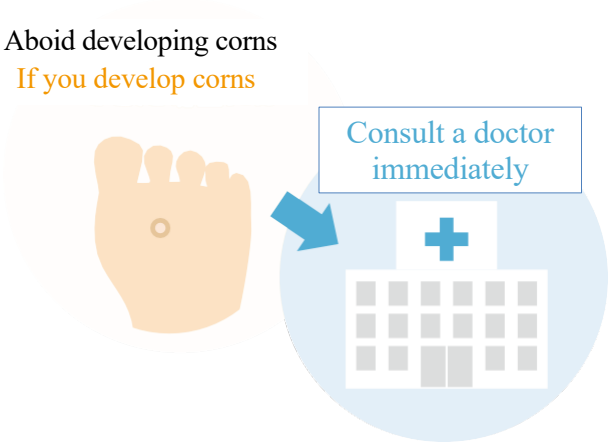
Fatty liver has no specific cure.
A previous study reported that the fatty liver in a Werner syndrome patient improved with the use of astaxanthin.

6 Infection

Infection of skin ulcers

Werner syndrome patients are prone to skin disorders and tend to develop corns (clavuses) on the soles of the feet. The skin surface where the corn is located becomes inflamed and collapses, often resulting in deep ulcers. This also occurs frequently in patients with diabetes. Since Werner syndrome is often complicated by diabetes, patients with this syndrome are prone to developing plantar ulcers. The ulcers develop not only on the soles of the feet but also on the knees and elbows.

Foot care is of utmost importance.
Patients should avoid developing corns. Otherwise, immediate medical advice should be sought. The attending physician should be consulted immediately if the skin becomes gouged and if an ulcer is suspected. At this point, the ulcer is not yet infected.



The ulcer may be infected if the surrounding area becomes red and swollen, feels hot, or is painful. In such cases, treatment is required.

The ulcer can be treated with oral antimicrobial drugs if the red and swollen area (redness) surrounding the ulcer measures 2 cm in diameter, although the depth of the ulcer should also be taken into consideration. In such case, the treatment will generally take two to four weeks. However, the possibility of undergoing intravenous antimicrobial treatment is relatively high if the inflamed area is not within 2 cm from the ulcer or the ulcer is deep. Hospitalization is often required in such cases, and treatment will generally take two to four weeks. The doctor may decide to switch to oral medication administration upon completion of intravenous treatment.

Not only the skin and subcutaneous tissue but also the joints and bones may also become infected as the ulcer extends more deeply. Such cases are called arthritis or osteomyelitis. If this occurs, hospitalization and treatment with intravenous antimicrobials are required. Surgical excision is often necessary if antimicrobials alone do not alleviate the infection. In general, the treatment period will take at least 4 weeks if the joints and bones are infected.

If repeated infection occurs, an infection caused by bacteria that are resistant to antimicrobials (resistant bacteria) is suspected. Intravenous treatment is necessary in such cases even if the infection is mild as it may not be possible to it treat with oral medications.

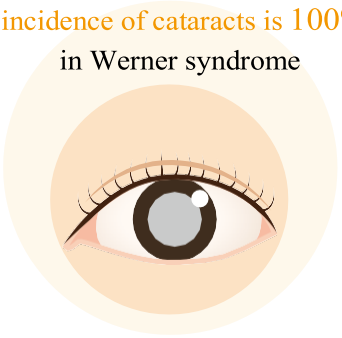
Other infections to look out for

Various infectious diseases can be prevented with vaccines such as pneumonia and influenza. Immediate consultation with a doctor and vaccination are recommended.

7 Diseases of the eye

Patients with Werner syndrome, also known as "progeria," experience premature aging. The eyes are no exception and tend to develop age-related conditions. The most common eye condition associated with aging is **cataract**. Werner syndrome patients develop cataracts as early as 20 years old. On average, they develop cataracts at the age of 30 years.

The incidence of cataracts is 100% in Werner syndrome



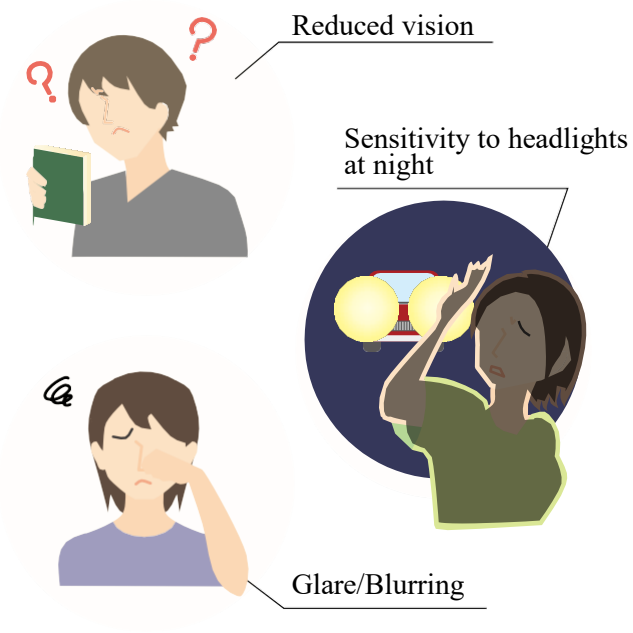
Approximately 10% of the general population develops cataracts at the age of 50 years, and more than 80% by the age of 70 years. By contrast, 100% of Werner syndrome patients develop cataracts. Hence, some patients are diagnosed with Werner syndrome after developing cataracts.

A cataract is a disease in which the lens becomes cloudy and vision is reduced. Its symptoms include reduced vision, glare, and blurred vision. Initial symptoms may not only include decreased vision but also sensitivity to headlights at night.

Myopia may also worsen as the cataracts progress. The diagnosis can be easily made by a slit lamp examination, which is commonly used in ophthalmology clinics, and a general practitioner can make the diagnosis. However, as early-onset cataracts have various causes, Werner syndrome will not be suspected based solely on these findings.

However, as a general rule, Werner syndrome is suspected if bilateral nuclear cataracts are observed at a young age as cataracts in Werner syndrome patients are characterized by opacity and hardening of the center (nucleus) at a younger-than-average age.

Main symptoms



Cataracts can be treated with small-incision (2–3 mm incision) lens reconstruction without serious complications.

Phacoemulsification and aspiration are generally used to ultrasonically break up and suck out the turbidity. An artificial lens is placed into the remaining pouch (lens capsule). In the case of Werner syndrome, the hardened nucleus, which is observed in many patients, tends to pose challenges during surgery. That said, serious complications such as incomplete wound closure do not occur as the incision wound is smaller compared with that in previous surgical procedures.

One characteristic postoperative complication that may occur is **cystoid macular edema** (swelling in the macula, the most important part of the retina, which causes symptoms such as blurred and distorted vision). It improves with eyedrops alone in patients with cataract alone, thanks to advances in postoperative eyedrops. However, care must be taken with Werner syndrome, as cystoid macular edema may become intractable and lead to permanent vision loss. It is generally caused by inflammation, but the factor that triggers the onset of cystoid macular edema in Werner syndrome patients remains unknown. Therefore, the exact incidence is unknown, but it does not seem to be common. Overall, cataract surgery can be safely performed on Werner syndrome patients, thanks to advances in cataract surgery techniques.

8 Sarcopenia and osteoporosis

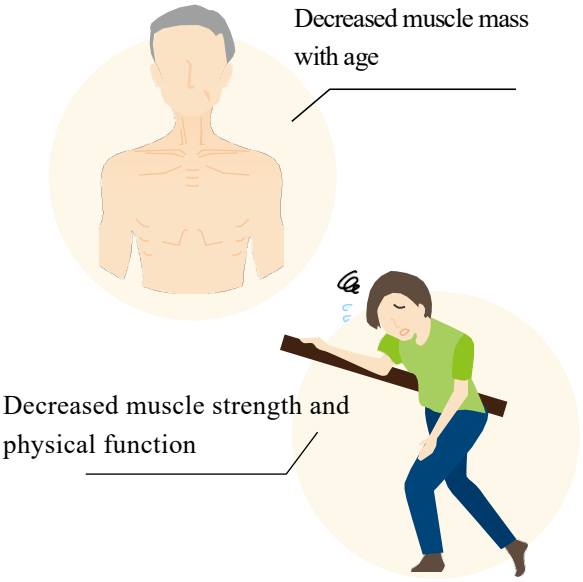
What is sarcopenia

Sarcopenia is a condition characterized by reduction of muscle mass with age, and decrease in muscle strength and walking speed.

Sarcopenia may require long-term care in the future and cause some difficulties in daily life. In other words, sarcopenia prevents an individual from living a long and healthy life.

The muscle mass of the hands and feet start to decrease at a relatively young age (below the age of 40 years) in Werner syndrome patients. Although the cause is unclear, it may be attributed to the patient's limited mobility due to the presence of contractures (impaired joint movement) and skin ulcers on the soles of the feet, which are common among Werner syndrome patients.

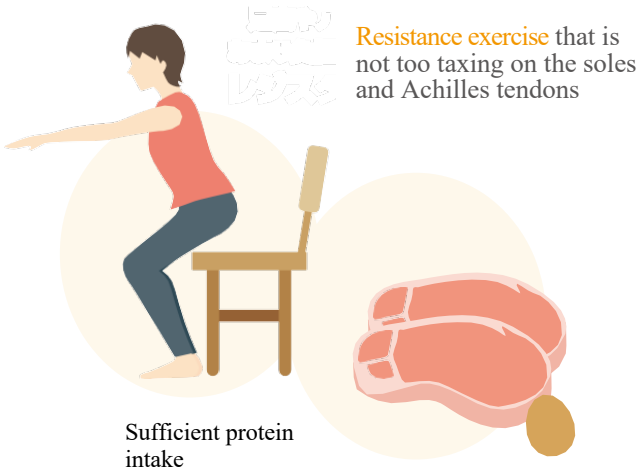
Main symptoms



In fact, some Werner syndrome patients who engage in habitual resistance exercise (exercise that puts a load on the muscles, so-called muscle training) do not experience a reduction in the skeletal muscle mass. As such, sarcopenia may be preventable by performing appropriate exercise.

Prevention

Engaging in resistance exercise that does not put too much strain on the soles of your feet and the Achilles tendons is recommended, and sufficient protein (ingredients for muscle) intake is highly encouraged.
Each meal should contain at least 25g of protein. However, if chronic kidney disease and other diseases develop, a family doctor should be consulted.



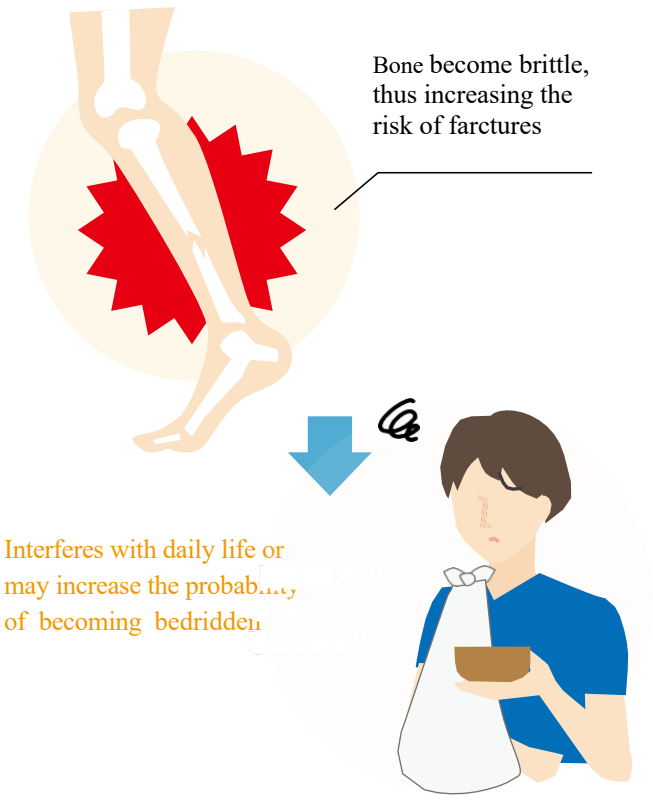
What in osteoporosis

Osteoporosis is a disease in which the bone mass decreases with age, making the bones brittle and prone to fractures.

Osteoporosis is also a dangerous condition that may affect an individual's life expectancy as fractures can interfere with daily life and increase the probability of becoming bedridden. Patients with Werner syndrome are prone to osteoporosis at a young age.

Although it depends on the patient's age, a previous Japanese survey reported osteoporosis in 41% of Werner syndrome patients, while an overseas study reported osteoporosis in >90% of patients. In patients with Werner syndrome, osteoporosis is more severe in the lower limbs than that in the vertebrae (spine).

Main symptoms



Prevention and treatment

Conventional osteoporosis medications can be used for treatment.

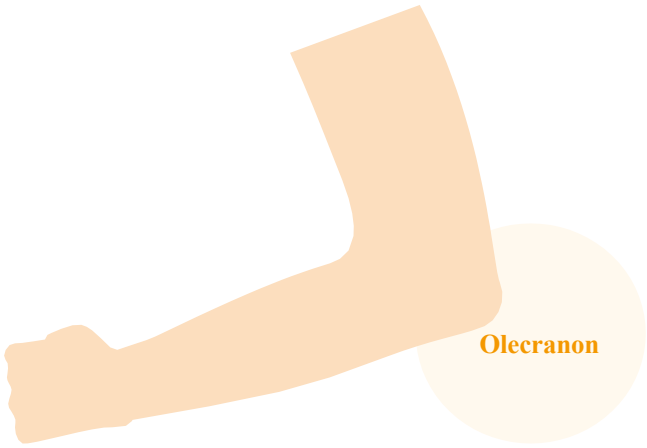
Similar to sarcopenia, performing exercises is one of the preventive measures. Vitamin D intake promotes the absorption of calcium from food and is important for the prevention of osteoporosis. As with sarcopenia, adequate dietary protein intake is also important.

Exercise is important for the prevention of both sarcopenia and osteoporosis. It is important to avoid excessive exercise and incorporate exercise that is not too taxing since some Werner syndrome patients are prone to developing ulcers on the soles of their feet and some have joint contracture.

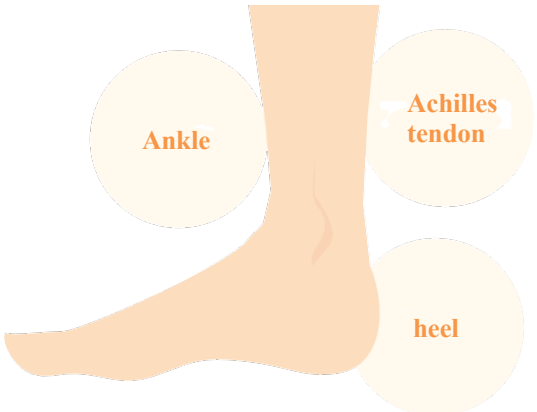
9 Foot ulcers (hard-to-heal wounds)

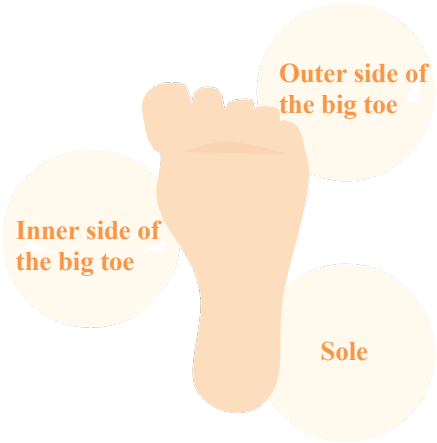
Werner syndrome causes hard-to-heal wounds on the skin. The most common areas are the elbows and below the knees.

Hard-to-heal wounds on the elbow form on **the lateral protruding portion of the elbow (olecranon)**.
If the wound may be extended to the elbow with thin skin, you need to consult the dermatologist



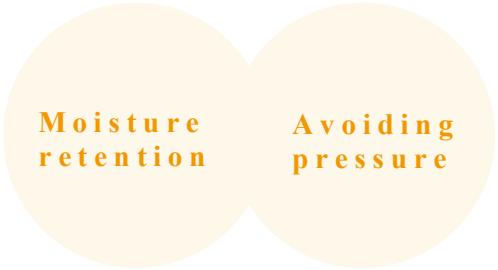
The areas where hard-to-heal wounds are likely to form include the Achilles tendon, ankles, heels, soles, inner side of the big toe, and outer side of the small toe.
The wound may extend deeply into the joint or bone because the skin is thin.





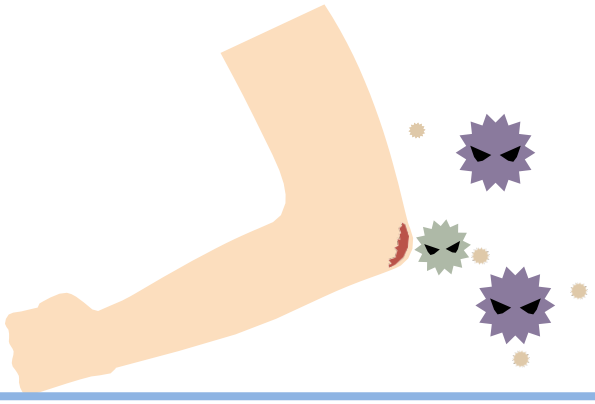
Prevention

Prevention is important because once a wound forms, it is difficult to heal. Moisture retention and avoiding pressure are important. A callus may form as a sign of pressure. The callus should be treated as the skin will be pressed further and a wound will possibly form if it is left unattended. **Well-fitting shoes should be worn to prevent the formation of calluses.**



Treatment

Bacteria may accumulate inside the hard-to-heal wounds. They should be removed to reduce the risk of spread. The tissues infected with bacteria should also be removed. Surgery may be performed to close the wounds that do not heal easily.

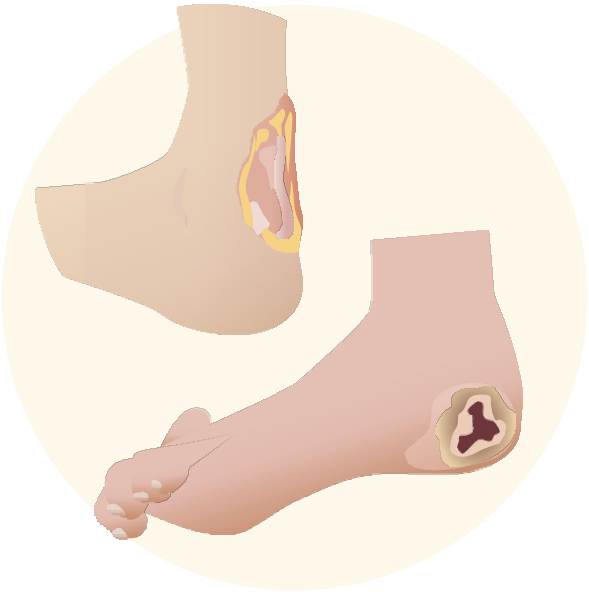


Prevention and treatment of intractable ulcers

One of the characteristics of Werner syndrome is that **wounds easily form on the skin (ulcers) and are hard to heal**. Wounds frequently develop in the **weight-bearing part of the sole of the foot**. In addition, they are common in areas where pressure is likely to be applied such as the **Achilles tendon, ankle joint, and elbow joint.**

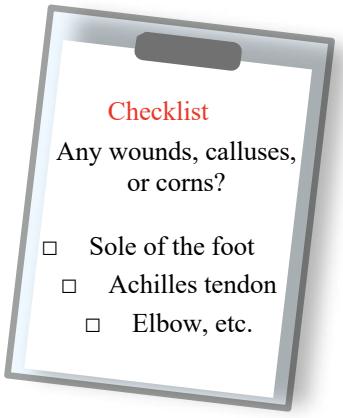
The wounds are difficult to heal in these areas because the skin has thickened/toughened and the amount of fat is relatively low. It is as if the cushion has been removed, and the bone comes in direct contact.

Moreover, poor blood flow due to narrowing of the blood vessels, calcium oxide formation in the skin, and deformation of the joints are also thought to cause ulcer formation.



The callus should be treated as the skin will be pressed further and a wound will possibly form if it is left unattended. **Well-fitting shoes should be worn to prevent the formation of calluses.** Prevention is important because once a wound forms, it is difficult to heal. Moisture retention and avoiding pressure are important. A callus may form as a sign of pressure.

The soles of the feet, Achilles tendons, and elbows should be assessed for presence of scratches, calluses, and corns. An ointment or plaster (various dead-skin-softening topical agents containing urea) that softens dead skin should be applied as soon as possible if thickened dead skin such as calluses or corns begin to form. Dead-skin-softening topical agents and plasters are sold at pharmacies, but a specialist such as a dermatologist should be consulted first. Scissors are used in some cases to remove calluses and corns that do not come off with ointment or plasters alone. However, a specialist such as a dermatologist should be consulted as doing so on your own may lead to wound formation.



If a callus or corn is left unattended, a wound will form in the center and will take a long time to heal. Care must be taken to prevent bacterial infection if a wound forms. It should be kept clean by washing it with soap every day. Ointment should be applied for wound healing after rinsing thoroughly. If necrotic areas are noted, a drug that dissolves them should be used. If red granulation occurs, an appropriate medication should be applied to further raise the granulation tissue and eventually reduce the wound size. If bacterial infection occurs, disinfectants, ointments that suppress infection, and oral antibiotics are needed. If bacterial infection is noted or if the scratch increases in size, it will be difficult to heal; hence, a dermatologist should be consulted as soon as possible.

A dermatologist should be consulted as soon as possible.

10 Tumor

What is a malignant tumor?

A malignant tumor is a tumor in which certain cells disregard the order established in the body and proliferate, spread to the surrounding tissues, or cause metastasis. Malignant tumors include epithelial tumors (cancer), non-epithelial tumors (such as sarcoma), and blood tumors such as leukemia. In general, cancer is common, while non-epithelial tumors are rare. When the incidence of cancer and that of non-epithelial tumors are compared, the ratio is about 10 to 1.

Malignant tumors and Werner syndrome.

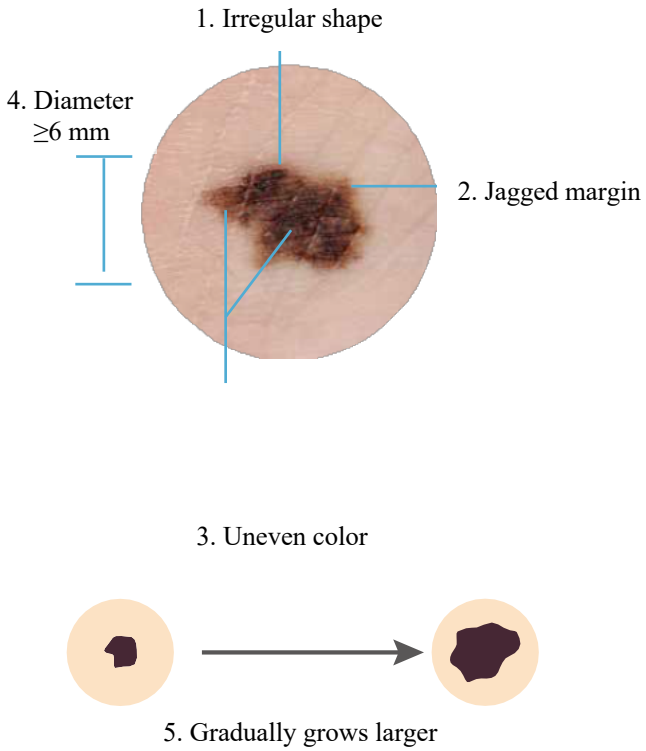
According to a previous survey conducted in Japan, malignant tumors were found in approximately 30% of people with Werner syndrome. They tend to develop at a relatively young age (40 years). Non-epithelial tumors, which rarely develop, are common in Werner syndrome patients with a cancer to non-epithelial tumors ratio of 1 to 2. Among them, malignant melanoma, malignant fibrous histiocytoma, and meningeal tumors are common. With regard to cancer, thyroid cancer is commonly observed. Moreover, it is not uncommon for a Werner syndrome patient to develop multiple cancers (multiple tumors), in which several comorbid malignant tumors develop. Recently, the number of cancer cases has dramatically increased as the life expectancy of people with Werner syndrome increases.

Screening and treatment for malignant tumors

Patients with Werner syndrome should be assessed for presence of malignant tumors. Regular medical checkups and cancer screening lead to early detection and treatment. Patients should undergo blood and urine tests at least once every 3 months, and chest X-rays, thyroid ultrasound, abdominal ultrasound, fecal occult blood tests, etc. every 6 months to 1 year. A whole body assessment should be performed daily. In particular, a doctor should be consulted if an irregularly shaped “mole” develops on the skin or if a “swelling” under the skin increases in size.

The treatment for malignant tumors that develop in Werner syndrome patients is the same as that in the general population. Some patients express concern about undergoing surgery because the wounds that form on their hands and feet do not easily heal. Wounds caused by surgery (e.g., lung cancer) on the central part of the body (trunk) easily heals, and the patients undergo the same procedures that are usually performed.

Characteristics of malignant mole melanoma



Ministry of Health, Labour and Welfare Research Grant
Intractable Disease Policy Research Project
Multidisciplinary research aimed at improving the medical standards and QOL for progeria

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Cooperation：Werner Syndrome Patient/Family Group

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