Management guideline for Werner syndrome

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1. Dyslipidemia and fatty liver associated with Werner syndrome

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Introduction

Arteriosclerosis is one of the two leading causes of death in Werner syndrome patients, along with malignancy. Among the various forms of arteriosclerosis they develop, coronary artery diseases and peripheral arterial disease have a high incidence, and the latter plays a role in making skin ulcer in Werner syndrome patients to be refractory. Arteriosclerosis in Werner syndrome is considered to be one of the features of disease-specific premature aging, while disorders of carbohydrate metabolism and lipid metabolism associated with Werner syndrome also act as promoting factors. Insulin resistance associated with a fatty liver (non-alcoholic fatty liver disease [NAFLD]) and accumulation of visceral fat have been considered to be greatly involved in these metabolic abnormalities. Recently, the ratio of hepatocellular cancer caused by NAFLD or non-alcoholic steatohepatitis (NASH) in all hepatocellular cancers has reportedly risen in the general population, thus the management of these diseases in Werner syndrome patients is also important.

It has been said that Werner syndrome patients develop dyslipidemia/fatty liver at a high rate. The previous guidelines indicated that hypercholesterolemia occurred in 53% of 15 Werner syndrome patients. However, there have been no data obtained by an extensive literature screening on the incidence of dyslipidemia and characteristics of dyslipidemia/fatty liver in Werner syndrome patients. To address this issue in the current edition of the guidelines, we screened cases reported on PubMed and Medical Online from 1996 to 2016 (98 articles, 119 cases), from which 44 cases (26 males with a mean age of 45.6 years)[1-36] including some descriptions or data relating to either lipid or fatty liver in the articles were selected for analysis (reports before 2005: 26 cases). Considering that Werner syndrome is likely to be associated with malignant diseases and that an onset of a malignant disease would possibly affect the lipid metabolism or fatty liver, the subjects were divided into 13 Werner syndrome patients with a malignant disease (6 males; mean age, 50.4 years) and the remaining 31 Werner syndrome patients with either no malignant diseases or no descriptions about malignant diseases (20 males; mean age, 43.6 years) for analysis. As to these data, the Werner syndrome patients with a malignant disease and the other Werner syndrome patients are represented as a group with M and a group without M, respectively, in the guidelines.

Meanwhile, the case reports obtained through the above literature search included neither adequate description on the treatment nor records on any treatment effect/rates of achieving control target values. Additionally, an anti-hyperlipidemic drug has shown remarkable progress in recent years. Under such circumstances, we researched treatments for dyslipidemia/fatty liver and their effects in 11 patients with no malignant diseases at the time of data acquisition (4 males and 7 females; mean age, 50.7 years [range 3960 years]) among 12 patients (5 males and 7 females; mean age, 50.1 [range, 3960 years]) under follow-up in Chiba University whose detailed data on their lipid levels and fatty livers from 2010 were available. We also examined patients with data of a liver-to-spleen attenuation ratio (L/S ratio), which was considered to reflect the degree of fatty liver.
Results obtained through literature search are represented as SR and results of case examination in Chiba University as CS in these guidelines.

Ⅰ. Dyslipidemia

Q1. How frequently does dyslipidemia occur in Werner syndrome? What type of dyslipidemia appears in these patients?
A1. The incidence of dyslipidemia in Werner syndrome patients is high at 85%. The most common type of dyslipidemia is hypertriglyceridemia occurring in 76%, followed by hyper-LDL cholesterolemia/non-HDL cholesterolemia in 68%, and hypo-HDL cholesterolemia in 32% (SR).

Descriptions on the presence or the absence of dyslipidemia were found in 41 (the group with M: 13 patients, the group without M: 28 patients) of 44 patients, and 35 of whom, or 85.4% developed dyslipidemia (the group with M: 84.6%, the group without M: 85.7%). Data on lipid were confirmed in 25 patients (the group with M: 7 patients, the group without M: 18 patients); hypertriglyceridemia (TG) accounted for 76.0% (the group with M: 57.1%, the group without M: 83.3%), hyper-LDL cholesterolemia/non-HDL cholesterolemia for 68.0% (the group with M: 42.9%, the group without M: 77.8%), and hypo-HDL cholesterolemia for 32.0% (the group with M: 14.2%, the group without M: 38.9%).

Q2. What are the characteristics of Werner syndrome with dyslipidemia?

A2. Werner syndrome with dyslipidemia develop diabetes at a high rate (90% or higher). The mean BMI of Werner syndrome with hypertriglyceridemia (TG) was 18.2, indicating lack of association with obesity (SR).

Records on the presence or the absence of diabetes were found in 33 out of 35 Werner syndrome patients with dyslipidemia, and 31 patients, or 93.9% of whom developed diabetes (the group with M: 88.9%, the group without M: 95.8%), showing an extremely high incidence of diabetes. Complication of arteriosclerosis were found in 4 Werner syndrome patients with dyslipidemia; they developed atherosclerosis with a mean age of 41 years , indicating premature arteriosclerosis in Werner syndrome.
Nineteen Werner syndrome patients with hypertriglyceridemia had a mean BMI of 18.2 (the group with M: 17.6, the group without M: 18.4), the maximum BMI of 22.8, and the minimum BMI of 12.49. There were 9 underweight patients who fell below 18.5 in BMI (47.3%) (the group with M: 7 patients, 46.7%; the group without M: 2 patients, 50%). The mean BMI of 9 patients with normal triglyceridemia was 16.5, and 8 of whom (88.9%) had a BMI not exceeding 18.5; there was no significant difference in BMI among normo- and hyper- triglyceridemic patients, but was a tendency to be more "underweight" in normo-triglyceridemic patients than those with hypertriglyceridemia. Thus, Werner syndrome patients with hypertriglyceridemia tended to have a higher BMI than patients with normal triglyceridemia in Werner syndrome; however, its characteristics were different from those in hypertriglyceridemic subjects in general population, who are strongly complicated with obesity.

Q3. What are the rates of achieving the lipid control target values in patients with Werner syndrome? Which drugs are effective?
A3. The rates of achieving the lipid control target values are high at 91% for LDL-C, 91% for HDL-C, and 82% for TG. Strong statin is mainly used as an antidyslipidemic drug and contributes to achieving the control target values (CS).

Of 12 Werner syndrome patients in CS, diabetes was documented in six, glucose intolerance in one, lower leg ulcer in nine, and peripheral arterial disease (PAD) in three (all developed diabetes and lower leg ulcer), but none had a history of myocardial infraction. Thus, there were six patients who were classified as the high risk group according to the categorization in the Japan Atherosclerosis Society (JAS) Guidelines for Prevention of Atherosclerotic Cardiovascular diseases 2017[37)].
Among 11 Werner syndrome patients who did not have malignant disease, five were

taking antidyslipidemic drugs, one was neither taking a statin nor achieved the LDL-C control target value based on risk factors, one had HDL-C below 40 mg/dL, two had TG levels of 150 mg/dL or higher; thus, taking all together, eight were diagnosed with dyslipidemia (a patient who met either criterion) (73%). All patients who were taking statin achieved the LDL-C control target value, and the achievement rates for LDL-C, TG, and HDL-C reached markedly high to 91%, 82%, and 91%, respectively. Antidyslipidemic drugs administered to the patients were all strong statins (atorvastatin, rosuvastatin, and pitavastatin).

The LDL-C level of Werner syndrome patients complicated with diabetes, which is classified as a high risk condition in JAS guidelines, was 84.5 ± 21.4 mg/dL (minimum: 51.0 mg/dL, maximum: 105.4 mg/dL), indicating successful control compared with the mean LDL-C level diabetic patients in general population [38)]who received special health checkups (male: 114.0 mg/dL, female: 122.9 mg/dL). Similarly, the LDL-C level of Werner syndrome patients with PAD, also a high-risk condition in JAS Guidelines, was 75.1 ± 23.2 mg/dL (minimum: 51.0 mg/dL, maximum: 97.4 mg/dL), which was a better outcome compared with special health checkup results of patients with a history of cerebral vascular disorder [38)], a high-risk condition as with PAD (male: 115.7 mg/dL, female: 123.2 mg/dL). As such, the rates of Werner syndrome patients achieving the lipid control target values reached 100% in high risk conditions, suggesting that the lipid was quite successfully controlled in high-risk Werner syndrome patients, compared with the approximately 60% achievement rate of LDL-C control target value in the general population with high risk conditions (with a history of diabetes or cerebrovascular disorder) based on special health checkup data[38)].

Ⅱ. Fatty liver

Q4. What are the characteristics of fatty liver in patients with Werner syndrome?
A4. Werner syndrome with fatty liver had a mean BMI of 18.8 and a maximum BMI of 22.6, and 83% of these patients are underweight (SR).

Descriptions of fatty liver were found in 12 (the group with M: 10 patients, the group without M: 2 patients) of 44 Werner syndrome patients, with a mean BMI of 18.8 (the group with M: 18.7, the group without M: 19.3). Among them, only two patients had a BMI of 22 or higher (in the group without M), and the maximum BMI was 22.6. In contrast, the prevalence of fatty liver (non-alcoholic fatty liver disease: NAFLD) in the general population is around 30% and increases with the degree of obesity. The reported

incidences of NAFLD in individuals with a BMI of ≥28, 25-<28, 23-<25, and <23 are approximately 85%, 60%, 40%, and 10%, respectively. Accordingly, the main characteristic of fatty liver in Werner syndrome patients would be that even "underweight" patients develop fatty liver at a high rate. Additionally, 91.6% of these 12 Werner syndrome patients with fatty liver had concomitant dyslipidemia (the group with M: 90.0%, the group without M: 100%) and 90.9% had disorders of carbohydrate metabolism (the group with M: 90.0%, the group without M: 100%), indicating that they also developed other metabolic disorders at a high rate.

Q5. Are there any differences in biochemical data between Werner syndrome patients with fatty liver and those without fatty liver?
A5. The liver-to-spleen attenuation ratio (L/S ratio) showed a positive correlation with HDL-C levels and a negative correlation with TG levels. It does not correlate with the liver enzyme levels (CS).

The following are analytical results of 9 patients with data on L/S ratios and without malignancy in CS. Four patients, or 44%, had concomitant fatty liver (L/S ratio not exceeding 1.0: FL). The mean BMI of these patients was 16.7 (maximum BMI: 17.8, minimum BMI: 15.5), consisting only of "underweight" patients (the mean BMI of non-fatty liver patients [non-FL]: 17.1). When individual laboratory test values (LDL-C, HDL-C, non HDL-C, TG, AST, ALT, γGTP, ChE, and AST/ALT ratio) of the fatty liver (FL) group were compared with those of the non-FL group (t-test) , the HDL-C levels stood at 46.0 ± 8.1 mg/dL in the FL group and 64.6 ± 13.3 mg/dL in the non-FL group, showing a significantly low value in the FL group ($P < 0.05$). As to the correlation of the L/S ratio with each laboratory value, it showed a positive correlation with the HDL-C levels ($R^2 = 0.609$, $p = 0.013$) and a negative correlation with the TG levels ($R^2 = 0.509$, $p = 0.031$).

Q6. Have there been any Werner syndrome patients with hepatocellular cancer?
A6. One of the 44 Werner syndrome patients reportedly developed hepatocellular cancer, though no specific description on a relationship with fatty liver was found (SR).

One report out of 44 indicated that hepatocellular cancer occurred in a 40-year-old male patient [23]. Although we cannot say for certain due to lack of description on a non-cancerous hepatic tissue, he has tested negative for hepatitis B and C viruses and

autoimmune hepatic disease, and thus it cannot be denied that hepatocellular cancer may be originally caused by NAFLD or NASH in this case.

Summary

1. Dyslipidemia

As described in the review article by Epstein, et al. in 1966[39] and in the report by Yokote, et al. in 1989[40], Werner syndrome is likely to be accompanied with dyslipidemia. We comprehensively collected recent relevant case reports (from 1996) and examined them according to the diagnostic criteria specified in the Japan Atherosclerosis Society (JAS) Guidelines for Prevention of Atherosclerotic Cardiovascular diseases 2017[37]. The results showed that (1) dyslipidemia occurred in 85% of Werner syndrome patients, 90% or more of whom developed diabetes; (2) all types of dyslipidemia (i.e. hyper-LDL cholesterolemia/non-HDL cholesterolemia, hypertriglyceridemia, and hypo-HDL cholesterolemia) were observed in Werner syndrome, although hypertriglyceridemia was relatively common, and (3) Werner syndrome patients developed hypertriglyceridemia without obesity ; the mean BMI of affected patients was 18.2. Mori, et al. examined abdominal CT images of three male and one female patients[14], which indicated that two male patients had a visceral fat area of >100 cm^2 and the other two patients showed a high visceral fat area/subcutaneous fat area ratio. There remain many unclear points about the molecular mechanism of accumulated visceral fat in Werner syndrome, but the accumulation of visceral fat is considered to increase insulin resistance, leading to dyslipidemia or disorder of carbohydrate metabolism. As to hyper-LDL cholesterolemia, Yokote and Mori et al. reported that thickened Achilles tendon and hypercholesterolemia occurred in six out of 10 Werner syndrome patients in their facilities[40] and five of them showed a decrease in the LDL receptor activity[41]; thus, it might be plausible that Werner syndrome itself possesses some sort of mechanism to decrease the LDL receptor activity. Given that increased LDL-C level is a disease-specific postnatal feature in Werner syndrome, it might be possible to assume that hypercholesterolemia in Werner syndrome has a risk equivalent to familial hypercholesterolemia considering the notion of cumulative LDL-C which has been recently proposed.

Of course, it remains unclear whether dyslipidemia occurs before diagnosis of Werner syndrome. However, considering that macrophages are likely to become foamy in Werner syndrome [42] and that Werner syndrome is characterized by overlapping risk factors including disorders of carbohydrate metabolism and accumulated visceral fat, it is necessary to proactively and adequately control dyslipidemia. The analyses of 12

Werner syndrome patients in CS revealed that an intensive treatment using strong statin might possibly achieve the lipid control target values. The rate of achieving the LDL-C control target value of high-risk patients in the special health checkup was around 60%, while that in Werner syndrome patients was 90% or higher, which might be because both healthcare professionals and patients have recognized the association between Werner syndrome and arteriosclerosis and proactively treated dyslipidemia in Werner syndrome.

2. Fatty liver

According to the questionnaire investigation to 102 Werner syndrome patients conducted by Imura, et al. in Japan in 1985, 35.4% of these patients had mild hepatic dysfunction, and fatty liver was suggested as its cause[43]. The analysis on 12 Werner syndrome patients in CS confirmed that around 40% of them developed fatty liver. Unlike common fatty liver disease, both the SR and CS analyses showed that fatty liver occurred in normal-weight and underweight Werner syndrome patients, and that the rates of developing dyslipidemia and glucose intolerance were extremely high in them. Similar mechanism for the onset of fatty liver in general population[44], i.e. excessive free fatty acids inflow into the liver from the accumulated visceral fat, would underlie for the onset of fatty liver in Werner syndrome, although Werner syndrome-specific mechanism might be involved in the onset of fatty liver.

Recently, an onset of hepatocellular cancer caused by NAFLD or NASH has become focus of interest. Hepatocellular cancer observed in a 40-year-old Werner syndrome patient of SR may have occurred in association with Werner syndrome, but the possibility of its occurrence in association with fatty liver or NASH cannot be excluded. Therefore, a treatment to ameliorate fatty liver also needs to be established. There is evidence about treatments with pioglitazone[45] [46], vitamin E[47], and ursodeoxycholic acid[48] in the general population, while Takemoto, et al. reported that astaxanthin, a kind of carotenoid, improved fatty liver in Werner syndrome [36]. Another study also showed an effect of resveratrol to improve fatty liver in a Werner syndrome-model animal[33]. Further therapeutic drug development is expected.

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2.Werner syndrome and Sarcopenia

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Introduction

Sarcopenia is characterized by a significant decrease in skeletal muscle mass and muscle weakness or a decline in the physical function with age[1)]. It is generally known that the skeletal muscle area decreases by 25–30% and the muscle strength by 30–40% by the age of 70 compared with those in the 20s, and the muscle mass decreases by around 1–2% every year after the age of 50[2)]. Age-related decrease in skeletal muscle mass is caused by a reduction in skeletal muscle fibers and atrophy of each muscle fiber. A decrease in skeletal muscle fibers has been known mainly to represent a reduction in type IIa muscle (fast-witch fibers, white muscle)[2)]. Sarcopenia is a term coined from "sarco" denoting "flesh" and "penia" representing "poverty" in Greek[1,2)].

Sarcopenia is classified into primary (age-related) sarcopenia caused only by advancing age and secondary sarcopenia marked by decreases in skeletal muscle mass, muscle strength, and physical function associated with inactivity (disuse), diseases (progressive malignancy and organ failure), or malnutrition[1)].

Sarcopenia is known to be associated with risks of falling, physical function impairment, needing nursing care, and frailty in the elderly, and this condition has recently been taken seriously in light of care prevention in Japan[3)].

Q1. Are patients with Werner syndrome likely to experience skeletal muscle mass loss in the extremities and develop sarcopenia at a young age?

A1. Werner syndrome is frequently associated with a decrease in extremity skeletal muscle mass in adults (below the age of 40 years) as well. Although its contributing factors are still unclear, there are some cases where habitual resistance exercise has prevented a decrease in skeletal muscle mass. Therefore, appropriate intervention with habitual resistance exercise may be a useful preventive measure.

Explanation

A literature search on the relationship between Werner syndrome and skeletal muscle yielded only one article reported from Japan in 2017[4]. According to that report, nine patients with Werner syndrome (four males and five females) with the mean age of 48 ± 8.8 years (SD) (range,39-60 years) underwent a diagnostic test for sarcopenia based on indexes including decreases in the appendicular skeletal muscle mass index and the grip strength using the diagnostic criteria for sarcopenia (appendicular skeletal muscle index obtained by Dual-energy X-ray absorptiometry (appendicular skeletal muscle mass (kg) / Body height $(m)^2$): <7.0 kg/m^2 (male), <5.4 kg/m^2 (female) and Grip strength: <26 kg (male), <18 kg (female))[5] suggested by Asian Working Group for Sarcopenia.

As to the grip strength, two out of four male patients did not meet the diagnostic criteria for sarcopenia, whereas none exceeded the cutoff value of appendicular skeletal muscle indexes, the index of skeletal muscle mass. The researchers also assessed the accumulation of visceral fat (evaluated by abdominal CT) in the nine patients. An age-adjusted evaluation revealed that the decrease in skeletal muscle mass had been observed before the accumulation of visceral fats. All had decreased motor functions. The analysis based on the presence or absence of diabetes indicated that Werner syndrome patients with diabetes had higher body-mass indexes and more visceral fat than those without diabetes, while there was no difference in the skeletal muscle index between the two groups.

In our study, the appendicular skeletal muscle index was examined by the bioimpedance method in seven patients with Werner syndrome (four males and three females) with the mean age of 49.1 ± 6.8 years (range, 39-70 years). The results revealed that their appendicular skeletal muscle indexes were below the standard value (the cutoff values of the skeletal muscle indexes obtained by the bioimpedance method suggested by the Asian Working Group for Sarcopenia are <7.0 kg/m^2 for males and <5.7 kg/m^2 for females)[5] except for one male patient. He was 43 years old and had continued resistance exercise from his school days[6].

As described above, age-related sarcopenia is generally associated with a decrease in skeletal muscle fibers (especially, fast-witch fibers muscle) and atrophy of each muscle fiber, whereas it is still unclear whether similar changes appear in patients with Werner syndrome, because of the lack of detailed muscle biopsy findings in this patient population. Additionally, sarcopenia is diagnosed by low extremity skeletal muscle mass, as mentioned above, as an obligatory symptom and accompanied by a decline in

muscle strength or physical function (walking speed, etc.) [1,2,3,5]. Werner syndrome patients are likely to develop refractory plantar ulcer, which makes it impossible to measure their walking speed in some cases. Hand deformity also occurs in some cases, which brings difficulty in measuring grip strength, and thus it is not always easy to diagnose them with sarcopenia.

Summary

The decrease in skeletal muscle mass, as discussed above, frequently occurs in patients with Werner syndrome before the age of 40. Although the mechanism is still unclear, various potential factors including aged skeletal muscle, metabolic abnormality, and inflammation, or decreased amount of activity due to low physical function are considered, which are expected in the future progress of the research. On the other hand, a Werner syndrome patient who was not diagnosed with sarcopenia, as in the above example, has also been observed, suggesting possible prevention of sarcopenia by appropriate intervention (resistance exercise, etc.).

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3.Diabetes associated with Werner syndrome

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Introduction

Werner syndrome is a disease representing progeria. Its clinical finding that is first observed is loss of the pubertal growth spurt, followed by geriatric symptoms including atrophy and hardening of the skin, partial loss of the subcutaneous fat, changes in hair such as graying and balding, and cataract. Glucose metabolism disorders are also seen at a high rate, making this a typical metabolic disorder in patients with Werner syndrome[1,2].

Q1. How frequently do the Werner syndrome patients develop diabetes?

A1. Approximately 55% of them develop diabetes.

The review article published by Epstein in 1966 indicates that diabetes was observed in 55 (28 males and 27 females) out of 125 patients diagnosed with Werner syndrome[1]. In Japan, the results of the research on domestic Werner syndrome patients were reported by Imura, et al., of the Health and Welfare Ministry's specific disease hormone receptor mechanism research group (Etsurou Ogata Group) in 1984. These researchers conducted a questionnaire survey consisting of 1,930 questions to domestic hospitals equipped with at least 200 beds, and 181 patients participated in this survey. Furthermore, a glucose tolerance test was conducted in 90 patients, 50 of whom (55.6%) developed diabetes[3].

Goto et al. reported that around 70% of Werner syndrome patients developed type 2 diabetes or borderline diabetes based on the results of the literature review from 1966 to 2004[4]. They further extended the target year of review to 2008 to review the articles by year and reported that the incidence of diabetes in Werner syndrome patients remained unchanged regardless of year and that the mean age of onset of diabetes was 33.7, 39.7, and 39.3 years in 1966, 2004, and 2008, respectively, which revealed a delay in onset over time[5].

As a nationwide epidemiological survey in 2011, a questionnaire survey consisting of 6,921 questions was conducted in medical institutions with at least 200 beds, through which 396 Werner syndrome patients were newly confirmed, and clinical findings of 196 patients were obtained. The results revealed that 55.7% of these patients developed diabetes and 6.5% had borderline diabetes[6]. As described by Goto et al., the incidence of diabetes in Werner syndrome patients in Japan was comparable to that reported by

Imura et al. in 1986.

Q2. What type of diabetes do the Werner syndrome patients develop?
A2. Diabetes associated with Werner syndrome are classified into "one accompanied with other diseases and conditions and one occurring mainly in association with other genetic syndromes." Such diabetes is marked by accumulated visceral fat and high insulin resistance despite low BMI.

Epstein reported that diabetes occurring in association with Werner syndrome is characterized by a gradual rise in blood sugar levels leading to prolonged hyperglycemia after the glucose tolerance test and less effective insulin therapy for such hyperglycemia despite normal blood sugar levels in many Werner syndrome patients. His study also indicated that although dead branch-like extremities and fat atrophy are observed in Werner syndrome, fat atrophy is not involved in an onset of [1)].
According to the report from Imura et al., the researchers measured the serum insulin levels of 53 Werner syndrome patients in the glucose tolerance test, observing hyperinsulinemia in 33% of them with basal insulin levels at 20 μU/mL and overreaction to insulin in 67% with the peak level at the glucose tolerance test showing 200 μU/mL. They suggested that a decrease in endogenous insulin secretion have been rarely seen and insulin secretion from the pancreatic β cells has been relatively maintained even though insulin resistance is higher in Werner syndrome patients. The report also indicates pathogenesis of high insulin resistance in which expression of insulin receptors on the erythrocyte surface is not decreased and malfunction of the insulin receptors expressed is associated with higher insulin resistance in the examination using cultivated dermal fibroblasts[3)].
An onset of diabetes generally correlates with obesity (an increase in BMI), whereas BMIs of most Werner syndrome patients are below 22. Yokote et al., reported that accumulated visceral fat, low serum adiponectin levels, and increases in tumor necrosis factor α (TNF-α) and interleukin-6 (IL-6) were observed in Werner syndrome patients with diabetes[7,8)]. A recent case report has suggested that although it was confirmed in one patient, abnormal glucagon secretion after a food load was put might be associated with carbohydrate metabolism disorders in Werner syndrome patients[9)]. Recently, the body compositions of Japanese Werner syndrome patients were examined in detail, and the results revealed that there were no differences in age, sex, and skeletal muscle mass between the diabetic (n = 4) non-diabetic (n = 5) groups, whereas they had dominantly higher BMI and amount of visceral fat (Table 1)[10)]. Accordingly, not fats in extremities

or atrophy of skeletal muscle but insulin resistance accompanied by accumulated visceral fat is associated with an onset of diabetes in Werner syndrome patients. Diabetes generally occurs in deep involvement with not only genetic background but also changes in environmental factors. Considering that the rate of diabetes occurring in Werner syndrome patients remains constant, the development of diabetes in Werner syndrome patients may be greatly influenced by genetic factors rather than environmental factors.

Q3. What is an effective treatment for diabetes in Werner syndrome patients?
A3. Thiazolidine derivatives are effective for glycemic control.

As reported by Epstein, insulin treatment for diabetes associated with Werner syndrome lacks efficacy. There have been many reports on the effectiveness of a thiazolidine derivative, an agonist, of peroxiome proliferator-activated receptor gamma (PPARg), an insulin sensitizer[7,8,11-18]. On the other hand, although concerns about the effect of thiazolidine derivatives on the bone and the onset of malignancy have been generally reported, no reports have suggested relationships between thiazolidine derivatives and the bone or the development of malignancy in Werner syndrome, which requires further examination. Other than those described above, availabilities of Biguanide[19], DPPIV inhibitors[9,20], and GLP-1 receptor agonists[21] have been reported, though a few in number. In Werner syndrome patients, not only short stature and low body weight but also a reduction in the skeletal muscle mass early in life has been observed [10]. Although dietary instructions to prevent an increase in visceral fat and a decrease in the skeletal muscle mass may be required, no dietary therapy for diabetes occurring in Werner syndrome has been established, which is one of important subjects to be examined.

Summary

Diabetes is highly prevalent among patients with Werner syndrome. Reportedly, thiazolidine derivatives increase the risks for weight gain and bone fracture, necessitating clinicians to be wary of the prolonged usage of thiazolidine derivatives. In Japan, thiazolidine derivatives had been widely used in the treatment of patients with Werner syndrome because of the reduced prevalence of biguanide owing to its side effects, such as lactic acidemia. With the growing usage of metformin in Japan and the fact that it reportedly exerts favorable effects on metabolism and acts as an anticancer agent, re-evaluation of the efficacy of metformin in the treatment of

patients with Werner syndrome is warranted. In our opinion, new antidiabetic drugs, such as DPP4 inhibitor and/or GLP-1 receptor analogue, could be potentially beneficial for patients with Werner syndrome. Furthermore, the establishment of not only diet therapy but also exercise therapy for patients with Werner syndrome is warranted in the future.

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Table 1: Differences in clinical findings affected by the presence or absence of diabetes

	Non-diabetic	n	Diabetic	n	p value
Age	44 ± 6.9	5	53 ± 9.1	4	0.16
25-questionGLFS score	40 ± 31.7	4	43 ± 18.8	4	0.88
Two-step test value	0.73 ± 0.49	5	0.60 ± 0.51	4	0.71
Grip strength (kg)	20.1 ± 7.1	5	12.5 ± 5.1	4	0.11
VFA (cm^2)	56.1 ± 43.6	4	142.6 ± 40.1	3	0.04*
SMI (kg/m^2)	4.2 ± 0.7	5	3.8 ± 0.4	3	0.4
BMD (L) (YAM)	89.4 ± 13.8	5	83.3 ± 8.4	3	0.47
BMD (F) (YAM)	75.3 ± 4.6	4	61.7 ± 5.7	3	0.03*
BW (kg)	40.4 ± 7.5	5	42.9 ± 6.6	4	0.61
BMI (kg/m^2)	16.2 ± 1.2	5	18.7 ± 1.3	4	0.02*
Adiponectin (ng/mL)	6.4 ± 2.8	4	6.6 ± 4.1	4	0.95
TNF-α (pg/mL)	1.4 ± 0.6	4	3.0 ± 4.3	4	0.51
Leptin (ng/nL)	7.2 ± 3.6	4	30.0 ± 16.9	4	0.07

GLFS: geriatric locomotive function scale, VFA: visceral fat area, SMI: skeletal muscle index, BMD (L): bone mineral density (lumbar spine), BMD (F): bone mineral density (femoral neck), YAM: young adult mean, BW: body weight. BMI: body mass index, TNF: tumor necrosis factor, * $p < 0.05$, quoted from Reference No. 10.

4.Osteoporosis associated with Werner syndrome

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Introduction

Werner syndrome is a typical genetic progeria syndrome that produces various pathological changes similar to those associated with human aging at a young age. Among these changes, osteoporosis is considered to be a sign of early aging typically seen in patients with this syndrome. This article analyzes the prevalence, the predilection sites, contributing factors, and treatment of osteoporosis associated with Werner syndrome based on the latest findings.

Q1. What percentage of Werner syndrome patients develop osteoporosis and which site does osteoporosis appear more commonly?

A1. Osteoporosis has been observed in approximately 41% of these patients. It is likely to be more severe in the femur than in the lumbar spine.

According to a report summarizing clinical characteristics of 24 Werner syndrome patients by Murata et al.[1], the radiographs showed osteoporosis in nine of 24 patients. Although osteoporosis was relatively rare in younger patients, almost all patients at least 40 years of age developed osteoporosis, with its degree being more severe in the lower extremities. Their review of the Japanese medical literature revealed that osteoporosis occurred in 41% of 153 Werner syndrome patients reported in Japan.

As the above report by Murata et al. was made before bone densitometry by dual energy x-ray absorptiometry (DXA) has become generalized, it was unclear whether the incidence of osteoporosis in patients with Werner syndrome using the current Diagnostic criteria for primary osteoporosis[2] was as high as that reported in previous studies. Therefore, a more detailed assessment of osteoporosis was made in 10 Werner syndrome patients visiting Chiba University Hospital[3]. As shown in Table 1, the patients consisted of five males and five females. Werner syndrome was diagnosed by genetic testing using DNAs extracted from peripheral blood leukocyte as well as the characteristic clinical signs (Table 1). Bone density was measured by DXA, and ≤70% of the young adult mean (YAM) value or T-score of ≤-2.5 SD was defined as osteoporosis. Osteoporosis was diagnosed by evaluation of the lumbar spine bone density in only case 1. Spine radiographs had positive findings in six patients but with no specific

osteoporosis-related fragility fractures. In contrast, osteoporosis was identified in six patients (cases 1, 2, 3, 5, 7, and 10) when assessed by the bone density of the femoral neck. The above results suggested that osteoporosis accompanied by Werner syndrome is more severe in the femur than in the lumbar spine.

Q2. Has the pathogenesis of osteoporosis been elucidated?
A2. It is considered that osteoporosis occurs because bone formation is inhibited while bone resorption is normal in Werner syndrome.

Osteoporosis has been considered to be caused by the imbalance between osteogenesis by osteoblasts and bone resorption by osteoclasts. For example, hyperfunction of osteoclasts mainly due to a decrease in estrogen levels has been known to be involved in the development of typical postmenopausal osteoporosis. From this perspective, Rubin et al., have reported examination results related to the pathogenesis of osteoporosis in Werner syndrome patients[4]. The researchers examined osteoporosis in a 43-year-old Caucasian female patient. The spine radiograph showed fragility compression fractures in almost all thoracolumbar spines. Her bone density stood at 0.776 g/cm^2 in the lumbar spine and 0.441 g/cm^2 in the femoral neck, which was equivalent to -2.38 SD and -3.93 SD, respectively, compared with the mean values in females of the same age. Hematological parameters were unremarkable, except for insulin-like growth factor-1 (IGF-1), which showed a low level of 86 ng/mL (normal range for age: 142-389 ng/mL). However, the basal serum growth hormone level was within the normal range, and the load tests using arginine and L-dopa showed a normal somatotropin secretory response pattern. The iliac bone of the patient was also biopsied, showing low cortical bone mass and thinning of the cortical bone. More important findings included a significant decrease in the osteoid mass and absence of osteoblasts in sampled tissues. To sum up these findings, it was considered that while the bone resorption was normal, osteogenesis was inhibited in patients with Werner syndrome.
Furthermore, Rubin et al., reported results obtained when Werner syndrome was treated with IGF-1[5]. They measured changes in bone density and the bone metabolism marker of Werner syndrome patients with osteoporosis before and after daily subcutaneous injection of recombinant human IGF-1 for six months. Serum type I procollagen C-peptide and serum osteocalcin, the osteogenesis markers, had increased, while urinary pyridinoline crosslinked products and urinary hydroxyproline, the bone resorption markers, had also risen during the treatment. The posttreatment bone density of the lumbar spine increased by 3%, showing an increment exceeding a variation coefficient in the testing. Given these results, they concluded that supplementation of IGF-1 might possibly relieve inhibition of osteogenesis in Werner

syndrome patients with osteoporosis displaying low IGF-1 levels.
Generally, age-related osteoporosis occurs more commonly in the bony skeleton including proximal sites of the vertebra and the femur, whereas osteoporosis in Werner syndrome tends to be more severe in the distal extremities, especially in the lower extremities. Since arthrogryposis associated with dermal sclerosis in the lower extremities or ulcerative lesions in the foot region often occur in Werner syndrome, the bones of the lower limbs are susceptible to disuse and inflammatory changes. This is considered to be one reason why osteoporosis in Werner syndrome tends to be more severe in the lower extremities.

Q3. Is osteoporosis related with the *WRN* gene polymorphism?
A3. The research results showing the relation between the *WRN* gene polymorphism and osteoporosis have suggested that genetic factors might also be involved in osteoporosis associated with Werner syndrome.

Osteoporosis is included as one of the premature aging signs in Werner syndrome, which, however, does not immediately indicate a direct relationship between a genetic abnormality causing Werner syndrome and the bone metabolism. Werner helicase, a product of the gene responsible for Werner syndrome, has been considered to play a role mainly in the DNA repair process. The *WRN* gene has been observed to be expressed in human dermal fibroblasts[6], whereas it has not been confirmed whether it is expressed in osteoblasts or osteoclasts, leading to difficulty in inferring a functional relationship between the *WRN* gene and bone metabolism. Lately, a research providing a new insight concerning this topic has been reported.
It has been known that there are single nucleotide polymorphisms (SNP) at eight positions in the *WRN* gene: four of them involve amino-acid substitution, while the other four do not.[7]. Some researchers have already reported examination results of a relationship particularly with rs1346044 (T > C, Cys1367Arg), that is, a polymorphism with the 1367th cysteine residue being replaced with an arginine residue, and osteoporosis[8]. They examined 377 healthy postmenopausal women with a mean age of 65.6 years. The genotype frequencies were 87.5% for T/T, 12.2% for T/C, and 0.3% for C/C. The subjects were classified into two groups of non-carriers of C (T/T) and carriers of C (T/C and C/C) for comparison, resulting in the carriers of C having significantly low bone density in the lumbar spine ($p = 0.037$).
We also conducted genotyping of rs2230009 (340G > A, V114I) of the *WRN* gene to examine the association with the prevalence of femoral fracture using DNAs obtained from 1,632 consecutive autopsy cases (mean age: 81; 924 males and 708 females) in Tokyo Metropolitan Geriatric Hospital[9]. Additionally, we analyzed the relationship with the bone density using DNAs taken from 251 patients with postmenopausal osteoporosis (mean age: 71) in Tokyo

Metropolitan Geriatric Hospital[9]. Table 2 shows the results of multiple logistic regression analysis adjusted for sex and age. The odds ratio of femoral fracture in rs2230009 with the AA or AG genotype was significantly high, standing at 2.528 times as frequently as that with the GG genotype. Additionally, the study found that the above odds ratio in females was 2.983 times as high as that in males, and a risk of femoral fracture increased by 1.746 times for every 10 year increase in age. Furthermore, we performed validation of rs2230009 that had been found to have a significant association with femoral fracture in a secondary cohort. Table 3 shows the relationship between the genotype of rs2230009 and each clinical indicator in patients with postmenopausal osteoporosis. A Student's t-test was employed for age, body weight, and body height, and a linear regression analysis (adjusted for age) for the others to conduct a significance test. As a result, it revealed that the AG genotype had a significantly lower bone density in the femoral neck than did the GG genotype.
The results obtained from a series of studies on the association between the *WRN* gene polymorphism and osteoporosis suggests genetic factors to potentially be involved in the onset of osteoporosis associated with Werner syndrome.

Q4. How should osteoporosis in Werner syndrome patients be treated?
A4. No clear evidence to date regarding treatment for osteoporosis associated with Werner syndrome has been found at present, and thus it is considered appropriate to treat osteoporosis according to the guidelines for treatment of osteoporosis[10].

As a typical drug to decrease a risk of osteoporosis-related fractures, bisphosphonates have been widely used. A report indicated that etidronate, one of bisphosphonates, has ameliorated painful soft tissue calcification[11], which provides a helpful perspective to select drugs. On the other hand, there has been a report suggesting that osteoporosis in Werner syndrome is caused mainly by inhibition of osteogenesis, for which parathormone (PTH) (teriparatide) is considered to be effective. Considering that sarcoma frequently develops in patients with Werner syndrome, the use of PTH requires special attention to the development of osteosarcoma.

Summary

Werner syndrome is often accompanied by osteoporosis. Age-related osteoporosis generally occurs more commonly in the bony skeleton including proximal sites of the vertebra and the femur, whereas osteoporosis is more severe in the distal extremities, especially in the lower extremities in Werner syndrome patients. Since arthrogryposis associated with dermal sclerosis in the lower extremities or ulcerative lesions in the foot region occur in Werner syndrome patients, the bones of the lower limbs are easily influenced by disuse and inflammatory changes.

These are considered to be one of the reasons that osteoporosis associated with Werner syndrome may become severer in the lower extremities. On the other hand, the research results indicating the association between the *WRN* gene polymorphism and osteoporosis have also been reported, suggesting that an onset of osteoporosis may be also genetically promoted in Werner syndrome.

As no specific evidence has been found to date regarding treatment for osteoporosis associated with Werner syndrome, it is considered appropriate to follow the conventional treatment for osteoporosis. Given that disuse may possibly be involved in the pathogenesis of osteoporosis, prevention against disuse through active rehabilitation is also important.

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Table 1. Bone density in 10 Werner syndrome patients

Case	Sex	Age	*WRN*mutation	Bone density in the lumbar spine（L_{2-4}）				Bone density in the femoral neck			
				g/cm^2	*T*-score SD	%YAM		g/cm^2	*T*-score SD	%YAM	
1	M	57	6/6	0.730	−2.7*	70¶		0.601	−2.1	70¶	
2	F	60	6/6	0.804	−2.1	78		0.452	−3.1*	57¶	
3	F	57	4/6	0.790	−1.9	78		0.351	−4.0*	45¶	
4	M	40	4/11	1.116	0.6	107		–	–	–	
5	F	60	4/4	0.803	−1.8	79		0.533	−2.3	68¶	
6	F	40	11/11	0.983	−0.2	97		0.582	−1.9	74	
7	M	51	4/7	0.971	−0.6	93		0.508	−2.8*	59¶	
8	F	42	4/4	0.892	−1.0	88		0.598	−1.7	76	
9	M	43	4/4	0.890	−1.3	85		0.697	−1.3	81	
10	M	53	4/−	0.901	−1.1	85		0.606	−2.0	70¶	

**T*-score ≦ −2.5

¶YAM ≦ 70%

Table 2. Association between the WRN gene polymorphism (rs2230009, 340G > A) and femur fractures

Factor	Odds ratio (95%CI)	*P*
Genotype: AA/AG vs GG	**2.528 (1.194-5.350)**	**0.0154**
Sex: Female vs Male	**2.983 (1.988-4.776)**	**<0.0001**
Age at autopsy (every 10 year increase in age)	**1.746 (1.396-2.185)**	**<0.0001**

Table 3. Association between the *WRN* gene polymorphism (rs2230009, 340G > A) and each clinical indicator

	GG (n=236)		AG (n=15)		Difference (95% CI)	*P*
	mean	SD	mean	SD		
Age (year)	70.9	8.09	71.7	6.83	0.76 (−3.43 - 4.94)	0.724
Body weight (kg)	48.0	6.81	44.7	5.00	−3.33 (−6.97 - 0.32)	0.074
Body height (cm)	150	11.4	140	38.5	−11.2 (−32.6 - 10.1)	0.279
BMI (kg/m^2)	21.0	2.88	20.1	2.51	−0.92 (−2.46 - 0.61)	0.240
Muscle mass in extremities (kg)	12.7	1.52	12.4	1.48	−0.24 (−1.18 - 0.71)	0.620
SMI (kg/m^2)	5.51	0.54	5.55	0.52	0.03 (−0.31 - 0.37)	0.850
Bone density in the lumbar spine (g/cm^2)	0.79	0.14	0.73	0.17	−0.07 (−0.14 - 0.00)	0.068
Bone density in the femoral neck (g/cm^2)	0.63	0.08	0.59	0.08	−0.04 (−0.08 - −0.00)	0.041*
Serum calcium (mg/dL)	9.65	0.41	9.53	0.31	−0.12 (−0.33 - 0.09)	0.270
Serum 25-OH vitamin D (ng/mL)	21.5	6.45	19.4	5.15	−2.02 (−5.35 - 1.30)	0.230

*$P < 0.05$

5.Infection associated with Werner syndrome

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Introduction

Werner syndrome (WS) is characterized by symptoms such as atrophy of subcutaneous tissues, decline in blood flow[2], and low activity of fibroblast cells[3] due to metabolic disorders in connective tissues[1], which may easily cause refractory skin ulcers[4]. Furthermore, it may occur with type 2 diabetes[5], which is likely to cause skin and soft tissue infections and osteomyelitis at an ulcer site. Generally, such symptoms may often become more severe than those in diabetic patients, leading to failure of conservative treatment and necessitating surgical excision of the infected site. The goal to treat infection caused by refractory skin ulcers in Werner syndrome patients is to minimize exacerbation of the ulcerated skin lesion by early detection and intervention.

Q1. What are the characteristic features of skin ulcer infection in Werner syndrome?
A1. The bacterial etiology of skin ulcers in Werner syndrome is nearly identical to that observed in a diabetic foot infection. However, skin ulcers are poorly healed in Werner syndrome patients comparing to that of diabetic patients, thereby raising a risk of long-term and chronic infection.

Prolonged infection causes emergence of a drug-resistant strain, resulting in a limited choice of antimicrobials capable of treating the lesion. Therefore, it is important to identify the bacterial etiology causing an infection in the skin ulcer and treat with an effective antimicrobials. For poorly controlled infection, debridement and surgical excision are required at an appropriate timing. This makes it essential to cooperate with plastic surgeons and orthopedists.

Q2. What are the clinical symptoms and severity classification of skin ulcer infection in Werner syndrome?
A2. The clinical symptoms and severity classification for diabetic foot is applicable to the majority of skin ulcer infections that occur in Werner syndrome. Table 1 shows the severity classification of diabetic foot suggested by the Infectious Diseases Society of America (IDSA) [6].

Clinical signs of infection	IDSA severity categories of infection
No symptoms and signs of infection	No infection
Erythema being locally found from a dermal tissue to a subcutaneous tissue, periphery of an ulcer: 0.5–2 cm	Mild
Erythema being >2 cm or reaching into the subcutaneous tissue Existence of abscess, osteomyelitis, and bacterial arthritis, fasciitis	Moderate
Satisfy at least two of the following items in addition to the above symptoms: • Body temperature > 38℃ orBody temperature < 36℃ • Heart rate > 90 beats/min • Respiration rate > 20 times/min or PaO2 < 32 mmHg • WBC > 12,000 or WBC < 4,000, or >10% of primitive leukocyte (stab cell)	Severe

Table 1. Severity categories of diabetic foot infection

Q3. How should we perform a microbiological examination of skin ulcer infection in Werner syndrome?

A3. We recommend to apply microbiological diagnosis method for diabetic foot infection.

The following are recommended for sample collection:

1) Clean the wounded area, perform debridement, and biopsy a deep tissue or take samples by curettage
2) Puncture fluid of purulent discharge
3) Obtain a bone biopsy tissue in cases of suspected osteomyelitis

When a sample is obtained from a wound without clinical symptoms of infection, obtained from a wounded area without debridement, or obtained simply by swabbing a wounded area, a normal bacterial flora, which may not be the cause of infection, can be detected, which poses a risk of administering unnecessarily broad spectrum antimicrobials. In cases of a deep ulcerated lesion with a symptom of infection, a Probe to Bone test (to check whether a probe inserted into the lesion reaches the bone) is performed[7]. If the bone is exposed, osteomyelitis is suspected, which necessitate to culture biopsied bone tissue[8].

Q4. How should we select drugs for the treatment of skin ulcer infection in Werner syndrome?

A4. As with treatment for a diabetic foot infection, a skin and soft tissue infection occurring with an ulcerated lesion in Werner syndrome patients is treated targeting Gram-positive bacteria which includes *Streptococcus* species and *Staphylococcus aureus*[9]. To determine if any other bacteria should be covered, the following four items should be checked:

1) A risk of methicillin-resistant *Staphylococcus aureus* (MRSA)
2) A history of antimicrobial use within a month
   If present, Gram-negative bacteria need to be covered.
3) A risk of *Pseudomonas* infection
4) Determination of the severity

Example of antimicrobials

(1) Mild or long-term/chronic case

Antimicrobial drug (Dosage and frequency should be adjusted to renal function.)	Comments
Oral administration of cephalexin(500mg) every 6 hours	Covers Gram-positive bacteria
Oral administration of amoxicillin (250mg)/clavulanate(125mg) + amoxicillin (250 mg) every 8 hours	Cover anaerobic bacteria
Oral administration of two sulfamethoxazole(400mg) /trimethoprim(80mg) tablets every 12 hours	Cover MRSA
Oral administration of minocycline (100mg) every 12 hours	Covers MRSA
Oral administration of clindamycin (300mg) every 8 hours	Covers anaerobic bacteria and a part of MRSA
Oral administration of levofloxacin (500mg) every 24 hours	Covers *Pseudomonas aeruginosa*. Often used in combination with clindamycin.

(2) Moderate to severe

Antimicrobial drug (Dosage and frequency should be adjusted to renal function.)	Comments
Intravenous injection of 3 g of ampicillin/sulbactam every 6 hours	Covers Gram-positive bacteria and anaerobic bacteria. The first-line drug in cases of no drug-resistant strains
Intravenous injection of 4.5 g of piperacillin/tazobactam every 6 hours	Covers Gram-positive bacteria, anaerobic bacteria, and *Pseudomonas aeruginosa*
Intravenous injection of 2 g of cefepime every 12 hours and 500 mg of metronidazole every 8 hours	Cover drug-resistant Gram-negative bacteria except *Pseudomonas aeruginosa* as well
Intravenous injection of 1 g of meropenem every 8 hours	Covers ESBL-producing Gram-negative bacteria and anaerobic bacteria as well
Vancomycin (Dosage and frequency differ according to the body weight and the drug blood level.)	Covers Gram-positive bacteria and MRSA
Daptomycin (Dosage and frequency based on body weight.)	Covers Gram-positive bacteria and MRSA In cases vancomycin cannot be used
ESBL: Extended Spectrum Beta Lactamase	

Q5. What is the treatment duration required for skin ulcer infection seen in Werner syndrome patients?

A5. The goal of treatment is to ameliorate symptoms of infection (red flare, pain, and swelling).

The treatment duration is according to that for diabetes foot infection[6)], but if the infected skin tissue is poorly healed, it should be determined on a case-by-case basis.

Soft tissue infection only			
Mild	Topical or oral	Outpatient	1–2 weeks, 4 weeks at longest
Moderate	Oral or intravenous (for the first time)	Outpatient /inpatient	1–3 weeks
Severe	Intravenous (Switch to oral if	Inpatient	2–4 weeks

	possible)		
Occurrence in conjunction with osteomyelitis and arthritis			
No residual infected tissues	Intravenous or oral		2–5 days
Residual infected soft tissue (but not bone)	Intravenous or oral		1–3 weeks
Residual infected (but viable) bone	Intravenous (Switch to oral if possible)		4–6 weeks
No surgery or residual dead bone postoperatively	Intravenous (Switch to oral if possible)		At least 3 months

Table 2. Administration route of antimicrobial drugs, the need of hospitalization, and planned treatment period

Summary

Skin ulcer infection in Werner syndrome should be treated by referring to diabetic foot treatment in terms of severity classification, method of microbiological examination, drugs, and duration of treatment, because of the high incidence of diabetes mellitus in Werner syndrome patients and the clinical similarity of Werner syndrome with diabetic foot infection. Meanwhile, the prognosis in Werner syndrome is poorer than in diabetes even when treated in the same manner, because of the subcutaneous tissue atrophy due to metabolic disorder of the connective tissue, decreased blood flow, and reduced activity of fibroblasts, and others. Since there are few case reports providing evidence in the treatment of infection in Werner syndrome, further studies on the bacteriology, treatment, and outcome of skin ulcer infection in Werner syndro are expected.

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6. Surgical treatment of skin ulcers associated with Werner syndrome

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Introduction

Skin ulcers are commonly observed in Werner Syndrome . This article aims to suggest certain guidelines for the epidemiology, diagnosis, treatment, and prevention of ulcers in Werner syndrome from a surgical perspective.

Skin ulcer in Werner syndrome is refractory and leads to reduced quality of life (QOL) of patients. Foot ulcer in Werner syndrome requires special care, because its clinical presentation is similar but not identical to that of ischemic limb ulcer or diabetic ulcer, both of which have recently increased in number. As Werner syndrome is an extremely rare disease, it is difficult to obtain adequate experience in treating the disease in actual clinical practice. It is also difficult to create evidence-based guidelines derived from clinical trials participated by many patients. Nonetheless, it is obviously necessary to make an appropriate diagnosis and provide treatment tailored to the skin ulcer in each Werner syndrome patient. Additionally, once an ulcer occurs in

these patients, it becomes refractory, which greatly increases the need to take measures to prevent an ulcer before its occurrence. Based on these observations, we believe it would be beneficial for Werner syndrome patients to provide certain guidelines and views on the diagnosis, treatment, and prevention of skin ulcers in Werner syndrome by collecting case reports including ours. This article also deals with elbow ulcers, which occur commonly in WS as well as lower limb ulcers.

Literature

Most studies on Werner syndrome are case reports, with a few case series. This article was created based on the literature from 1996, when *WRN* was identified as a gene responsible for Werner syndrome, to extract many authentic clinical cases in which patients were genetically diagnosed.

There were 63 Werner syndrome patients in the Japanese reports searched on Medical Online from January 1996 to December 2017 . We had 56 Werner syndrome patients in English reports written by Japanese authors retrieved from PubMed during the same period. Both reports were used in this article. These Japanese reports, however, include abstracts of conference presentations as well, and thus some cases may be overlapped. Similarly, cases reported in Japanese may also be overlapped with those in English.

I. Overview of skin ulcers

Q1. What is the complication rate of skin ulcers in patients with Werner syndrome?
A1. Approximately 40% of Werner syndrome patients are complicated by skin ulcers.

Werner syndrome is a very rare disease, and thus it is difficult to accurately obtain the morbidity and prevalence of skin ulcers in Werner syndrome patients. Records on skin ulcers were found in 27 (43%) out of 63 patients and 22 (40%) out of 56 patients from the Japanese and English reports, respectively (Table 1). Occurrence of ulcers was often reported at the olecranon of the elbow joint in the upper limbs, whereas they were observed at site below the distal one-third of the lower legs in lower limbs in many cases. Some reports have indicated ulcers in the extensor surfaces of knee joints as well.

Q2. Which part of the lower limb is typically affected in Werner syndrome patients?
A2. The distal one-third of the lower limb and the foot are typically affected

Werner syndrome patients often have thin lower limbs and dry skin. Poikiloderma and

scleroderma-like changes occur particularly in the foot, intensively in the distal one-third of the lower legs (Figure 1). Hereafter, the distal one-third of the lower legs and the foot will be discussed. The skin is often poorly-extensible and shiny. Contracture of ankle often limits the range of motion with less pes equinus position. Flat foot has been known to be one of the typical symptoms in Werner syndrome. Flame-like calcification in Achilles tendon shown in radiographs is a typical symptom in Werner syndrome, and skin ulcers are sometimes observed there. Additionally, Werner syndrome may be associated with lateral and medial malleoli on the ankle and multiple ulcers in the leg. Callosities are also frequently observed. Even on an ulcer-free foot in relatively good condition, a callosity is often found when observed. Toe deformities frequently occur and sometimes progress rapidly.

Q3. What are the underlying diseases that can cause lower limb ulcers?
A3. Glucose metabolism disorders are present in many cases.

The incidence of carbohydrate metabolism disorders in Werner syndrome patients was high at 43% and 39% in the Japanese and English reports, respectively (Table 2).In contrast, hypertension was not necessarily found in many cases. Lower limb ischemia was not observed in many Werner syndrome cases, either. Attention is required because the clinical presentation of a foot ulcer in Werner syndrome is partly similar to but not necessarily identical to that in diabetes and hypertension that have been increasing in number recently. Furthermore, scleroderma-like changes and foot deformity are non-negligible factors that contribute to foot ulcer development in Werner syndrome.

Q4. Are there ulcers associated with malignancy?
A4. Yes, such ulcers are occasionally seen.

Malignancy has been known to occur at a high rate from a young age in Werner syndrome. The incidence of a non-epithelial tumor in Werner syndrome patients has also been reported to be higher than that in the healthy population. As to the association with skin ulcers, a study reported that calcaneal osteosarcoma was observed in a patient with a heel ulcer[1]. A possibility of malignancy should be considered in skin ulcers of WS patients.

Q5. Are callosities frequently observed?
A5. Yes, they are frequently observed.

A callosity appears in the foot of Werner syndrome patients at a high rate. There were records

on callosities in 8 patients from the Japanese reports and 9 patients from the English reports. It brings pain and decreases QOL, and an ulcer may occur at a site of a callosity. Moreover, pain caused by a callosity worsens gait, which contributes to an increased load on the other sites, leading to potential development of a new callosity or an ulcer. Accordingly, a callosity in Werner syndrome is an important therapeutic target from a viewpoint of prevention from ulcers that can occur in the future.

Werner syndrome is characterized by the hardened and quite poorly-extensible skin. Additionally, symptoms including flat foot, toe deformity, and ankle contracture may progress. Such conditions are considered to cause callosities at a high rate in Werner syndrome.

As mentioned above, a callosity sometimes becomes the origin of a skin ulcer. Thus, for Werner syndrome patients who have only a callosity without a skin ulcer, particularly intensive and appropriate prevention is would be necessary, considering the risk of developing an ulcer. Such cases have been shown in two patients from the Japanese reports and five from the English reports. The following are the reasons why interventions to prevent or treat a callosity in ulcer-free Werner syndrome patients are important: (1) many patients do not take preventive measures including use of a foot orthosis and shoe orthosis because they have never developed any ulcer or experienced any refractory ulcer and (2) patients at the stage of mild symptoms are quite active, which results in high pressure to be applied on a callosity for a long period of time. In our patient, a load on a callosity on the heel ruptured the calcaneal bony cortex, leading to possible calcaneal bone osteomyelitis (Figure 2). Although this patient had presented changes typical of Werner syndrome including poikiloderma, scleroderma-like skin changes, and ankle contracture from the distal one-third of the lower legs to the foot, the skins in the lower legs and feet had been in relatively good condition. The causes of a heel ulcer were considered to include failure to treat a callosity on the heel, the use of commercial shoes, and repeated and continuous pressure applied to a callosity on the heel due to the patient's high activity levels.

These observations demonstrate that a callosity is a prodrome of skin ulcers in Werner syndrome. Interventions for a callosity may prevent severe and difficult-to-treat symptoms such as skin ulcers and osteomyelitis.

II. Diagnosis

Q6. Are macroscopic evaluations of ulcers important?

A6. Yes, they are important.

As macroscopic findings, records on sites and characters of ulcers are important. It is useful to keep records with the items included in DESIGN-R®(edited by the Japanese Society of

Pressure Ulcers)[2] in mind, which helps to reduce the number of omissions. DESIGN-R® is the criteria for evaluating pressure ulcers, yet it can also be used to assess ulcers other than pressure ulcers. The evaluation items are as shown below:

1. Depth
2. Amount of exudate
3. Size
4. Inflammation/infection
5. Granulation tissue
6. Necrotic tissue
7. Pocket

DESIGN-R is a detailed evaluation method, and it can be utilized for therapeutic effect determination and assessment of time-dependent changes. Its negative side includes slightly cumbersome records.

The following are points that are considered important in the assessment for ulcers in WS:

1. Depth of an ulcer: An ulcer in Werner syndrome easily reaches the bone or the articular cavity. It is necessary to consider possibilities of osteomyelitis in case of an ulcer rupturing and reaching into the bone marrow, osteomyelitis and of purulent arthritis in case of an ulcer reaching the articular cavity.
2. Amount of exudate: In cases of purulent exudate, a possibility of osteomyelitis or purulent arthritis should be considered.
3. Size: Important to determine the condition of an ulcer and the therapeutic effects
4. Inflammation/infection: It is important to identify where the focus of infection is, that is, any one of a skin and soft tissue, bone marrow, or articular cavity.
5. Granulation tissue: Generally, granulation tissue is poorly formed at the site of an ulcer in Werner syndrome. In cases with poorly formed granulation tissue, it is necessary to investigate the cause, which may include poor blood flow, infection, and necrotic tissue, and provide treatments to eliminate these conditions.
6. Necrotic tissue: The following should be determined: what the necrotic tissue is, and the depth and range of the necrotic tissue.
7. Pocket: In not many of Werner syndrome patients, formation of a pocket in a foot ulcer becomes a problem.

Q7. Are plain radiography and CT of the foot region useful?

A7. A plain radiography and CT are helpful to examine the shape of the whole foot and conditions of individual bones consisting of the foot.

It is important to understand time-dependent changes because the shape of the foot region and the state of each bone may change rapidly in Werner syndrome.

Q8. Is an MRI examination useful?
A8. An MRI examination is useful for a suspected case of osteomyelitis (Figure 2).

Q9. Is vascular evaluation necessary?
A9. Yes, it is necessary.

In cases of lower limb ischemia, it is necessary to examine whether revascularization is possible. Lower limb ischemia should be considered in a patient with a history of hypertension or diabetes, cold feet, or non-palpable dorsalis pedis and posterior tibial pulses, a possibility of. There were suspected cases of lower limb ischemia in one patient from the Japanese report and two from the English. One of these patients reportedly underwent revascularization in a femoropopliteal artery bypass operation using a saphenous vein [3].

III. Treatment

Q10. Is the combination of surgical treatment and wound bed preparation important in treating skin ulcers?
A10. Yes, it is important to combine these treatments.

A skin ulcer in Werner syndrome is generally intractable. Even if a wound is finally closed through surgical treatments including skin grafting and skin flap grafting, preparation before a wound closure would greatly influence the outcome of surgery. By adopting a recently advanced technique for wound healing, there has been a rise in the number of cases of ulcers which had so far difficulty in healing and those requiring major operations that could be closed with minimally invasive surgery. Such an attempt to improve a condition of an ulcer in the preoperative step is called as wound bed preparation, the importance of which has been increasing. This section discusses a process from wound bed preparation to operation in Werner syndrome patients by incorporating our own experience.

A) Debridement and curettage: In treatment and control of skin ulcers, removal of necrotic tissue and cleaning of the wounded surface are important. Thus, daily cleaning of wounded surface by patients themselves is extremely necessary. At the same time,

curettage and surgical debridement are desirable every time they visit medical institutions.

For obviously infected wounds, incisional drainage or debridement should be immediately performed. Lately, a condition where an ulcer site had no obvious symptoms of infection yet had increased bacterial volume has been called critical colonization and attracted attention. The critically colonized bacterial mass forms a biofilm of glycocalyx, etc., makes host immunity and external medicine work poorly, and inhibits wound healing. A soft yellow to white colored tissue attached on a surface of an ulcer (sometimes called a slough) may include a biofilm, which is a finding suggestive of critical colonization. Additionally, NERDS has also been reported as clinical findings suggestive of critical colonization [4] (Table 3). It is considered effective as a countermeasure against critical colonization to remove a soft yellow colored to white colored tissue attached on a bottom of an ulcer using a sharp spoon, etc., when the ulcer in Werner syndrome is examined, because this procedure removes a biofilm and reduces bacterial volume.

Debridement is useful from the perspective of diagnosis because the range and depth of an ulcer can be determined. During the procedure, it is also important to collect samples for bacterial cultivation from wounded surface, necrotic tissue, or pus. Some ulcers reach into the bone marrow, by which osteomyelitis may be found in the process of debridement. In such case, pus for bacterial cultivation from the bone marrow should be obtained.

Pain is the most problematic in performing debridement for Werner syndrome patients. They develop carbohydrate metabolism disorders at a high rate yet suffer less perceptual decline than is observed in patients with diabetic ulcers and rather experience stronger pain than do healthy people during the procedure. This often makes debridement under non-anesthesia difficult. In case of local infiltration anesthetic injection, hardening of tissue makes pain caused by injection strong and prevents injected anesthetic agent from penetrating into tissue, leading to a different range that anesthetic injection can cover and a poor analgesic effect compared with other patients. One of measures may include block injection to sites with soft skin away from an ulcer such as the center of the lower thigh (Figure 3). In any case, the significance and necessity of debridement in Werner syndrome should be explained to patients, followed by adequate preparations before applying this procedure.

B) Topical medication: It is important to use an appropriate topical medication tailored to the condition of an ulcer. The basic idea of moist wound healing in ulcer treatment is to

maintain a proper moist environment and facilitate wound healing. However, ulcers in Werner syndrome rarely heal only with drugs that directly promote a moist environment and wound healing (Vaseline ointment, prostaglandin-containing ointment, and basic fibroblast growth factor [bFGF] spray, etc.). Critical colonization of bacteria is often addressed with iodine preparation or silver preparation. Heavy exudate exceeding the range of moist wound healing inhibits wound healing, and thus preparations made of water-absorbing base (cadexomer iodine preparation, and iodine-sucrose preparation) are often used to absorb exudate.

C) Washing: Washing a wounded surface is thought to be effective. There have been not many evidences to prove the effectiveness of washing, but a clinical consensus about its efficacy is considered to have been reached. Wound irrigation with a shower by a patient as self-care is one of the personal hygiene measures that are desirable. Accordingly, prohibition of washing the foot with a shower should be avoided just by reason of an ulcer despite of lack of any particular reason to control a wound.

On the other hand, the following risks caused by washing should be recognized: (1) multiple-drug-resistant bacteria in the environment are attached on a wounded surface and (2) multiple-drug-resistant bacteria on a wounded surface may spread into the environment.

Water-related equipment (water faucets, showerheads, bathtubs, perineal irrigation bottles, etc.) may be contaminated by various bacteria in medical institutions. Wound irrigation is likely to splatter contamination into the environment. In light of the above risks in (1) and (2), a wound is required to be irrigated according to the standard preventive measures.

D) Negative pressure wound therapy (NPWT): NPWT is a treatment procedure for refractory ulcers that has rapidly spread in recent years. It promotes neovascularization and granulation by continuous negative pressure and facilitates ulcer healing by controlling exudate. It showed a certain level of effectiveness in our own cases (Figure 3) and is thought to be a significant therapeutic method that should be proactively employed in the future. General precautions for NPWT include (1) not using for infected wounds and (2) attention to skin diseases around ulcers, which should also be followed accordingly in Werner syndrome. Skin ulcers associated with purulent arthritis frequently occur in Werner syndrome. Infected ulcers are not an indication for NPWT monotherapy, but a combination with continuous irrigation may be effective.

Attentions especially required when administering NPWT for the foot in Werner

syndrome include tissue being severely indurated and skin and soft tissue being thin and close to the bone, leading to the likelihood of developing skin and soft tissue disorders by pressure from a foam agent. A foam agent should be cut into an appropriate width and thickness for effective use.

E) Surgical procedure:

a Attachment of artificial dermis: The skin and soft tissue in Werner syndrome becomes thin and indurated, which is likely to cause loss of all layers on the bone and tendon. Artificial dermis is essential to treat foot ulcers in Werner syndrome (Figure 3). In Werner syndrome, the bony cortex is often ruptured, leading to exposure of the bone marrow, but artificial dermis can be also attached on the exposed bone marrow. Dermis-like tissue is constructed on a surface of the exposed bone marrow, thereby preventing osteomyelitis and enabling epidermization.

b Skin grafting: Many skin ulcers in Werner syndrome previously had been accompanied with bone exposure at the levels of losing periosteum and aponeurosis and hard to be applied to skin grafting. However, the advent of artificial dermis, bFGF preparation, and NPWT has raised the number of cases capable of creating a base bed for skin grafting for ulcers in Werner syndrome, accompanied by which, patients undergoing skin grafting may be on the increase. Descriptions on skin grafting were found in one case from the Japanese report and two cases from the English reports. Figure 3 shows our cases where skin grafting was performed on lateral malleolus in the ankle, etc.

c Flap surgery: With or without Werner syndrome, the percentage of comparatively major surgeries such as flap surgery has decreased in treatment of intractable ulcers, and their roles have been relatively declining. This is because the progress of drugs including topical medication and bFGF preparation, the advent of artificial dermis which has made skin grafting possible even in situations previously thoroughly incapable of skin grafting, and a powerful granulating effect and an effect to reduce ulcers by NPWT. On the other hand, the advantages of flap grafting are that it can close ulcers that could not be closed by the other therapeutic procedures, ulcers can be closed using good thick skin and soft tissue, and the treatment period is shortened.

(1) Elbow ulcers: The olecranon bone is curved eminence, highly flexible soft tissue is required because of elbow flexion-extension movements, and furthermore the articular cavity is often exposed in elbow ulcers of Werner syndrome patients. For these reasons, flap surgery may be appropriate in many cases rather than skin grafting. As to flap surger for elbow ulcers, there have been reports on the use of

radial recurrent flap[5], flexor carpi ulnaris muscle flap [6], and radial forearm flap [7]. Other than those above, skin grafting [8] and partial ostectomy [9] have been reported.

(2) Knee ulcers: Flap grafting is highly applicable to ulcers with a knee-joint cavity being exposed. There are reports on cases of anterior tibial artery flap, sartorius muscle flap, and free latissimus dorsi myocutaneous flap [10, 11].

(3) Heel ulcers: A free serratus anterior muscle flap has been reported for a heel ulcer associated with osteomyelitis [12].

(4) Ulcers in the Achilles tendon: Calcification with a flame-like shape in the Achilles tendon observed in radiographs is a characteristic finding of Werner syndrome. Infection of calcification often causes ulcers in the Achilles tendon. It has been reported to be treated with the lateral supramalleolar flap [13].

d Amputation: Amputation of affected parts cannot be avoided in some refractory ulcers. Records on amputation were found in one case each of the foot and the toe from the Japanese reports and one case below the knee and another case of the toe from the English reports. A case of below-knee amputation caused by calcaneal osteosarcoma has also been reported [1].

F) Others

a Hyperbaric oxygen therapy: The hyperbaric oxygen therapy for calcaneal ulcers accompanied with calcaneal osteomyelitis has been reported [14].

b Lumbar sympathetic ganglion block: There are reports on the lumbar sympathetic ganglion block for foot ulcers and pain [15, 16].

G) Skin care

a Moisture retention: In Werner syndrome, skin dryness is frequently observed, especially in the lower leg and foot.It may become factors predisposing to callosities and exacerbating skin ulcers. Desquamation or rash caused by cutaneous dryness is considered to induce contamination in surgical wounds and inhibit wound healing. Application of a moisturizer may be effective.

Q11. Is the management for a callosities necessary?

A11. Yes, it is necessary.

A callosity occurs in the foot in Werner syndrome at a high rate (Figure 1B) and may induce skin ulcers, rupture of the bony cortex in the calcaneal bone, and osteomyelitis (Figure 2). Once

an ulcer or osteomyelitis occurs in Werner syndrome, it may become quite intractable, and thus preventive measures against such symptoms are desirably taken at the stage of a callosity. As such, proactive intervention for callosities is thought to be significant.

A) Prevention against callosities: A callosity occurs by applying excessive pressure for a long time. It is important to avoid excess pressure on the feet to prevent callosity formation.
   a Use of an appropriate foot orthosis or shoe-shaped orthosis: A foot orthosis or shoe-shaped orthosis tailored to each patient's foot may prevent a callosity and an ulcer. An article have reported a foot orthosis and a shoe-shaped orthosis used for two Werner syndrome patients [17]. According to the report, it was challenging to make orthoses for both cases yet one patient was satisfied with it. In our cases, shoe-shaped orthoses have been proactively made (Figure 4). There are outdoor type shoes and indoor type shoes, which are made according to the lifestyle of each patient by a prosthetist. These shoes are more comfortable than commercial shoes made for healthy people and relieve pain. We are currently examining the effects of these orthoses in preventing callosities and ulcers. As a problem, a toe deformity may progress rapidly in Werner syndrome, which often renders a prepared orthosis unfit after a brief period.

B) Treatment of a callosity: Proactive treatment of a callosity is desirable in Werner syndrome. With attention to the fact that a callosity recurs unless continuously excessive pressure on it, the cause, is eliminated, treatment should be continued. The specific methods include:
   a Shaving of a callosity: capable of reducing the thickness of a callosity with a razor and smoothing a shape of a callosity. These make possible to prevent extremely heavy pressure from being applied to the narrow range of the skin.
   b Attachment of salicylic acid preparation: capable of macerating keratin and manually exfoliating it.

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Table 1. Number of reported skin ulcers by body part in Werner syndrome

Body part	No. of cases in the Japanese reports (n = 63)	No. of cases in the English reports (n = 56)
Elbow	11 (17%)	1 (2%)
Knee	1 (2%)	2 (4%)
Lower leg	2 (3%)	4 (7%)
Achilles tendon	4 (6%)	5 (9%)
Medial and lateral malleoli in the ankle	2 (3%)	6 (11%)
Sole	4 (4%)	3 (5%)
Heel	6 (10%)	4 (7%)
Toe	4 (6%)	3 (5%)
Foot	1 (2%)	1 (2%)

Table 2. Underlying diseases that can cause a lower extremity ulcer

	Japanese reports (n = 63)	English reports (n = 56)
Carbohydrate metabolism disorders	27 (43%)	22 (39%)
Hypertension	3 (5%)	1 (2%)
Lower limb ischemia	1 (2%)	2 (4%)

Table 3. Signs suggestive of critical colonization*

English terms	Meaning
N: Non healing wounds	Treatment-resistant ulcers
E: Exudative wounds	Heavy effusion
R: Red and bleeding wound surface and granulation tissue	Red granulation tissue with bleeding
D: Debris	Existence of necrotic tissue, etc.
S: Smell or unpleasant odor	Odious smell

* Signs suggestive of critical colonization are termed NERDS, an acronym of the terms shown in the above list (quoted from Reference [4]).

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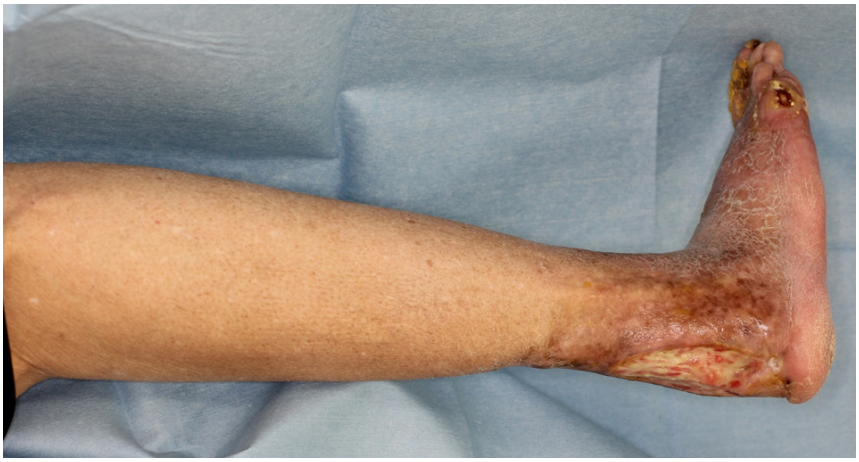

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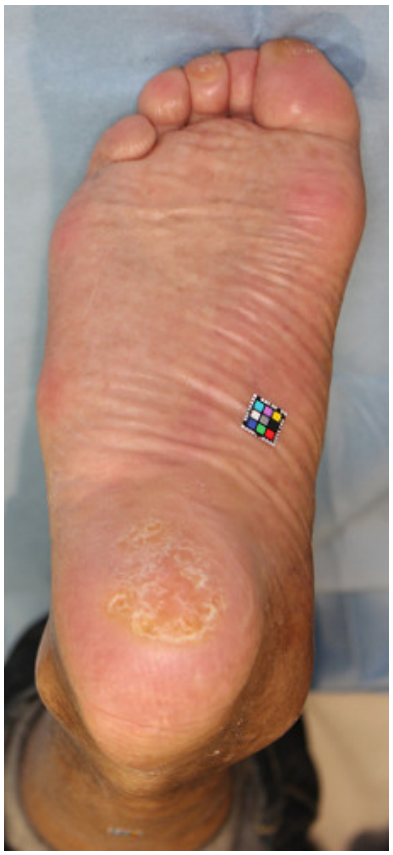
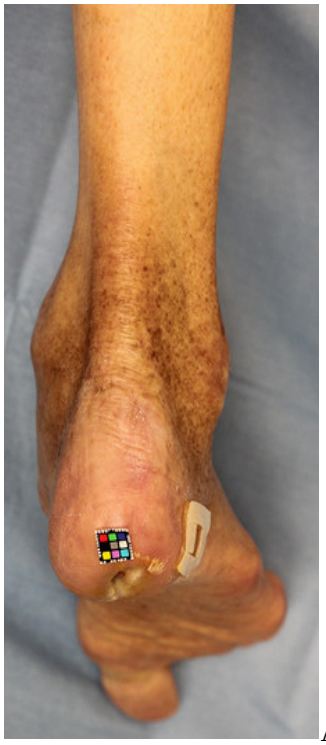


Figure 1. (A) Typical images of lower limbs in Werner syndrome. Significant hardening and atrophy of the skin and soft tissue are observed below the distal one-third of the lower extremities. (B) The foot is in relatively good condition without ulcers yet with a callosity on the heel region.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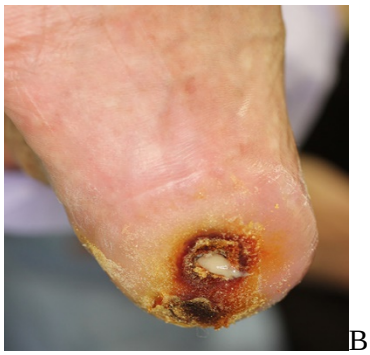
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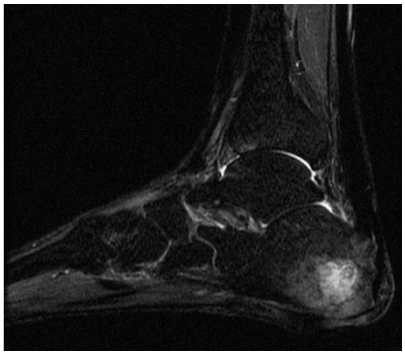
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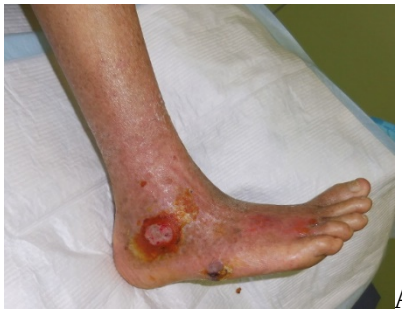
Figure 2. A case of a calcaneal callosity developing into possible calcaneal bone osteomyelitis
(Top) The skin is generally in good condition from the distal one-third of the lower extremities to the foot region.
(Center) Pus from the ulcer on the heel region

(Bottom) Sagittal section of the foot MRI. The fat-suppressed T2-weighted image shows high signal intensity in the calcaneal bone marrow, which reflects osteomyelitis.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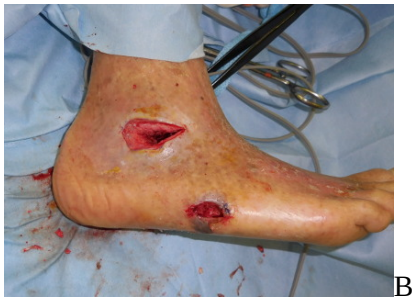
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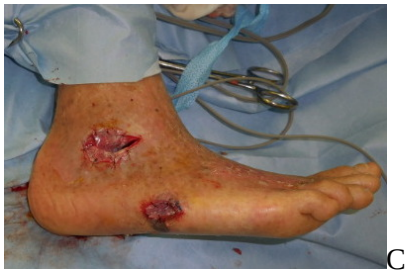
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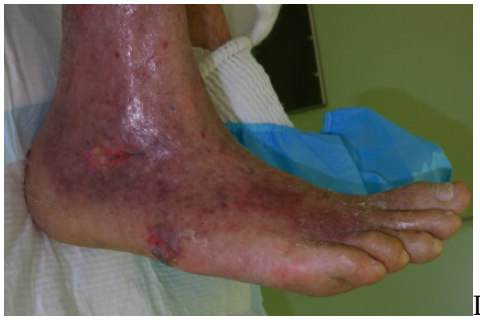
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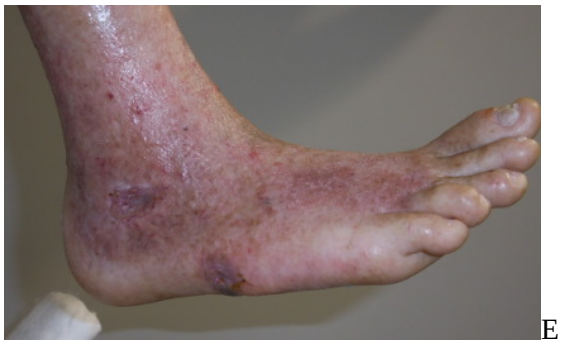
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Figure 3. (A) Ulcers are observed on the lateral malleolus in the ankle and the lateral aspect of

the foot. (B) Post-debridement. Anesthesia is administered on a site with the soft skin slightly distal from the center of the lower limb for a sural nerve block. The ulcer on the lateral malleolus reaches into the bone marrow, and the ulcer on the lateral aspect of the foot to the fifth metatarsal bone. (C) After artificial dermis was attached on the ulcers, the negative pressure wound therapy (NPWT) started. (D) Post-NPWT. The granulated and reduced-size ulcers are observed. They were determined applicable to skin grafting, and split-thickness skin grafts for meshing was performed. (E) Post-skin grafting. Successful engraftment and ulcer closure are confirmed.

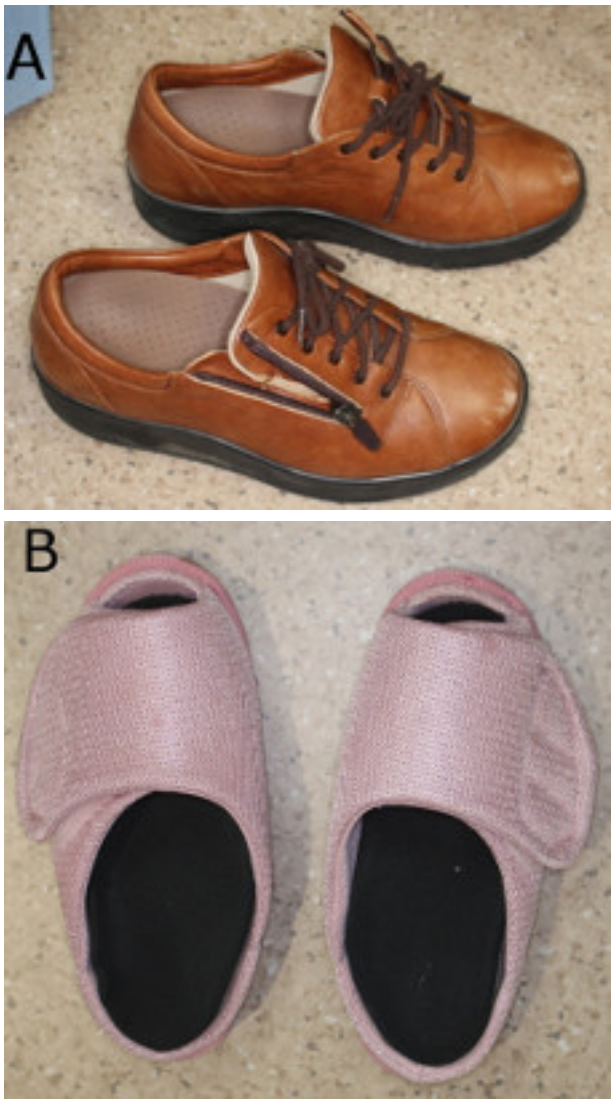

Figure 4. Samples of shoe-shaped orthoses: (A) Outdoor type shoes; (B) Indoor type shoes

7. Skin ulcer associated with Werner syndrome -Dermatological treatment-

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Introduction

Patients with Werner syndrome are likely to develop refractory skin ulcers. These ulcers most commonly occur in the plantar weight-bearing area. The potential causes include decreased adipose tissue due to thinness and decreased wound-healing potential due to scleroderma-like changes, impaired blood flow, and continuous compression. Treatment consists of both conservative and surgical approaches. This guideline was created with reference to the reports on skin ulcer treatment in patients with Werner syndrome published in PubMed from 1996 to 2016.

Q1.What are the factors contributing to the easy development of refractory skin ulcer in Werner syndrome?

A1. These factors include impaired blood flow, scleroderma-like changes, decreased adipose tissue, and continuous compression due to bone deformity. Calcifications and others likely lead to skin ulcer development and delayed wound healing.

A skin ulcer in Werner syndrome is caused by various factors. It has been recognized that impaired metabolism of the connective tissue component is involved[1)]. Additionally, the following factors are considered to be concurrently associated with ulcer development: greater weight bearing on the distal extremities due to thin limbs for the body trunk, a deformed bone and joint such as hallux valgus and a flat foot, localized hyperkeratosis on the sole of the foot, physical pressure on dermal connective tissue due to subcutaneous calcification, thinning or sclerosing of the skin, decreased adipose tissue, delayed wound healing due to decreased fibroblast proliferation capacity, occurrence of diabetes, and hematogenous disorder accompanied by an arteriosclerotic lesion[2].

A skin ulcer occurs more commonly at sites on which pressure is exerted including the Achilles tendon, ankle, elbow, and plantar region[3)]. It sometimes presents with prodromal symptoms of a corn, callus, and trauma. Due to the atrophied skin and decreased subcutaneous adipose tissue at sites of predilection for skin ulcers, formation of an ulcer causes a tendon or bone to be projected easily[2)]. Werner syndrome patients often develop tumors, and thus, it is desirable to consult a dermatologist when in doubt in consideration of a possibility of a refractory skin ulcer attributed to squamous cell carcinoma or a malignant melanoma. Especially, it requires careful attention since Werner syndrome

patients have been known to develop an acral lentiginous malignant melanoma occurring commonly on the sole of the foot at a high rate [4].

Q2. What is the treatment policy of skin ulcers in patients with Werner syndrome?
A2. While treatment of diabetes mellitus and others is continued, conservative treatment is administered by the use of following methods: topical medications that help eliminate factors interfering with healing, and topical medications or wound dressings that accelerate the wound-healing process.

A skin ulcer in Werner syndrome is attributed to the factors shown in Q1, which makes it intractable. It is conservatively treated with topical medications and wound dressings first, while systemic treatment including diabetic control is required to be concurrently performed. For hyperkeratosis around a skin ulcer, keratin softeners such as salicylic acid Vaseline and urea ointment are used topically. Treating a corn and callus with keratin softeners is important to prevent the occurrence of a skin ulcer as well. In cases which a skin ulcer is not improved with conservative medical treatment, surgical treatment should be considered.
A skin ulcer in Werner syndrome is a chronic cutaneous wound. Prolonged inflammation caused by various cytokines and increased activity of protease that plays a role in melting necrotic tissue protein cause an extracellular matrix acting as a scaffold of tissue to be melted, leading to failure to reconstruct tissues in the chronic cutaneous wound[5]. Additionally, impaired molecular composition in the effusion inhibits the proliferation of the cells that are involved in tissue reconstruction[5]. To facilitate the healing process of a chronic wound, helpful topical medications to eliminate causes that interfere with healing, topical medications or wound dressings that accelerate the repairing process are required to be appropriately selected before use [6].

Q3. What is the treatment of skin ulcers with infected or necrotic tissue?
A3. Removal of necrotic tissue by surgical debridement followed by the selection of topical medications with antibacterial effects and necrotic tissue removal effects are selected.

A skin ulcer is washed with saline or lukewarm water, followed by surgical debridement for necrotic tissue using a scalpel and a scissor as much as possible. If it is being infected or already infected, an ulcer is disinfected with povidone iodine, chlorhexidine gluconate, or benzalkonium chloride to control infection[6]. In case of failure to perform debridement, chemical debridement is conducted using necrotic tissue removers including CADEX OINTMENT®, Isodine gel®, and Bromelain ointment®. GEBEN cream® containing more water facilitates softening and melting of necrotic tissue, which is effective for a wound site with small effusion. In cases with heavy exudate from a wound

site due to infection or intense inflammation, CADEX OINTMENT® and U-Pasta® KOWA that have an effect to absorb exudate are effective. As to an ulcer associated with infection or necrotic tissue, closure of an ulcer worsens infection, and thus it should be treated not with wound dressings (closed dressings) but mainly using topical preparations with an antibacterial effect[6].

Q4. What is the treatment of skin ulcers without infection nor necrotic tissue?

A4. Granulation-promoting agents, topical medication with epithelialization-promoting effects, and wound dressings that maintain a moist environment are used.

At an infection-free wound site with necrotic tissue being removed, a granulation is generally formed, whereas it is not easily formed in most skin ulcers occurring in Werner syndrome patients. Therefore, a wound site is washed with saline or lukewarm water, followed by application of granulation promoting drugs including Olcenon Ointment®, Prostandin Ointment®, and Reflap Ointment®. A basic fibroblast growth factor (Fibrast spray®) is also effective, but attention is required because a skin ulcer in WS is often associated with malignancy.

An ulcer site is filled with good granulation tissues, leading to epithelization. At this stage, epithelization promoters including Prostandin Ointment ® and Actosin Ointment® are used. Wound dressings are also effective to maintain a moist environment at the wound site. Hydrocolloid is recommended for wounds with a small amount of exudate, while alginate (Sorbsan®), chitin (Beschitin®), hydrofiber (AQUACEL®), hydropolymer (TIELLE®), and polyurethane foam (HYDROSITE®) are for those with heavy exudate[6].

Recently, a case where endothelin receptor antagonist worked for a refractory ulcer has been reported[7].

Q5. What other treatment options are available?

A5. Surgical intervention, including application of artificial dermis and flap reconstruction, may be considered if conservative treatment is not successful.

Hyperbaric oxygen therapy and vacuum-assisted closure therapy, both of which are used for general wounds and pressure ulcers, may also promote wound healing of skin ulcers in Werner syndrome. With regard to surgical treatment, skin grafting has limited success in many cases, and application of artificial dermis[8] and flap reconstruction[9, 10] are often more effective. One should also bear in mind that debridement may enlarge an ulcer due to decreased fibroblast division capacity[8].

Summary

Skin ulcers associated with Werner syndrome are often caused by a corn, callus, or trauma occurring at sites on which pressure is exerted, including the Achilles tendon, ankle, elbow, and plantar region, and are more refractory than wounds in healthy individuals. This may be attributable to the thinning or hardening of the skin, a decrease in adipose tissue, inadequate blood flow, calcification, and excess pressure due to a deformed bone and joint. To treat skin ulcer, a keratin softener is topically used for hyperkeratosis around an ulcer. Treatment for an ulcer associated with Werner syndrome is the same as that for a common ulcer. If it is accompanied by infection or necrotic tissue, however, the ulcer is washed with saline or lukewarm water or disinfected with an antiseptic, followed by surgical debridement for necrotic tissue using a scalpel and a scissor as much as possible. Topical medications that promote softening and melting of necrotic tissue are concurrently used with careful attention being paid to moisture control at the surgical wound site. For infection-free wound sites with the necrotic tissue being removed, topical medications with a granulation promoting effect are used. Wound dressings are also effective to maintain a moist environment at the wound site. In cases where a skin ulcer is not ameliorated with conservative medical treatment, surgical treatment should be considered.

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8. Calcification in tendons associated with Werner syndrome

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Introduction

While asymmetrical calcification in ligaments and tendons has been reported in Werner syndrome patients, the mechanism of which remains unclear[1]. Multiple calcifications of articular capsules and tendinous insertions may be observed in the hand, wrist, foot, knee, and elbow[2]. The Achilles tendon may also be calcified[3], and characteristically shaped calcified substances may be widely observed in some cases[4]. Ectopic calcification had previously been reported in one third of Werner syndrome patients[5], while it has recently been reported in 85.3% of patients[6]. Na-Pi cotransporter (Pit-1), which plays a role in phosphoric acid uptake, has been observed to increase in the fibroblast cells of the skin tissue in Werner syndrome patients[6].

Q1. Does the Achilles tendon calcification in Werner syndrome patients differ from that in non-Werner syndrome patients?

A1. Calcification of the Achilles tendon in Werner syndrome patients is depicted as multiple and extensive lesions with strongly graded calcification pattern expressed as a flame-like shape. This calcification pattern clearly differs from that of non-Werner syndrome patients.

Results of a recent investigation revealed that a bone spur on the calcaneus at the Achilles tendon insertion, which may be confused with calcified Achilles tendon, is caused by apoptosis of fibrocartilaginous components on the surface of the Achilles tendon insertion and subsequent enchondral ossification, proving that it differs from calcified Achilles tendon[7].

Some studies reported calcification in the Achilles tendon to be found in patients with Achilles tendinitis and Achilles enthesitis[8][9], while another study reported it to be observed after the operative treatment of Achilles tendon rupture[10]. Werner syndrome patients develop multiple blocky calcification in a wide area of the Achilles tendon with a calcification pattern that is also expressed as a flame-like shape, which clearly differs from Achilles tendon calcification in non-Werner syndrome patients.

Q2. Is the Achilles tendon calcification found in a plain radiograph useful for the diagnosis of Werner syndrome?

A2. The frequency of the Achilles tendon calcification in Werner syndrome patients far exceeds that of non-Werner syndrome patients. Thus, it is beneficial to incorporate calcification of the main body of the Achilles tendon into the diagnostic criteria of Werner syndrome.

There are clear differences between Achilles tendon calcification in Werner syndrome patients and that in non-Werner syndrome patients in the frequency, area and pattern of its occurrence. In 2010, a nationwide secondary survey was performed as part of the Nationwide Study for the Understanding of the Clinical Conditions, Creation of Practice Guidelines, and Development of a New Treatment for Werner Syndrome, showing that Achilles tendon calcification was observed in 70 (76.1%) out of 92 Werner syndrome patients who offered responses regarding calcification of Achilles tendon. The plain radiographs of 2,151 feet of 1,853 non-Werner syndrome patients, who underwent foot and ankle surgeries at the department of orthopedic surgery in Nara Medical University from 2004 to 2015, revealed that Achilles tendon calcification was observed only in 19 feet (0.88%), accompanied by 1 to 4 calcified masses with a maximum diameter ranging from 9.7 mm to 63.2 mm.

The frequency of Achilles tendon calcification in Werner syndrome patients is far higher than that of non-Werner syndrome patients, and thus it is beneficial to incorporate calcification in Achilles tendon into the diagnostic criteria for Werner syndrome.

Summary

Achilles tendon calcification includes:

1) A calcification with the length of at least 2 cm that is not contiguous with the calcaneus (a single large segmental calcification) in a plain radiograph (Figure 1)

2) At least two calcific masses with the length of not exceeding 2 cm which is not contiguous with the calcaneus (several small segmental calcific masses) (Figure 2)

3) Clearly abnormal flame-like calcification in a large area of the Achilles tendon (Figure 3).

In cases where any one of the above items applies, we should make a diagnosis, suspecting that a patient may develop Werner syndrome -specific Achilles tendon calcification.

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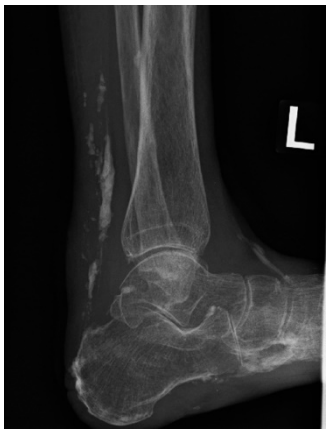
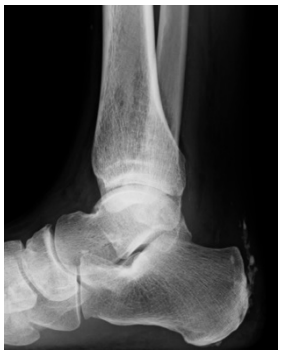
Figure 1



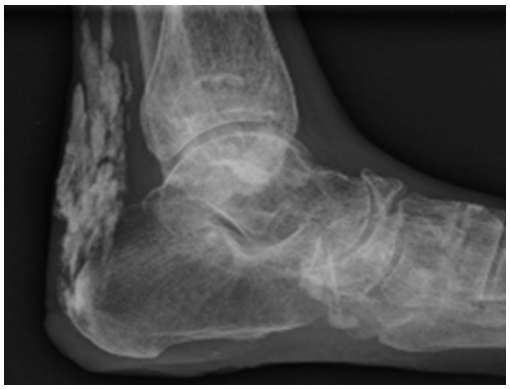
Calcification exceeding 2 cm is observed in the Achilles tendon (a single large segmental calcification)

Figure 2



Several calcifications not exceeding 2 cm in length are observed (several small segmental calcifications)

Figure 3



Flame-like calcifications are observed widely in Achilles tendon insertion (flame-like calcifications).