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早老症の実態把握と予後改善を目指す集学的研究

平成 27 年度～29 年度　総合研究報告書

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Ⅰ．総合研究報告書

早老症の実態把握と予後改善を目指す集学的研究

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研究要旨
早老症は、全身に老化徴候が早発・進展する疾患の総称である。その代表例として Werner 症候群（以下 WS と略）と Hutchinson-Gilford Progeria 症候群（以下 HGPS と略）が知られる。WS は思春期以降に発症し、がんや動脈硬化のため 40 歳半ばで死亡する早老症であり、国内推定患者数は約 2,000 名、世界の報告の６割を日本人が占める。平成 21～25 年度の難治性疾患克服研究事業により 25 年ぶりの診断基準改訂と治療の標準化や世界初の WS 診療ガイドラインが作成され、平成 26 年度の政策研究事業により WS 重症度分類が作成され、平成 26 年 5 月指定難病に指定された。一方、HGPS は 1～2 歳時に早老徴候が出現し、10 歳代でほぼ全例が死亡する重篤な小児疾患であり、確立した診断基準や診療ガイドラインがない。平成 25 年度に我々が施行した全国調査により、我が国で６名の患者が新規に同定された。
本研究では WS の診療ガイドライン改訂や WS の重症度分類の検証、HGPS の診断基準作成を行い、内科医・外科医・小児科医・臨床研究専門家の連携・融合による集学的な取り組みを通じて、小児から成人までの「早老症」の予後改善を目指している。

Ａ．研究目的

早老症は、全身に老化徴候が早発・進展する疾患の総称である。その代表例として Werner 症候群（以下 WS と略）と Hutchinson-Gilford Progeria 症候群（以下 HGPS と略）が知られる。WS は思春期以降に発症し、がんや動脈硬化のため 40 歳半ばで死亡する早老症であり、国内推定患者数は約 2,000 名、世界の報告の６割を日本人が占める。平成 21～25 年度の難治性疾患克服研究事業により 25 年ぶりの診断基準改訂と治療の標準化や世界初の WS 診療ガイドラインが作成され、平成 26 年度の政策研究事業により WS 重症度分類が作成され、平成 26 年 5 月指定難病に指定された。一方、HGPS は 1～2 歳時に早老徴候が出現し、10 歳代でほぼ全例が死亡する重篤な小児疾患である。平成 25 年度に施行した全国調査により、我が国で６名の患者が新規に同定している。このような背景の下、本事業ではエビデンスに基づく早老症の診断基準、重症度分類、診療ガイドラインの作成・改訂と普及を研究目的とした。

Ｂ．研究方法

難治性疾患実用化研究において施行されている「早老症レジストリー」と、すでに開始している医師主導治験と情報を共有しつつ、全国調査に基づき①Minds ガイドラインセンターの「診療ガイドラインの手引き」に基づく WS の診療ガイドライン改訂、②WS の重症度分類の検証、③HGPS の診断基準作成を行なった。

Ｃ．研究結果

【WS に関して】

WS の診療に関わる、下肢潰瘍治療、2. 糖尿病、3. 脂質異常症、脂肪肝、4. サルコペニア、5 感染症、6. 骨粗しょう症といったクリニカルクエスチョンに対して過去 10 年間の WS に関する症例報告の文献データベースを作成し、システマィクレビューを行い、診療ガイドラインを Minds ガイドラインセンターの「診療ガイドラインの手引き」に基づいて改訂を行った。
(分担研究報告書参照)。

現在、診療ガイドライン全て英訳を行い、今後英文誌に報告予定である。解析結果の一部は英文誌に報告した(資料 1-4)。さらに重症度分類に関して、一部文言の改定を行った(資料 5)

【HGPS に関して】

平成 25 年度に全国の 200 床以上の病院の小児科を対象にして一次アンケート調査を行い、続いて臨床症状に関するアンケート調査を行った。その結果、９名の HGPS 患者の臨床所見に関する結果を得ることができた。これまで学会報告あった 1 名の所見と併せて、その臨床的特徴を解析した。そして平成 27 年 8 月、平成 28 年 2 月、8 月開催の班会議にて HGPS 患者の診断基準に関して審議が行われ、最終的に平成 28 年 9 月に診断基準（初版）が完成し、日本小児遺伝学会の承認を受け、英文誌にも掲載された（資料 1-3)。重症度分類も作成され、今後学会の承認を受ける予定である（詳細は井原分担研究報告を参照)。

【国際シンポジウム-RECQ2019-】

これまでの研究成果の国内外への発信や早老症に関する啓蒙、国内外の老化研究者との意見交換を目的として難病医学研究財団の助成により 2019 年 2 月に千葉県木更津で国際シンポジウムを企画開催した。この国際会議はアジアで初めての、ウェルナー、ブルーム、ロスムンド・トムソンの RECQ ヘリカーゼ関連早老症候群を対象としたもので、総勢 135 名（うち 29 名が外国人）の参加を得た。海外からの 5 名を含む計 21 名の患者様、ご家族も参加され、研究者と患者の間に活発な交流がなされた。なお、本シンポジウムの様子は神戸新聞をはじめとする全国 11 紙で報道された。（資料 6）

Ｄ．考察

WS に関しては、平成 21～25 年度の難治性疾患克服研究事業により 25 年ぶりの診断基準改訂と治療の標準化や世界初の WS 診療ガイドラインが作成され、平成 26 年度の政策研究事業により WS 重症度分類が作成され、平成 26 年 5 月指定難病に指定された。さらに難治性疾患実用化研究として推進されている早老症レジストリー研究と連携し、本研究においては診療ガイドライン、重症度分類を改訂した。

HGPS に関しては、平成 25 年度に施行した全国調査に基づき平成 29 年度には世界初の HGPS 診断基準が作成された。これらを真の患者予後改善につなげるために、研究の継続と新たな発展が必要不可欠と思われる。今後我々は、①WS 診療ガイドラインの普及啓蒙、②早老症レジストリー研究と連携した診療ガイドラインの検証、③その他の早老症研究（Rothmund-Thomson 症候群の現状把握、WS 類似疾患の診断基準作成）、④HGPS の診療ガイドライン作成、⑤ WS、HGPS の早期診断の実現と小児成人期移行医療の推進、さらに⑥本研究の成果をベースとして新規研究課題が採択された、AMED「再生医療実現拠点ネットワークプログラム（疾患特異的 iPS 細胞の利活用促進・難病研究加速プログラム）」（課題名：早老症疾患特異的 iPS 細胞を用いた老化促進メカニズムの解明を目指す研究）および「老化メカニズムの解明・制御プロジェクト／個体・臓器老化研究拠点」（課題名：早老症に立脚したヒト老化病態の解明とその制御への応用）の研究推進を支援してゆく。

かくして、本研究班では、内科医・外科医・小児科医・臨床研究専門家・基礎研究者の連携・融合による集学的な取り組みを通じ、小児から成人までの「早老症」の予後改善を今後も目指してゆきたい。

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Ｇ．知的財産権の出願・登録状況（予定を含む）

１．特許取得

なし

２．実用新案登録

なし

ウェルナー症候群の診療ガイドライン

2018 年版

１．ウェルナー症候群と脂質異常症，脂肪肝

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はじめに

動脈硬化症は悪性腫瘍と並んでウェルナー症候群の 2 大死因である。動脈硬化症の中では冠動脈疾患と閉塞性動脈硬化症の発症頻度が高く、後者はウェルナー症候群患者の皮膚潰瘍を難治性とする一因となっている。ウェルナー症候群における動脈硬化症の成因は、疾患特異的な早老現象も寄与すると考えられるが、ウェルナー症候群に合併する糖代謝異常・脂質代謝異常もその促進因子として作用している。そして、このような代謝異常には、脂肪肝（NAFLD）や内臓脂肪蓄積によるインスリン抵抗性が大きく関与すると考えられる。また近年、NAFLD あるいは NASH からの肝細胞癌の全肝細胞癌に占める割合が一般人において上昇してきていることが報告されており、ウェルナー症候群においてもその対応が重要である。ウェルナー症候群症例における脂質異常症・脂肪肝の合併頻度は高いといわれており、前回のガイドラインでは自験 15 症例のうち 53%に高コレステロール血症が合併すると記載されている。しかし、これら脂質異常症の頻度、ウェルナー症候群における脂質異常症・脂肪肝の特徴について、広範に文献スクリーニングを行って検討したデータはない。これらを明らかにするため、本ガイドラインでは、1996 年から 2016 年に PubMed および Medical Online に報告された症例（98 文献、119 症例）をスクリーニングし、その中から脂質・脂肪肝のいずれかに関する何らかの記載あるいはデータのある 44 症例（平均年齢 45.6 歳、男性 26 例）[1-36]を選択して解析を行った（2005 年以前の報告：26 症例）。なお、ウェルナー症候群は悪性疾患を合併しやすい症候群であり、悪性疾患を合併した場合に脂質代謝や脂肪肝に影響がある可能性を考慮し、悪性疾患を合併している 13 症例（平均年齢 50.4 歳、男性 6 例）とそれ以外の 31 症例（悪性疾患合併なし、または記載なし：平均年齢 43.6 歳、男性 20 例）に分類しての解析も行った。これらデータは、悪性疾患合併あり：M 有群、それ以外：M 無群、として文中に記載した。

一方、上記の文献検索での症例報告には治療法が十分に記載されておらず、治療による効果・管理目標値達成率に関する記載もない。また、近年は脂質異常症治療薬の進歩もめざましい。そのような状況を鑑み、千葉大学にて経過観察中の 2010 年以降の脂質値および脂肪肝に関する詳細なデータが利用可能な 12 症例（男性 5 例、女性 7 例、平均年齢 50.1 歳、39-60 歳）のうち、データ取得時に悪性疾患の合併のない 11 症例（男性 4 例、女性 7 例、平均年齢 50.7 歳、39-60 歳）を対象として治療・治療効果などに関して調査して記載した。さらに、脂肪肝の程度を反映すると考えられている肝/脾 CT 値比（以下、LS 比）の

データのある症例についての検討も行った。
なお、文献検索より導かれた結果は SR で示し、千葉大学の症例検討での結果は CS で示した。

Ⅰ．脂質異常症

CQ1. ウェルナー症候群における脂質異常症合併頻度は？合併する脂質異常症のタイプは？
A1. 脂質異常症合併率は 85%と高率である。脂質異常症のタイプとしては、高中性脂肪血症が 76%と最も多く、高 LDL-C/non-HDL-C 血症 68%、低 HDL-C 血症 32%である。（SR）

44 症例のうち、脂質異常症に関する記載のある症例は 41 例（M 有群 13 例、M 無群 28 例）であり、そのうち 35 症例 85.4%（M 有群 84.6%、M 無群 85.7%）に脂質異常症の合併を認めた。脂質データのある症例は 25 症例であり（M 有群 7 例、M 無群 18 例）、高中性脂肪（TG）血症 76.0%（M 有群 57.1%、M 無群 83.3%）、高 LDL-C/non-HDL-C 血症 68.0%（M 有群 42.9%、M 無群 77.8%）、低 HDL-C 血症 32.0%（M 有群 14.2%、M 無群 38.9%）であった。

CQ2. 脂質異常症合併ウェルナー症候群の特徴は？
A2. 高率（90%以上）に糖尿病を合併する。高 TG 血症を呈する症例の平均 BMI は 18.2 であり、肥満を合併せずに発症する。（SR）

脂質異常症合併 35 症例のうち、糖尿病に関する記載のある症例は 33 例であり、糖尿病を合併しているものは 31 症例 93.9%（M 有群 88.9%、M 無群 95.8%）と、非常に高率に糖尿病を合併していた。また、動脈硬化症合併の記載のある症例は 4 症例であったが、その平均年齢は 41 歳と早発性動脈硬化症を示していた。

高 TG 血症 19 症例の平均 BMI は 18.2（M 有群 17.6、M 無群 18.4）、最大 BMI 22.8、最小 BMI 12.49 であり、また BMI 18.5 未満の低体重症例は 9 症例 47.3%（M 有群 7 症例 46.7%、M 無群 2 症例 50%）であった。なお、正 TG 血症 9 症例においては、平均 BMI 16.5、BMI 18.5 未満 8 症例（88.9%）と、有意差はないものの高 TG 血症例よりもさらに“やせ”であった。このように、ウェルナー症候群高 TG 血症例は、正 TG 血症例よりも BMI は高い傾向ではあるものの、肥満との関連が強い一般人高 TG 血症とは異なっていた。

CQ3. ウェルナー症候群における脂質管理目標値達成率は？有効な薬剤は？
A3. 脂質管理目標値達成率は LDL-C 91%、HDL-C 91%、TG 82%と高い。脂質異常症治療薬としては、ストロングスタチンが主として用いられ、管理目標値達成に寄与する。（CS）

CS 12 症例において、糖尿病合併例は 6 例、耐糖能異常合併例は 1 例、下腿潰瘍合併例は 9 例、閉塞性動脈硬化症（PAD）合併例は 3 例（すべて糖尿病・下腿潰瘍を合併）であり、心筋梗塞の既往のあるものは 0 名であった。2017 年版動脈硬化性疾患予防ガイドライン[37]のカテゴリー分類で高リスク群に該当する者は 6 名であった。

悪性疾患を合併していない 11 症例のうち、脂質異常症治療薬内服中の患者が 5 例、スタチン非内服でリスクに応じた LDL-C 管理目標値に達していないものが 1 例、HDL-C 40 mg/dL 未満の症例が 1 例、TG 値 150 mg/dL 以上の症例が 2 例、であり、脂質異常症と診断できるもの（いずれかの項目を満たすもの）は 8 症例（73%）であった。スタチン内服中の症例ではすべての症例が LDL-C 管理目標値を達成しており、LDL-C、TG、HDL-C の管理目標値達成率は、LDL-C 91%、TG 82%、HDL-C 91%と、非常に高かった。使用されていた脂質異常症治療薬はすべてストロングスタチン（アトルバスタチン、ロスバスタチン、ピタバスタチン）であった。なお、高リスク病態である糖尿病患者の LDL-C 値は 84.5 ± 21.4 mg/dL（最小値 51.0 mg/dL、最大値 105.4 mg/dL）であり、特定健診糖尿病患者[38]の平均 LDL-C 値（男性 114.0 mg/dL、女性 122.9 mg/dL）よりも良好な管理を達成していた。また、同様に高リスク病態である PAD を有するウェルナー症候群の LDL-C 値は 75.1 ± 23.2 mg/dL (最小値 51.0 mg/dL、最大値 97.4 mg/dL)であり、PAD と同様に高リスクに分類される脳血管障害既往者の特定健診受診者における値（男性 115.7 mg/dL、女性 123.2 mg/dL）よりも良好な値であった。このように、高リスク病態での脂質管理目標値達成率は 100%であり、特定健診データでの高リスク病態（糖尿病、脳血管障害既往）における LDL-C 管理目標値達成率約 60%[38]と比べ、ウェルナー症候群高リスク患者では極めて良好な管理が達成されていた。

Ⅱ．脂肪肝

CQ4. 脂肪肝合併ウェルナー症候群の特徴は？

A4. 平均 BMI 18.8、最大 BMI 22.6 であり、83%の症例が標準体重以下である。（SR）

解析対象 44 症例中、脂肪肝の記載があった症例は 12 症例（M 有群 10 症例、M 無群 2 症例）であり、平均 BMI は 18.8（M 有群 18.7、M 無群 19.3）、BMI 22 以上の症例数は 2 症例（いずれも M 無群）で、最大 BMI は 22.6 であった。一般人における脂肪肝（非アルコール性脂肪性肝疾患：NAFLD）罹患率は 30%程度であるが、肥満に伴いその有病率は上昇し、BMI 別の NAFLD 合併率として、28 以上で約 85%、25-28 で約 60%、23-25 で約 40%、23 未満では 10%程度、と報告されている。それゆえ、“やせ”でも高率に脂肪肝を合併することがウェルナー症候群における脂肪肝の特徴といえる。また、12 症例の脂質異常症合併率 91.6%（M 有群 90.0%、M 無群 100%）、糖代謝異常合併率 90.9%（M 有群 90.0%、M

無群 100%）であり、高率に他の代謝疾患を合併していた。

CQ5. 脂肪肝合併症例と非合併症例で、生化学データにおける相違は？
A5. 肝/脾 CT 値比（LS 比）は、HDL-C と正の相関、TG 値と負の相関を示すが、肝逸脱酵素とは相関を認めない。（CS）

CS において、LS 比の値が揃っており、かつ悪性腫瘍を合併していない 9 症例での解析を示す。9 例のうち脂肪肝合併症例（LS 比 1.0 未満：以下 FL）は 4 例で 44%であった。FL の平均 BMI は 16.7（最大 17.8、最小 15.5）と“やせ”の症例のみであった（非脂肪肝症例[以下非 FL]の平均 BMI 17.1）。各種検査値（LDL-C、HDL-C、non HDL-C、TG、AST、ALT、γGTP、ChE、AST/ALT 比）の FL 群と非 FL 群の比較（t 検定）では、HDL-C 値が FL 群 46.0 ± 8.1 mg/dL、非 FL 群 64.6 ± 13.3 mg/dL と、FL 群で有意に低かった（$P < 0.05$）。LS 比と各種検査値との相関では、HDL-C 値と正の相関（R^2=0.609、p=0.013）、TG 値と負の相関（R^2=0.509、p=0.031）を示した。

CQ6. 肝細胞癌発症症例は存在するか？
A6. 脂肪肝との関連は明記されていないものの、44 症例中 1 症例の肝細胞癌症例報告がある。（SR）

全 44 症例のうち 40 歳男性症例にて肝細胞癌合併の報告[23]があった。非癌部の肝組織に関する記載はないため確定的なことは言えないが、B 型肝炎ウイルス・C 型肝炎ウイルス・自己免疫関連肝疾患に関する検査はすべて陰性であり、NAFLD または NASH を素地として発症した症例である可能性は否定できない。

まとめ

1. 脂質異常症

1966 年の Epstein らの総説[39]や 1989 年の横手らの報告[40]にみるように、以前よりウェルナー症候群は脂質異常症を合併しやすいことが報告されていたが、近年（1996 年以降）の症例報告を網羅的に拾い上げて 2017 年版動脈硬化性疾患予防ガイドライン[37]の診断基準に照らし合わせることにより、85%のウェルナー症候群に脂質異常症が合併しており、そのうち 90%以上に糖尿病を合併していること、高 LDL-C/non-HDL-C 血症・高 TG 血症・低 HDL-C 血症のいずれのタイプもとるが比較的高 TG 血症の者が多いこと、高 TG 血症症例の平均 BMI は 18.2 と肥満を合併することなく発症していること、が確認された。Mori らは男性 3 名、女性 1 名の腹部 CT 画像の検討を行い[14]、2 例の男性患者には＞100cm^2 の内臓脂肪面積を認めること、他の 2 例においても内臓脂肪面積/皮下脂肪面積比が高いことを報告している。

ウェルナー症候群において内臓脂肪蓄積が生じる分子メカニズムは不明な点が多いが、内臓脂肪蓄積の結果インスリン抵抗性が増加し、脂質異常症・糖質代謝異常をきたすものと考えられる。高 LDL-C 血症に関しては、横手および Mori らは自験 10 症例のうち 6 症例にアキレス腱肥厚と高コレステロール血症を伴うこと[40]、このうちの 5 症例の検討では LDL 受容体活性が低下していること[41]を報告しており、ウェルナー症候群自体に LDL 受容体活性を低下させる何らかの機序が存在することが想定される。疾患特異的に診断前から LDL-C がウェルナー症候群で上昇していると仮定すれば、近年唱えられている累積 LDL-C を考慮すると、ウェルナー症候群では家族性高コレステロール血症と同等のリスクを有していると仮定してもよいかと考えられる。

さて、ウェルナー症候群の脂質異常症がウェルナー症候群診断前から存在するかどうかは不明だが、ウェルナー症候群のマクロファージが泡沫化されやすいこと[42]や糖代謝異常・内臓脂肪蓄積などの危険因子がウェルナー症候群では重複することを考慮すると、脂質異常症の積極的かつ十分な管理が望ましい。今回の CS12 症例の検討結果より、ストロングスタチンも用いた集約的治療を行えば脂質値の管理目標値達成は可能であろうことが明らかとなった。また、特定健診での高リスク患者の LDL-C 管理目標値達成率は 60%程度であるのに対しウェルナー症候群では 90%以上であるのは、ウェルナー症候群と動脈硬化症の関連を医療サイド・患者サイドともに認識しているゆえ、積極的に治療を行っている結果と考えられる。

2. 脂肪肝

1985 年の Imura らによるわが国ウェルナー症候群 102 症例のアンケート調査では、35.4%に軽度の肝機能異常があり、その原因として脂肪肝の存在が示唆されていたが[43]、今回の CS12 症例での解析からウェルナー症候群の 4 割程度に脂肪肝が合併していることが確認された。また一般の脂肪肝と異なり、SR・CS いずれの解析においても標準体重～やせの状態で脂肪肝を発症しており、かつ脂質異常症・耐糖能異常の合併率が極めて高いことが確認された。 この脂肪肝発症には、ウェルナー症候群疾患特異的な機序が関与する可能性があるものの、一般人における脂肪肝発症と同様の内臓脂肪蓄積とインスリン抵抗性による遊離脂肪酸の肝臓への過剰流入によるもの[44]も想定される。

近年、NAFLD、NASH からの肝細胞癌発症が注目されている。SR にて確認された 40 歳の症例はウェルナー症候群に伴う発癌の可能性もあるが、脂肪肝・NASH に伴ったものの可能性も否定はできない。それゆえ、脂肪肝改善のための治療法の確立も必要である。一般人においてはピオグリタゾン[45) 46)]、ビタミン E[47)]、ウルソデオキシコール酸[48)]などのエビデンスがあるが、Takemoto らはカロテノイドの一つであるアスタキサンチンが脂肪肝を改善させたと報告[36)]しており、またウェルナー症候群モデル動物では Resveratrol の脂肪肝改善効果 33）も報告されている。今後の治療薬開発が期待される。

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２．ウェルナー症候群とサルコペニア

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はじめに

サルコペニアとは加齢により著しく骨格筋量が減少しかつ筋力または身体機能が低下した状態を指す[1)]。一般的に 70 歳までに 20 歳台に比較すると骨格筋面積は 25-30%、筋力は 30-40%減少し、50 歳以降毎年 1-2%程度筋肉量は減少すると一般に言われている[2)]。さらに加齢とともにおこる骨格筋量の低下は骨格筋線維の減少ならびに個々の筋線維の萎縮による。さらに骨格筋線維の減少は主に速筋であるタイプ IIa（速筋、白筋）の減少であることが知られる[2)]。サルコペニア（sarcopenia）は造語であり、ギリシャ語で肉という意味の”sarco”と、欠乏という意味の”penia”から出た言葉である[1,2)]。サルコペニアは加齢以外特別な要因がない一次性（加齢性）サルコペニアと不活発（廃用）や疾病（進行した悪性腫瘍や臓器不全）や低栄養に伴う骨格筋量ならびに筋力、身体機能が低下した二次性サルコペニアに分類される[1)]。

サルコペニアの存在は高齢者に転倒や身体機能障害、要介護状態、フレイルのリスクになることが知られ、日本においては介護予防の点からも近年重要視されている[3)]。

CQ1. ウェルナー症候群では早期に四肢骨格筋量が低下し､若くしてサルコペニアになりやすいか？

A1. ウェルナー症候群では成年期（40 歳未満）においても高頻度で四肢骨格筋量の低下が起こる。その要因は不明であるが、習慣的レジスタンス運動により骨格筋量の低下を認めない症例も存在していることより、適切な介入により予防できる可能性がある。

ウェルナー症候群と骨格筋に関する論文は検討した限り 2017 年に日本から報告された一本のみである[4)]。その報告では 9 名のウェルナー症候群、男性 4 名、女性 5 名、平均年齢 48 ± 8.8 歳（SD）（39 歳から 60 歳）を対象に、Asian Working Group for Sarcopenia の提言したサルコペニアの診断基準（二重エネルギーX 線吸収測定法にての四肢骨格筋指数（四肢骨格筋量 (kg) ÷身長 $(m)^2$）: < 7.0 kg/m^2 （男性）、<5.4 kg/m^2 （女性）ならびに握力 : <26kg（男性）、<18kg（女性））[5)] を使用し、四肢骨格筋指数の低下ならびに握力低下を指標としてサルコペニアとして診断している。

握力に関してはこの基準を満たしていない症例が男性 4 例中 2 例存在したが、骨格筋量の指標である骨格筋指数は全てカットオフ値以下であった。同研究では同時に内臓脂肪の蓄積（腹部 CT で評価）を評価しているが、9 名の年齢を考慮した検討では骨格筋量の低下は内臓脂肪の蓄積する以前にも認められた。全例運動機能自体が低下していたが、糖尿病

の有無別の検討では糖尿病を発症している対象者で体格指数が高値で内臓脂肪が多いものの、骨格筋指数に関して両群で差を認めなかった。

自験例ではあるが、7 名のウェルナー症候群（平均年齢 49.1±6.8 歳、39 歳から 70 歳、男性 4 例、女性 3 例）のバイオインピーダンス法にて骨格筋指数を検討したところ、一例の男性を除いて 6 例は基準値（Asian Working Group for Sarcopenia の提言したバイオインピーダンス法による骨格筋指数のカットオフ値は< 7.0 kg/m^2 （男性）、<5.7 kg/m^2 （女性））[5] を下回った．一例は 43 歳の男性で学生時代からレジスタンス運動を継続している対象者であった [6]。

上記の様に通常加齢に伴うサルコペニアは骨格筋線維の減少（特に速筋）ならびに個々の筋線維の萎縮を伴うが、ウェルナー症候群症例の筋生検による詳細な検討がなく、ウェルナー症候群患者においても同様な変化があるかどうかは不明である。またサルコペニアの診断は上記の四肢骨格筋量の低下を必須項目として、筋力または身体機能（歩行速度など）を併せ持つ場合とされる [1,2,3,5]。ウェルナー症候群では難治性足底潰瘍を起こしやすく、歩行速度の計測ができないケースがあり、また手指変形などを伴うケースもあり握力測定自体が困難なケースがあり、診断が必ずしも容易ではない。

まとめ

以上より、ウェルナー症候群では高頻度で 40 歳前に既に骨格筋量の低下が起こっている。その要因に関してはなお不明であるが、骨格筋自体の加齢の進行、代謝異常、炎症、または身体機能低下により活動量の低下など様々な可能性があるが、今後の研究の進展に期待したい。一方で上記の例のようにサルコペニアを認めない例も存在することより、適切な介入（レジスタンス運動など）により予防できる可能性も示唆された。

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３．ウェルナー症候群と糖代謝異常

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はじめに

ウェルナー症候群は早老症の代表的疾患である。最初に現れる臨床所見は思春期成長スパートの欠如であり、その後、皮膚の萎縮、硬化、部分的な皮下脂肪の喪失、白髪や禿頭などの毛髪の変化、白内障などの老化徴候が出現する。糖代謝異常も高率に合併し、ウェルナー症候群における代表的な代謝異常である[1,2]。

CQ1. ウェルナー症候群における糖尿病の合併頻度は？

A１．ウェルナー症候群患者のおよそ 55%に糖尿病を合併する。

1966 年に発表された Epstein の総説によると、ウェルナー症候群と診断された 125 名のうち、55 名（男性 28 名、女性 27 名）に糖尿病を認めたと記載がある[1]。我が国からは、1984 年の厚生省特定疾患ホルモン受容体機構調査研究班（尾形悦郎班）において井村らにより国内のウェルナー症候群患者の調査結果が報告されている。この調査では全国の 200 床以上の病院に 1930 通のアンケート調査が施行され、181 名の患者が集まり、さらにブドウ糖負荷試験が施行された 90 例中 50 例（55.6%）に糖尿病が認められている[3]。

後藤らの 1966 年から 2004 年までの文献報告例を調査した報告では 70%前後に 2 型糖尿病もしくは境界型糖尿病を合併するとある[4]。さらに 2008 年まで文献調査が延長され、年代別に検討した所、ウェルナー症候群における糖尿病の発症率は時代を超えて一定であること、1966 年の報告では糖尿病の平均発症年齢は 33.7 歳、2004 年では 39.7 歳、2008 年では 39.3 歳と、糖尿病の発症年齢が遅れていると報告している[5]。

2011 年に施行された全国疫学調査では、200 床以上の施設に 6921 通のアンケート調査が施行され、396 例の患者が新たに確認され、196 例の臨床所見が得られた。その結果、55.7%に糖尿病、6.5%に境界型糖尿病の合併が認められた[6]。後藤らが記載しているように、我が国のウェルナー症候群における糖尿病の発症率は 1986 年の井村らの報告とほぼ同等であった。

CQ2. 合併する糖尿病のタイプは？

A2. ウェルナー症候群に合併する糖尿病は成因分類では「他の疾患、条件に伴うもの、その他の遺伝的症候群で糖尿病を伴うことの多いもの」に分類され、BMI が少ないにも関わらず、内臓脂肪が蓄積し、インスリン抵抗性が強いことが特徴である。

Epstein はウェルナー症候群に合併する糖尿病の特徴として、多くの患者で血糖値は正常にも関わらず、ブドウ糖負荷試験後に緩徐に血糖値が上昇し高血糖が遷延すること、この高血糖に対するインスリン治療の効果が少ないことを報告している。またウェルナー症候群では四肢は枯れ枝状であり脂肪萎縮が観察されるが、脂肪萎縮は糖尿病の発症に関与しないと記載がある[1)]。

井村らの報告では 53 例でブドウ糖負荷試験血中インスリン値が測定されており、33%に基礎インスリン値が 20μU/mL と高インスリン血症を認め、67%にブドウ糖負荷試験の際の頂値が 200μU/mL と過剰反応が観察されるとある。内因性インスリン分泌が低下している例はまれであり、ウェルナー症候群ではインスリン抵抗性が強くとも膵 β 細胞からのインスリン分泌は比較的保たれることが示唆されている。またインスリン抵抗性の発症機序として、赤血球表面のインスリン受容体発現は低下しておらず、培養皮膚繊維芽細胞を用いた検討によりインスリン受容体後の機能異常が関与すると報告されている[3)]。

一般的には糖尿病の発症と肥満（BMI の増加）には相関関係が見出されることが多いが、ほとんどのウェルナー患者では BMI22 を下回る。横手らは糖尿病を合併したウェルナー症候群患者では内臓脂肪蓄積が観察され、血中のアディポネクチン低値、tumor necrosis factor α（TNF-α）や interleukin-6 (IL-6)が増加することを報告している[7,8)]。最近、一症例報告ではあるが、食事負荷後のグルカゴン分泌異常がウェルナー症候群の糖代謝異常に関与する可能性も示唆されている[9)]。また日本人ウェルナー症候群患者の体組成が詳細に検討され、糖尿病群（n=4）は非糖尿病群（n=5）と比較して年齢、性別、骨格筋量に差を認めなかったものの、BMI や内臓脂肪量が優位に多いことも報告されている（表１）[10)]。つまりウェルナー症候群における糖尿病の発症には四肢の脂肪、骨格筋萎縮は関与せず、内臓脂肪蓄積に伴うインスリン抵抗性が関与すること、一般的には糖尿病の発症には遺伝的背景に加えて、環境要因の変化が深く関与するが、ウェルナー症候群における糖尿病の発症率が一定な事を鑑みるとウェルナー症候群の糖尿病の発症には環境要因よりも遺伝要因の影響が大きい可能性がある。

CQ3. ウェルナー症候群に合併した糖尿病に対する有効な治療法は
A3. ウェルナー症候群の血糖管理にはチアゾリジン誘導体が有効である。

Epstein の報告にあるように、ウェルナー症候群に合併する糖尿病に対してはインスリン治療の有効性は乏しい。これまでインスリン抵抗性改善薬である、peroxiome proliferator-activated receptor gamma (PPARg)のアゴニストであるチアゾリジン誘導体の有効性が数多く報告されている 7,8,11-18)。一方、一般的にはチアゾリジン誘導体の骨への影響を危惧する報告や悪性腫瘍発症に関する報告があるも、ウェルナー症候群においてチアゾリジン誘導体と骨、悪性腫瘍発症との関連を示唆する報告はまだなく、今後検討が必要である。その他、少数例の報告ではあるが、ビグアナイド薬[19)]、DPPIV 阻害剤[9,20)]、

GLP-1 受容体作動薬[21]の有用性が報告されている。ウェルナー症候群では低身長、低体重に加えて、若年期より骨格筋量の減少が観察される[10]。内臓脂肪を増加させず、骨格筋量を落とさないような食事指導が必要と思われるも、ウェルナー症候群に合併する糖尿病に対する食事療法は確立しておらず今後の重要な研究課題の一つである。

まとめ

ウェルナー症候群ではインスリン抵抗性を伴った糖尿病を高率に合併する。チアゾリジン誘導体には、体重や骨折の増加など、ウェルナー症候群にとって好ましくない作用が知られているため、その長期的な使用にあたっては注意が必要である。また、本症候群に対するチアゾリジン誘導体の使用成績の多くは、我が国でまだビグアナイド薬が十分に普及していなかった年代に報告されている。メトホルミンの作用機序や近年の未公表データを勘案すると、今後、ウェルナー症候群の糖尿病治療や予後改善に本薬が有用な可能性も検討すべきと考えられる。DPP4 阻害剤や GLP-1 受容体作動薬などの新しい糖尿病薬の効果も期待される。さらに効果的な食事・運動療法の確立が必要である。

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表１ 糖尿病の有無による臨床所見の違い

	非糖尿病	n	糖尿病	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, * $p < 0.05$, 文献 10 より

４．ウェルナー症候群と骨粗鬆症

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CQ1. 骨粗鬆症の合併頻度はどのくらいで好発部位はどこか？
A1. およそ 41%に骨粗鬆症が認められている。腰椎に比較して大腿骨において重症となりやすい。

ウェルナー症候群は代表的な遺伝性早老症候群の一つであり、ヒト加齢に伴う様々な変化と類似した病態を若年期より呈する。その中で骨粗鬆症は、本症候群に見られる特徴的な早期老化徴候の一つとされている。

本症候群 24 例の臨床的特徴をまとめた村田らの報告[1)]によれば、24 例中 9 例にレントゲン所見として骨粗鬆症が認められたとしている。若年患者では比較的まれだが、40 歳以上の症例ではほぼ全例に骨粗鬆症が認められ、また骨粗鬆症の程度は下肢において重症であったとしている。さらに村田らは同論文の中で、わが国で報告されている本症候群 153 例においては、そのうちの 41%に骨粗鬆症の記載が認められたとしている。

村田らの報告は、DXA（dual energy x-ray absorptiometry）法による骨密度測定が一般化する以前の報告であるため、現在の骨粗鬆症の診断基準[2)]を用いた場合、骨粗鬆症の合併頻度が以前に報告されているほど高いか否かは不明であった。そこで今回、千葉大学医学部附属病院に通院する本症候群患者 10 例を対象に、より詳細な骨粗鬆症の評価を行った[3)]。表 1 に示すとおり、女性 5 例、男性 5 例であった。本症候群の診断は特徴的な臨床症状に加え、末梢血白血球より抽出した DNA を用いた遺伝子診断によって確定した（表 1）。骨密度は DXA 法によって測定し、若年成人平均値（YAM）の 70%以下または T-スコア－2.5 SD 以下を骨粗鬆症と判定した。腰椎骨密度で評価すると、骨粗鬆症レベルの骨密度を示したのは症例 1 のみであった。椎骨レントゲン所見は 6 例で得られたが、明らかな骨粗鬆症性の脆弱性骨折は認めなかった。一方、大腿骨頸部骨密度で評価すると、骨粗鬆症レベルの骨密度を示したのは 6 例（症例 1、2、3、5、7、10）であった。以上の結果から、本症候群に合併する骨粗鬆症は、腰椎に比較して大腿骨において重症となることが確認された。

QC2. 骨粗鬆症の発生機序は明らかにされているのか？
A2. 本症候群では骨吸収は正常に行われているが、骨形成が抑制されているため骨粗鬆症を発症すると考えられる。

骨粗鬆症の発症には、骨芽細胞による骨形成と破骨細胞による骨吸収のバランスの乱れが原因として考えられている。例えば、典型的な閉経後骨粗鬆症においては、その発症には

主としてエストロゲンの減少による破骨細胞の機能亢進が関与していることが知られている。このような観点から Rubin ら [4]は、本症候群における骨粗鬆症の発生機序を検討した成績を報告している。

彼らが経験した症例は 43 歳の白人女性であった。脊椎骨レントゲン検査では、ほぼ全ての胸腰椎に脆弱性圧迫骨折が認められた。骨密度は腰椎 0.776 g/cm^2、大腿骨頸部 0.441 g/cm^2 であり、これは同年齢女性の平均値に比較すると、それぞれ－2.38 SD、－3.93 SD に相当する。血液学的所見には特記すべき異常は認められなかったが、血中インスリン様増殖因子 1（insulin-like growth factor-1; IGF-1）が 86 ng/mL（この年齢での正常範囲: 142-389）と低値を示した。しかしながら、血中成長ホルモンの基礎値は正常範囲内であり、アルギニン・L-ドーパ負荷による成長ホルモンの分泌反応パターンも正常であった。本症例では腸骨生検も施行され、皮質骨の骨量減少ならびに皮質骨の菲薄化が認められた。さらに重要な所見として、類骨の量が著明に減少しており、採取された組織には骨芽細胞の存在を確認できなかった。これらの所見を総合すると、本症候群では骨吸収は正常に行われているが、骨形成が抑制されているものと考えられた。

彼らはさらに、本症例を IGF-1 で治療した時の成績を報告している [5]。リコンビナントヒト IGF-1 を 6 ヶ月間､毎日皮下注射した前後で骨密度と骨代謝マーカーの変化を測定した。治療中は、骨形成マーカーである血清タイプ 1 プロコラーゲン C-ペプチドならびに血清オステオカルシンは増加し、また骨吸収マーカーである尿中ピリジノリン架橋産物ならびに尿中ハイドロキシプロリンも増加した。治療後は腰椎骨密度が 3%増加し、これは本検査の変動係数を超える増加量であった。以上の結果から、彼らは IGF-1 が低値を示す本症例においては、IGF-1 補充により抑制された骨形成を回復できる可能性が示唆された、としている。

一般的に加齢性の骨粗鬆症は椎骨や大腿骨近位部などの体幹骨に好発するが、本症候群に見られる骨粗鬆症は、四肢末端、特に下肢において重症となる傾向が認められる。本症候群では、しばしば下肢の皮膚硬化に伴う関節拘縮、あるいは足部の潰瘍性病変などが生じるため、下肢骨は廃用性ならびに炎症性変化の影響を受けやすい。そのことが本症候群において、骨粗鬆症が下肢において重症となる理由の一つであると考えられる。

QC3.*WRN* 遺伝子多型との関わりはあるのか？

A3. *WRN* 遺伝子多型と骨粗鬆症との関連を示す研究結果は、本症候群に合併する骨粗鬆症の発症に遺伝的因子も関与している可能性を示唆している。

本症候群の早期老化徴候の一つに骨粗鬆症があるからと言って、そのことが直ちに本症候群の遺伝子異常と骨代謝との直接的な関係を意味するものではない。本症候群の責任遺伝子産物である Werner helicase は､主として DNA の修復過程に関与すると考えられており、また本遺伝子はヒト皮膚線維芽細胞での発現は確認されているものの [6]、骨芽細胞ないし破

骨細胞において発現しているか否かについては未確認であるため、機能的にも骨代謝との関連性を類推するのは困難である。最近、この点に関して新たな洞察を与える研究が報告された。

WRN 遺伝子には 8 箇所の一塩基多型（single nucleotide polymorphism; SNP）が知られており、そのうち 4 箇所はアミノ酸置換を伴うもの、もう 4 箇所はアミノ酸置換を伴わないものである [7]。その中で rs1346044（T>C, Cys1367Arg）、すなわち 1367 番目のシステイン残基をアルギニン残基に置換する多型と骨粗鬆症との関わりを検討した成績が既に報告されていた [8]。対象は 377 名の健康な閉経後女性であり、平均年齢は 65.6 歳であった。ゲノタイプ頻度は T/T 87.5%、T/C 12.2%、C/C 0.3%であった。これらの対象を大きく C 非保有者（T/T）ならびに C 保有者（T/C と C/C）の 2 群に分けて比較すると、C 保有者において有意（$p = 0.037$）に腰椎骨密度が低値を示したとしている。

我々も、東京都健康長寿医療センター連続剖検 1632 例（平均年齢 81 歳、男 924 例、女 708 例）から得られた DNA を用いて、*WRN* 遺伝子上の rs2230009（340G>A、V114I）のタイピングを行い、大腿骨骨折罹患率との関連性を検討した [9]。さらに当センター閉経後骨粗鬆症患者 251 例（平均年齢 71 歳）から得られた DNA を用いて骨密度との関連解析を行った [9]。表 2 に、性別と年齢を調整した多重ロジスティック回帰分析の結果を示す。rs2230009 の AA 型ないし AG 型を有する場合、GG 型と比較して、大腿骨骨折のオッズ比は 2.528 倍と有意に高値であった。ちなみに、女性は男性の 2.983 倍、年齢は 10 歳ごとに 1.746 倍骨折リスクが増加することも明らかとなった。大腿骨骨折との有意な関連性を見いだした rs2230009 に関して、さらに二次コホートを用いたバリデーションを行った。閉経後骨粗鬆症患者を対象に、rs2230009 の遺伝子型と各種臨床指標との関連性を検討した成績を表 3 に示す。有意差検定は年齢、体重、身長は Student's t-test、その他は線形回帰分析（年齢補正）で行った。その結果、大腿骨頸部骨密度は GG 型に比較して AG 型では有意に低値を示すことが明らかとなった。

これら一連の *WRN* 遺伝子多型と骨粗鬆症との関連を示す研究結果は、本症候群に合併する骨粗鬆症の発症に遺伝的因子も関与している可能性を示唆している。

QC4. 治療はどうしたらよいか？

A4. 本症候群に合併する骨粗鬆症の治療法に関しては、現時点では明らかなエビデンスは見当たらないため、通常の骨粗鬆症の治療ガイドライン [10]に従って行うことが妥当と判断される。

骨粗鬆症性骨折のリスクを減少させる代表的な薬物としてビスフォフホネート製剤が汎用されているが、本製剤の一つである etidronate が本症候群の有痛性軟部組織石灰化を改善したとする報告 [11]もあり、薬剤選択において参考となる。一方、本症候群では骨粗鬆症の成因に骨形成の抑制が主として関与しているとする報告があり、この点からは副甲状腺ホル

モン（PTH）製剤（teriparatide）が効果的であると推察されるが、本症候群では肉腫の発生頻度が高いことを考慮すると、PTH 製剤を使用する場合は骨肉腫の発生に特段の注意を要する。

まとめ

ウェルナー症候群ではしばしば骨粗鬆症を合併する。通常、加齢性骨粗鬆症では好発部位が椎骨ならびに大腿骨近位部などの体幹骨であるが、本症候群では四肢末梢、特に下肢において重症となる。本症候群では下肢の皮膚硬化に伴う関節拘縮、あるいは足部の潰瘍性病変などが生じるため、下肢骨は廃用性ならびに炎症性変化の影響を受けやすい。そのことが本症候群において、骨粗鬆症が下肢において重症となる理由の一つであると考えられる。一方、*WRN* 遺伝子多型と骨粗鬆症との関連を示す研究結果も報告されており、本症候群では遺伝的にも骨粗鬆症の発症が促進している可能性が示唆される。

本症候群に合併する骨粗鬆症の治療法に関しては、現時点では明らかなエビデンスは見当たらないため、通常の骨粗鬆症の治療に準じて行うことが妥当と判断される。また骨粗鬆症の発生機序に廃用が関与している可能性を考慮すれば、積極的なリハビリテーションによる廃用防止も重要である。

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表 1 ウェルナー症候群 10 例の骨密度

症例	性別	年齢（歳）	*WRN* 変異	腰椎骨密度（L_{2-4}）			大腿骨頸部骨密度		
				g/cm^2	*T*-score SD	%YAM	g/cm^2	*T*-score SD	%YAM
1	男	57	6/6	0.730	−2.7*	70¶	0.601	−2.1	70¶
2	女	60	6/6	0.804	−2.1	78	0.452	−3.1*	57¶
3	女	57	4/6	0.790	−1.9	78	0.351	−4.0*	45¶
4	男	40	4/11	1.116	0.6	107	−	−	−
5	女	60	4/4	0.803	−1.8	79	0.533	−2.3	68¶
6	女	40	11/11	0.983	−0.2	97	0.582	−1.9	74
7	男	51	4/7	0.971	−0.6	93	0.508	−2.8*	59¶
8	女	42	4/4	0.892	−1.0	88	0.598	−1.7	76
9	男	43	4/4	0.890	−1.3	85	0.697	−1.3	81
10	男	53	4/−	0.901	−1.1	85	0.606	−2.0	70¶

*T-score ≦ −2.5

¶YAM ≦ 70%

表 2 WRN 遺伝子多型（rs2230009, 340G>A）と大腿骨骨折との関係

因子	オッズ比(95%信頼区間)	*P*
遺伝子型, AA/AG vs GG	2.528 (1.194-5.350)	0.0154
性別，女性 vs 男性	2.983 (1.988-4.776)	<0.0001
剖検時年齢, 10 歳毎	1.746 (1.396-2.185)	<0.0001

表 3 WRN 遺伝子多型（rs2230009, 340G>A）と各種臨床指標との関係

	GG (n=236)		AG (n=15)		Difference (95% CI)	*P*
	mean	SD	mean	SD		
年齢（歳）	70.9	8.09	71.7	6.83	0.76 (−3.43 - 4.94)	0.724
体重（kg）	48.0	6.81	44.7	5.00	−3.33 (−6.97 - 0.32)	0.074
身長（m）	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
四肢筋肉量（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
腰椎骨密度（g/cm^2）	0.79	0.14	0.73	0.17	−0.07 (−0.14 - 0.00)	0.068
大腿骨頸部骨密度（g/m^2）	0.63	0.08	0.59	0.08	−0.04 (−0.08 - −0.00)	0.041*
血清カルシウム（mg/dL）	9.65	0.41	9.53	0.31	−0.12 (−0.33 - 0.09)	0.270
血清 25 水酸化ビタミン D（ng/mL）	21.5	6.45	19.4	5.15	−2.02 (−5.35 - 1.30)	0.230

*$P < 0.05$

５．ウェルナー症候群と感染症

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はじめに

ウェルナー症候群は結合組織の代謝異常があり[1]、に皮下組織の萎縮、血流の低下[2]、線維芽細胞の活性低下[3]などを認めるため難治性皮膚潰瘍が出現しやすい[4]。さらに２型糖尿病の合併もみられるため[5]、潰瘍部における皮膚・軟部組織感染症および骨髄炎を起こしやすい。一般的には糖尿病患者に見られるものより重篤な場合が多く、保存的な治療ができずに外科的に感染部位を切除するリスクが高い。ウェルナー症候群の難治性皮膚潰瘍における感染症治療の目標は、感染兆候の早期発見と治療により皮膚潰瘍病変の増悪を最小限に留めることだと考えられる。

CQ1. ウェルナー症候群における皮膚潰瘍感染症の特徴は？
A1. ウェルナー症候群の皮膚潰瘍が感染を起こしたときの起因菌は糖尿病足病変でみられるものとほぼ一致する。ただし、糖尿病患者よりも皮膚潰瘍の治癒が悪いために感染が長期化および慢性化するリスクは高い。感染が長期化すると耐性菌の出現が問題となり、治療できる抗菌薬が限られてくる。そのため皮膚潰瘍における感染症の起因菌同定と、その起因菌に絞った抗菌薬の投与が重要である。感染症のコントロールが難しい場合には、適切なタイミングでデブリードマンおよび外科的切除が必要になる。そのため形成外科医や整形外科医との連携は欠かせない。

CQ2. ウェルナー症候群における皮膚潰瘍感染症の臨床症状と重症度分類は？
A2. ウェルナー症候群で見られる皮膚潰瘍感染の多くは糖尿病足病変の症状と重症度を使用することができる。米国感染症学会（IDSA）が提示している糖尿病足病変の重症度分類を提示する[6]。

CQ3. ウェルナー症候群における皮膚潰瘍感染症の微生物検査はどのようにすべきか？
A3. 糖尿病足病変の微生物学的検査の手法に準じる。
検体の採取については以下が推奨される。

１）創部の汚れをとり、デブリードマンしたのちに、深部組織から生検かキュレッテージにより組織を採取
２）膿性分泌物の穿刺液
３）骨髄炎合併が疑われる場合は骨生検組織を採取

臨床的に感染兆候のない創からの採取、デブリードマンされていない創部からの採取や創部の簡単なスワブによる検体の提出は、感染症の原因となっていない定着菌なども検出されるために必要以上に広域な抗菌薬を投与するリスクがある。感染兆候のある潰瘍病変が深い場合には Probe to Bone test（ゾンデを挿入して骨に当たるか確認）を施行[7]し、もし骨露出が認められれば、骨髄炎合併を疑い骨生検組織の培養が推奨される[8]。

CQ4. ウェルナー症候群における皮膚潰瘍感染症の治療薬の選択は？
A4. ウェルナー症候群における皮膚潰瘍感染症は糖尿病足病変の治療と同様、レンサ球菌や黄色ブドウ球菌などのグラム陽性菌をターゲット[9]とする。その他のターゲットの必要性を検討して抗菌薬を決定するのに以下の 4 点を確認する。

１）メチシリン耐性黄色ブドウ球菌（MRSA）のリスクがあるか
２）1 ヶ月以内に抗菌薬の投与歴があるか
　ある場合にはグラム陰性菌のカバーを必要とする
３）緑膿菌のリスクがあるか
４）重症度の確認

処方例
①低度もしくは長期・慢性化

抗菌薬（腎機能で用量・用法は調節が必要）	コメント
セファレキシン 500mg を 6 時間おき内服	グラム陽性菌をカバー
アモキシシリン（250mg）/クラブラン酸（125mg）配合錠＋アモキシシリン（250mg）を 8 時間おき内服	嫌気性菌をカバー
スルファメトキサゾール（400mg）／トリメトプリム（80mg）配合錠 2 錠を 12 時間おき内服	MRSA のカバー
ミノサイクリン 100mg を 12 時間おき内服	MRSA カバー
クリンダマイシン 300mg を 8 時間おき内服	嫌気性菌と MRSA の一部をカバー
レボフロキサシン 500mg を 24 時間おき内服	緑膿菌カバー、クリンダマイシンと組み合わせて使用することが多い

②中等度～重度

抗菌薬（腎機能で用量・用法は調節が必要）	コメント
アンピシリン/スルバクタム 3g を 6 時間おき静注	グラム陽性菌と嫌気性菌をカバー 耐性菌がない場合第一選択薬
ピペラシリン/タゾバクタム 4.5g を 6 時間おき静注	上記に緑膿菌カバーを追加
セフェピム 2g を 12 時間おき＋メトロニダゾール 500mg を 8 時間おき静注	緑膿菌以外の耐性グラム陰性菌もカバーする
メロペネム 1g を 8 時間おき静注	ESBL 産生グラム陰性菌、嫌気性菌もカバー
バンコマイシン（用量・用法は体重・薬物血中濃度で異なる）	グラム陽性菌、MRSA をカバー
ダプトマイシン（用量・用法は体重で異なる）	グラム陽性菌、MRSA をカバー バンコマイシンが使えない場合
ESBL: Extended Spectrum Beta Lactamase	

CQ5. ウェルナー症候群における皮膚潰瘍感染症の治療期間は？

A5. 感染兆候（発赤、疼痛、腫脹）の改善を目標に治療する。治療期間は糖尿病の治療期間に準じる [6]が、ウェルナー症候群では皮膚組織の改善が乏しく、個別に判断すべきである。

まとめ

ウェルナー症候群における皮膚潰瘍感染症は、糖尿病の合併が多いことと糖尿病足病変の病態と類似する点から、糖尿病足病変における重症度分類、微生物学的検査、治療薬と治療期間を参考にする。一方、ウェルナー症候群で見られる結合組織の代謝異常による皮下組織の萎縮、血流の低下、線維芽細胞の活性低下などを認めるため、糖尿病足病変と同様に治療しても予後が悪い。先行するウェルナー症候群の症例報告では感染症治療に関するエビデンスはほとんどないため、今後はウェルナー症候群における皮膚潰瘍感染症の細菌学、治療とその転帰に関する研究が望まれる。

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感染の臨床的症状	IDSA 感染重症度分類
感染の症状や兆候なし	感染なし
局所的に皮膚・皮下組織まで 紅斑がある場合、潰瘍周囲 0.5cm～2cm	低度
紅斑>2cm もしくは 皮下組織以下に達する 膿瘍、骨髄炎、細菌性関節炎、筋膜炎の存在	中等度
上記症状に加え、下記２項目以上を満たす • 体温＞38℃、＜36℃ • 心拍数＞90 拍/分 • 呼吸数＞20 回/分もしくは PaO2 ＜32 mmHg • WBC＞12,000 もしくは＜4,000 もしくは＞10%の幼若白血球（桿状核球）	重度

表 1. 糖尿病足病変の重症度分類

軟部組織感染のみ			
軽症	局所 or 経口	外来	1-2 週、長くて 4 週
中等症	経口 or 最初は経静脈	外来/入院	1-3 週
重症	経静脈 可能ならば経口に切り替え	入院	2-4 週
骨髄炎・関節炎合併			
感染組織の残存なし	経静脈 or 経口		2-5 日
軟部組織残存	経静脈 or 経口		1-3 週
骨髄炎残存 （腐骨化なし）	経静脈 可能ならば経口に切り替え		4-6 週
手術(-)or 腐骨(+)	経静脈 可能ならば経口に切り替え		3 ヶ月以上

表 2. 抗菌薬の投与経路、入院の必要性、投与期間の目安

６．ウェルナー症候群の皮膚科的治療

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はじめに

ウェルナー症候群の患者は皮膚潰瘍が生じやすく、治癒しにくいという特徴がある。特に足底の荷重部位に生じることが多い。原因として、やせによる脂肪組織の減少、皮膚硬化、血流障害、持続圧迫などによる創傷治癒能力の低下が考えられる。治療としては保存的治療と外科的治療が行われるが、1996 年から 2016 年に PubMed に報告された皮膚潰瘍の治療例を参考にして作成した。

CQ1. ウェルナー症候群の皮膚潰瘍が生じやすく、難治である原因は？
A1. 血流障害、皮膚硬化、脂肪組織の減少、骨変形による持続圧迫。石灰沈着などによって皮膚潰瘍が発生しやすく、創傷治癒が遅延する。

ウェルナー症候群の皮膚潰瘍の成因は多因子であるが，結合組織成分の代謝異常が関連しているといわれている[1)]。その他，体幹の割に四肢が細くやせているため四肢末端への荷重負荷が大きいこと，外反母趾や偏平足などの骨関節変形，足底の限局性角化病変や皮下石灰化による皮膚結合織への物理的圧迫，皮膚の菲薄化，皮膚硬化，脂肪組織の減少，線維芽細胞分裂能低下による創傷治癒の遅延，糖尿病の合併や動脈硬化性病変に伴う血行障害が重なるためと考えられている[2)]。

好発部位はアキレス腱部，足関節，肘関節，足底部など圧のかかりやすい部位に多くみられる[3)]。また鶏眼や胼胝腫，外傷が前駆症状となることがある。潰瘍好発部位の皮膚は萎縮し皮下脂肪織が減少しているため，潰瘍を形成すると容易に腱や骨が突出する[2)]。ウェルナー症候群の患者には腫瘍の発生が多く、有棘細胞癌や悪性黒色腫による難治性皮膚潰瘍の可能性も念頭において、疑わしい場合は皮膚科専門医へ相談することが望ましい。特にウェルナー症候群患者では足底に好発する末端黒子型悪性黒色腫の発生頻度が高いことが知られており注意を要する[4)]。

CQ2. ウェルナー症候群における皮膚潰瘍の治療方針は？
A2. 糖尿病などの治療も並行しながら、治癒を妨げている原因除去に役立つ外用薬や，治癒過程を促進する外用薬やドレッシング材を選択して保存的治療を行う。

ウェルナー症候群 の潰瘍は Q1 で示した様々な成因が関与していることもあり難治である。外用薬やドレッシング材などでの保存的治療をまず行うが，糖尿病のコントロールなど全

身的治療も並行して行う必要がある。また、潰瘍周囲の角質増生に対してはサリチル酸ワセリンや尿素軟膏などの角質軟化剤の外用を行う。角質軟化剤による鶏眼や胼胝腫の治療を行うことは皮膚潰瘍の発生予防にもつながるため重要である。保存的治療で改善が見られない場合，外科的療法を考慮する。

本症の潰瘍は慢性皮膚創傷である。慢性皮膚創傷では，各種サイトカインによる炎症の遷延化と，壊死組織タンパクを融解させる役割をもつプロテアーゼの活性が上昇することにより，組織の足場になる細胞外基質も融解し，組織の再構築ができない状態にある[5)]。また，滲出液中の分子の組成バランスが崩れることにより，組織再構築を担う細胞の分裂能が低下している[5)]。慢性創傷の創傷治癒過程を促進するためには，治癒を妨げている原因除去に役立つ外用薬や，治癒過程を促進する外用薬やドレッシング材を選択して使用する必要がある[6)]。

CQ3. 感染・壊死組織を伴う皮膚潰瘍の治療法は？

A3. 外科的デブリドマンによる壊死物質の除去と壊死物質除去作用・抗菌作用を持つ外用剤を選択する。

生理食塩水や微温湯で洗浄後，壊死組織に対し，できるだけメスやハサミを用いて外科的デブリードマンを行う。感染に移行しつつある状態や感染が成立した状態では、ポビドンヨード、グルコン酸クロルヘキシジン、塩化ベンザルコニウムによる消毒を行い感染を抑える[6)]。デブリードマンが困難な場合はカデックス軟膏®，イソジンゲル®，ブロメライン軟膏®などの壊死組織除去剤による化学的デブリードマンをおこなう。また水分を多く含むゲーベンクリーム®は壊死組織の軟化・融解を促進するとされており，滲出液の少ない創部で有効である。感染や強い炎症により創部の滲出液が多い場合は，滲出液吸収効果を持つカデックス軟膏®やユーパスタ®コーワが有効である。また、感染や壊死組織を伴う潰瘍は、閉塞することにより感染が悪化するため、ドレッシング材（閉鎖性ドレッシング）は行わない方がよく、抗菌作用を有した外用剤を中心に治療すべきである[6)]。

CQ4. 感染・壊死組織を伴わない皮膚潰瘍の治療法は？

A4. 肉芽形成促進薬や上皮化形成促進作用をもつ外用剤や湿潤環境を保持するためのドレッシング材を用いる。

感染もなく壊死組織が除去された創部は，通常肉芽が形成されるが，本症の潰瘍はなかなか肉芽が形成されないことが多い。そのため，生理食塩水や微温湯で洗浄後，オルセノン軟膏®やプロスタグランディン軟膏®，リフラップ軟膏®などの肉芽形成促進薬を使用する。塩基性線維芽細胞増殖因子（フィブラストスプレー®）も有効ではあるが，ウェルナー症候群 の皮膚潰瘍は悪性腫瘍を合併することも多いため，注意が必要である。

潰瘍部が良好な肉芽で充填されると，上皮化が生じてくる。プロスタグランディン軟膏®やアクトシン軟膏®などの上皮形成促進作用を持つ薬剤を使用する。この時期は創部の湿潤環境を保持するためのドレッシング材も有効である。滲出液の少ない場合はハイドロコロイドを、滲出液の多い場合はアルギン酸塩（ソーブサン®）、キチン（ベスキチン®）、ハイドロファイバー（アクアセル®）、ハイドロポリマー（ティエール®）、ポリウレタンフォーム（ハイドロサイト®）などを使用することが薦められる[6)]。近年，エンドセリン受容体拮抗薬が難治性潰瘍に有効した一例が報告されている[7)]。

CQ5. その他の治療法は？

A5. 保存的治療で改善が見られない場合は、人工真皮貼付や皮弁形成などの外科的治療を考慮する。

一般的な創傷・褥瘡治療で用いられる高圧酸素療法や陰圧閉鎖療法も創傷治癒を促進させる可能性をもつ。外科的治療については、植皮術では治癒させることが困難な場合が多く，人工真皮貼付[8)]や皮弁形成[9,10)]などの方が有用であることが多い。また線維芽細胞の分裂能の低下などから，デブリードマンにより潰瘍が拡大する可能性のあることも念頭に置く必要がある[8)]。

まとめ

ウェルナー症候群の皮膚潰瘍はアキレス腱部，足関節，肘関節，足底部など圧のかかりやすい部位に生じた鶏眼や胼胝腫，外傷から発生することが多く、健常人の創傷治癒と比べて難治である。ウェルナー症候群の皮膚潰瘍が難治である原因としては、皮膚の菲薄化、硬化、脂肪組織の減少、血流不全、石灰化、骨関節変形による過剰圧迫など多因子が関与する。治療としては、潰瘍周囲の角質増生に対しては角質軟化剤の外用を行う。潰瘍の治療は通常の潰瘍の治療と同様であるが、感染・壊死組織を伴う場合は、生理食塩水や微温湯で洗浄ないし消毒薬で消毒後，壊死組織に対し，できるだけメスやハサミを用いて外科的デブリードマンを行う。また、創部の水分コントロールに注意しながら壊死組織の軟化・融解を促進する外用薬を併用する。感染もなく壊死組織が除去された創部には，肉芽形成促進外用薬を使用する。また、創部の湿潤環境を保持するためのドレッシング材も有効である。保存的治療で改善が見られない場合，外科的療法を考慮する。

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７．ウェルナー症候群の皮膚潰瘍の外科的治療

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はじめに

ウェルナー症候群では皮膚潰瘍がよく見られる。本項目はウェルナー症候群における皮膚潰瘍に対して外科的治療の観点から、潰瘍の疫学、診断、治療、予防について一定の指針を示すことを目的とする。

ウェルナー症候群における皮膚潰瘍は難治で QOL を低下させる。ウェルナー症候群における足潰瘍の病態は、近年増加してきた虚血肢潰瘍、糖尿病性潰瘍の病態と共通する部分もあるが同一ではないため特別な配慮が必要である。ウェルナー症候群は極めて稀な疾患であることから、実地臨床において各施設が十分な治療経験を得ることが難しい。また、多数の症例が参加した臨床研究のエビデンスに基づく指針を作成することは困難である。しかし一方で、個々のウェルナー症候群患者に対して皮膚潰瘍の診断と治療を適切に行うことの必要性は言うまでもない。また、ひとたび潰瘍が生じると難治となるため、潰瘍が生じる前の段階での潰瘍発生予防措置の必要性が極めて高い。よって、ウェルナー症候群の皮膚潰瘍の診断、治療、予防に関して、症例報告の集積や自験例に基づいて一定の方針や見解を示すことは患者にとって有益であると考えられる。また、本項目では下肢潰瘍の他にウェルナー症候群でよくみられる肘潰瘍も取り上げる。

文献

ウェルナー症候群に関する報告の殆どは症例報告か数例のケースシリーズである。本項目では遺伝子診断されている確実例を多く抽出するため、ウェルナー症候群の原因遺伝子として *WRN* が同定された 1996 年以降の文献を元に作成した。

1996 年 1 月から 2016 年 10 月にメディカルオンラインで検索された和文報告のウェルナー症候群患者は 63 例だった。また、同期間に PubMed で検索された日本人著者による英文報告のウェルナー症候群は 56 例だった。本項目ではこれらの報告を用いた。なお、これらの報告においては、和文報告では学会抄録も含んでいるため症例の重複がありうることを予め述べておく。また、和文報告と英文報告の間においても症例の重複がありうる。

I. 皮膚潰瘍概要

CQ1. ウェルナー症候群における皮膚潰瘍の合併率は?
A1. およそ 4 割で皮膚潰瘍を合併する

ウェルナー症候群は極めて稀な疾患であり、ウェルナー症候群患者の中での皮膚潰瘍有病率や罹患率を正確に求めることは困難である。和文報告 63 例中 27 例(43%)、英文報告 56 例中 22 例(40%)で皮膚潰瘍の記載がみられた（表 1）。上肢では肘関節肘頭部の潰瘍の報告が多い。下肢では、下腿遠位 1/3 以遠の部位の潰瘍が多い。膝関節伸側の潰瘍の報告もみられる。

CQ2. ウェルナー症候群下肢病変の典型的な出現部位は？
A2. 下腿遠位 1/3 と足である。

下肢は細く、皮膚は乾燥していることが多い。多形皮膚萎縮、皮膚硬化は下腿遠位 1/3 と足で特に強い（図 1）。以下、下腿遠位 1/3 と足について述べる。皮膚は伸展性が殆ど無く、光沢を持っていることが多い。足関節拘縮により可動域制限がみられることが多いが尖足位となっていることは少ない。扁平足はウェルナー症候群の典型的な症状の一つとして知られている。X 線でみられるアキレス腱の火焔様石灰化はウェルナー症候群の典型的な症状であり、同部位の皮膚潰瘍がしばしばみられる。また、足関節内果・外果、足に多発潰瘍を呈することがある。胼胝もよくみられる。足潰瘍がなく比較的状態が良好な足であっても、観察すると胼胝がみられることが多い。足趾の変形がよくみられ、急速に進行することがある。

CQ3. 下肢潰瘍の発生要因となりうる基礎疾患の合併は？
A3. 糖代謝障害の合併が多い。

糖代謝異常が存在する割合が和文報告 43%, 英文報告 39%と高かった（表 2）。一方、高血圧は多数とは言えなかった。また、下肢虚血に関してもウェルナー症候群で多いとは言えなかった。ウェルナー症候群における足潰瘍の病態は、近年増加の一途をたどっている糖尿病・高血圧による足潰瘍の病態と共通する部分もあるが、決して同一ではないことに留意しなければならない。またウェルナー症候群における足潰瘍の成因として、皮膚硬化と足変形は無視できない要素である。

CQ4. 悪性腫瘍による潰瘍はみられるか?
A4. みられることがある。

ウェルナー症候群では悪性腫瘍が若年から高率に発生することが知られている。また、非上皮性腫瘍の割合が健常人集団と比べて高いことが報告されている。皮膚潰瘍との関連では、踵潰瘍が見られた症例で踵骨骨肉腫が存在した報告[1)]がある。ウェルナー症候群における皮膚潰瘍においては悪性腫瘍の可能性も念頭に置く必要がある。

CQ5. 胼胝はみられるか?
A5. 高率にみられる。

ウェルナー症候群の足では胼胝が高率にみられる。文献では、和文報告 63 例中 8 例(13%)、英文報告 56 例 9 例(16%)で胼胝の存在が記載されていた。自験例ではほぼ全例で胼胝がみられる。胼胝は疼痛をもたらし QOL を低下させ、また胼胝部に潰瘍を生じることがある。さらに胼胝による疼痛が歩容を悪化させ、他部位の負荷が増し新たな胼胝や潰瘍が発生する可能性もある。よってウェルナー症候群において胼胝は、将来発生しうる潰瘍発生予防の点から重要な治療対象である。

ウェルナー症候群では皮膚は硬化し極めて伸展性に乏しい状態となる。加えて、扁平足、足趾変形、足関節拘縮が進行する。これらによって、ウェルナー症候群では胼胝が高率に発生すると思われる。

胼胝は皮膚潰瘍の発生母地になることがあるためウェルナー症候群で皮膚潰瘍がなく胼胝のみ存在する段階の症例は、今後の潰瘍発生のリスクをふまえ特に重点的に適切な予防措置を講ずる必要があると考えている。潰瘍がなく胼胝のみ存在する段階の症例は和文 2 例、英文 5 例が報告されていた。潰瘍がない患者の胼胝予防および処置が重要な理由としては、①患者が潰瘍発生とその難治化を経験していないため、足底装具、靴装具などの予防措置が行われていないケースが多いこと、②ウェルナー症候群としては軽症の段階であるため活動性が高く、胼胝に高い圧が長時間加わりやすいこと、などが挙げられる。自験例では、踵胼胝への荷重により踵骨骨皮質が破綻し踵骨骨髄炎へ至った可能性がある症例を経験した（図 2）。本症例は、下腿遠位 1/3 から足部に多形皮膚萎縮、硬化、足関節拘縮などウェルナー症候群に典型的な変化がみられたものの、下腿や足の皮膚は比較的良好と考えられる状態だった。踵潰瘍発生の原因としては踵胼胝に対し特に処置を行っていなかったこと、市販の靴を使用していたこと、活動性が高く繰り返し踵胼胝に圧が加わり続けたこと、などが考えられた。

以上のことから、ウェルナー症候群において胼胝は皮膚潰瘍発生の前段階と考えられる。胼胝に対して介入を行うことにより、皮膚潰瘍、骨髄炎などの重篤で治療困難な状態に陥ることを予防できる可能性がある。

II. 診断

CQ6. 潰瘍の肉眼的評価は重要か?
A6. 重要である。

肉眼所見として潰瘍の部位、性状などの記録は重要である。記録に際しては、DESIGN-R®(日

本褥瘡学会編)[2]に含まれている項目を念頭に置いて記録すると記載漏れが少なくて有用である。DESIGN-R®は褥瘡の評価基準であるが、褥瘡以外の潰瘍評価にも用いることができる。評価項目は以下の通りである。

1. 深さ
2. 滲出液の量
3. 大きさ
4. 炎症/感染
5. 肉芽組織
6. 壊死組織
7. ポケット

DESIGN-R は詳細な評価法であり、治療効果判定、経時的変化の評価などに活用できる。欠点としては、やや記録が煩雑である点が挙げられる。

以下、ウェルナー症候群の潰瘍評価において重要と考えられる点を述べる。

1. 潰瘍の深さ： ウェルナー症候群において潰瘍は容易に骨や関節腔に達する。骨皮質を穿破して骨髄内に達している場合は骨髄炎を、関節腔に達している場合は化膿性関節炎を疑う必要がある。
2. 滲出液の量： 滲出液が膿性である場合は、骨髄炎や化膿性関節炎の可能性を考慮する。
3. 大きさ： 病勢や治療効果の判定に重要である。
4. 炎症/感染： 感染巣が皮膚軟部組織であるか、骨髄や関節腔であるかの鑑別が重要である。
5. 肉芽組織： ウェルナー症候群の潰瘍では一般に肉芽形成は不良である。肉芽形成が不良の場合には、血流不良、感染、壊死組織などの原因を考慮し、それらを解消する方法を検討する。
6. 壊死組織： 壊死した組織が何であるか、壊死組織の深さ、範囲などを把握する。
7. ポケット：ウェルナー症候群の足潰瘍でポケット形成が問題となることは多くはない。

CQ7. 足部単純 X 線、CT は有用か?

A7. 有足全体の形状や、足を構成する個々の骨の状態把握に単純 X 線および CT は有用である。

ウェルナー症候群では足部形態や個々の骨の状態が急速に変化することもあるため経時的変化を把握することは重要である。

CQ8. MRI は有用か?
A8. 骨髄炎を疑う症例では MRI 検査が有用である（図 2）**。**

CQ9. 血行評価は必要か?
A9. 必要である。

下肢虚血がある場合、血行再建が可能か検討する必要がある。
高血圧や糖尿病などの既往、足部冷感、足背動脈・後脛骨動脈触知不能などの場合に下肢虚血を疑う。和文報告 1 例、英文報告 2 例で下肢虚血が疑われる記載があった。うち 1 例で伏在静脈により大腿膝窩動脈バイパスによる血行再建が行われたと報告されている [3]。

III. 治療

CQ10. 皮膚潰瘍の外科的治療と wound bed preparation の組み合わせは重要か?
A10. 重要である。

ウェルナー症候群の皮膚潰瘍は一般に難治である。最終的に植皮術や皮弁術などの外科的治療により創閉鎖を図る場合であっても、そこに至るまでの準備が手術の結果を大きく左右する。創傷治癒に関する近年の進歩を取り入れることにより、これまで治癒させるのが困難だった潰瘍や大きな手術を要していた潰瘍を侵襲の低い手術で閉鎖できるケースが増えた。このような手術の前段階として潰瘍状態の改善を図ることは wound bed preparation と呼ばれ、その重要性は増す一方である。本項では、ウェルナー症候群において wound bed preparation から手術へと至る際の流れについて自験例も交えて述べる。

A) デブリードマン、掻爬： 皮膚潰瘍の治療・管理において、壊死組織を除去し創面の清浄化を図ることは重要である。そのため、患者自身が自己処置で行う創面の清浄化は日々の創管理において必要度が高い。同時に、医療機関受診の際に掻爬や外科的デブリードマンをこまめに行うのが望ましい。
　明らかな感染状態においては、切開排膿やデブリードマンを速やかに行う必要がある。また近年、明らかな感染兆候はないが潰瘍部の菌量が増えた状態が臨界的定着(critical colonization)と呼ばれ注目されている。臨界的定着状態において菌塊はグリコカリックスなどによるバイオフィルムを形成し、宿主免疫や外用薬の作用が及びにくくなり創傷治癒を阻害する。潰瘍面に付着した柔らかい黄色～白色調組織（slough と呼ばれることがある）はバイオフィルムを含んでいる可能性があり臨界的定着を疑う所見の一つである。他に、臨界的定着を疑う臨床所見として NERDS が報告されている [4](表 3)。ウェルナー症候群の潰瘍の診察時に潰瘍底に付着した柔

らかい黄色～白色調組織を鋭匙等で除去することはバイオフィルムを除去し、菌量を減らすので臨界的定着に対する対策として有用と考えられる。

デブリードマンは潰瘍の範囲と深さの判定という診断面でも有用であり、その処置の際に創面や壊死組織、膿の細菌培養検体を採取することも重要である。デブリードマン中に骨髄内に達し骨髄炎が判明することもある。その場合、骨髄内膿の細菌培養検体採取を忘れてはならない。

ウェルナー症候群におけるデブリードマンの実施上、最も問題となるのは疼痛である。ウェルナー症候群では糖代謝障害の合併率が高いが糖尿病性潰瘍でみられる知覚低下があることは少なく、むしろ健常人より処置時の疼痛は強い。そのため無麻酔でのデブリードマンは難しいことが多い。局所浸潤麻酔薬注射の場合、組織の硬化により注射自体の疼痛が強く、また注射された麻酔薬が組織内で浸透しにくく、一般の患者で得られるような鎮痛の範囲・効果が得にくい。対策として、潰瘍から離れた下腿中央などの皮膚が柔らかい場所にブロック注射を行うことを考慮しても良い（図 3）。いずれにせよ、ウェルナー症候群におけるデブリードマンは患者に意義･必要性を説明の上、十分な準備のもとに行われる必要がある。

B) 外用剤：潰瘍の状態にあわせて適切な外用剤を用いることは重要である。潰瘍治療においては適切な湿潤環境を保ち創傷治癒を促進する moist wound healing の考え方が基本となる。しかしウェルナー症候群の潰瘍において、湿潤環境と創傷治癒を直接促進する薬剤(ワセリン軟膏、プロスタグランディン入り軟膏、basic fibroblast growth factor [bFGF]スプレーなど)だけで治癒に至ることは稀である。細菌の臨界的定着に対して、ヨウ素製剤、銀製剤を要することも多い。また、moist wound healing の範囲を超える多量の滲出液は創傷治癒を阻害するため、滲出液を吸収する吸水性基材の製剤（カデキソマーヨウ素製剤、ヨード･白糖製剤）がしばしば用いられる。

C) 洗浄： 洗浄により創面の汚れを洗い流すことは有用と考えられる。洗浄の有効性を実証したエビデンスは多くないが、臨床上、洗浄の有効性については合意が得られていると考えられる。また、患者が自己処置としてシャワー等で創洗浄することは身体保清のひとつであり望ましいと考えられる。創管理上特段の理由がないにもかかわらず、潰瘍の存在だけを理由に足部シャワーを禁止することは避けなければならない。

一方で、洗浄処置により以下のリスクがあることも認識する必要がある：①環境中の多剤耐性菌が創面に付着する、②創面の多剤耐性菌が環境中に拡散する。

医療施設の水回り（水道蛇口、シャワーヘッド、浴槽、陰洗ボトルなど）は様々な菌で汚染されている場合がある。また、洗浄処置は周囲環境に汚染物を飛散させやすい。①、②のリスクを踏まえ、標準予防策を遵守したうえで洗浄処置を行うこ

とが必要である。

D) 陰圧閉鎖療法(negative pressure wound therapy, NPWT)： NPWT は難治性潰瘍に対して近年急速に普及しつつある治療法である。持続陰圧による血管新生促進、肉芽新生促進、滲出液コントロールにより潰瘍治癒が促進するとされている。自験例でも一定の有効性が認められ(図 3)、今後積極的に取り組む意義のある治療法と考えられる。NPWT における一般的な注意事項である、①感染創には用いない、②潰瘍周囲皮膚の障害に注意する、などの事項はウェルナー症候群においても十分留意する必要がある。ウェルナー症候群では化膿性関節炎に伴う皮膚潰瘍を生じている場合も多く、感染状態では NPWT 単独での治療は適応外である。持続洗浄等を併用した治療を考慮すると有効な可能性がある。

NPWT をウェルナー症候群の足に用いる場合に特に注意を要する点としては、組織硬化が強いこと、皮膚軟部組織が薄く骨と近いこと、などからフォーム剤による圧力で皮膚軟部組織障害が生じやすいことが挙げられる。フォーム剤を適切な広さ、厚さに切って用いることが有用である。

E) 手術：

(ア) 人工真皮貼付： ウェルナー症候群では皮膚軟部組織が薄く硬化しており、容易に骨上や腱上の全層欠損になる。人工真皮はウェルナー症候群の足潰瘍治療において欠かせないものである(図 3)。ウェルナー症候群では骨皮質が破綻し骨髄露出に至ることもしばしばみられるが、人工真皮は骨髄露出創にも貼付可能であり、真皮様組織が骨髄露出面に構築されることにより骨髄炎を予防し、また植皮を可能にする。

(イ) 植皮術： 従来、ウェルナー症候群の皮膚潰瘍では骨膜が失われるレベルの骨露出、腱膜が失われるレベルの骨露出が多く植皮が適応しづらいことが多かった。しかし、人工真皮、bFGF 製剤、NPWT の登場によりウェルナー症候群の潰瘍で植皮の母床形成が可能となるケースが増加し、伴って植皮術は増加傾向になってくると思われる。植皮術の報告は和文 1 例、英文 2 例がある。自験例で足関節外果などに植皮術を行った例を示す（図 3）。

(ウ) 皮弁術： ウェルナー症候群に限らず難治性潰瘍治療において、皮弁術などの比較的大きな手術が占める割合は減少し、その役割は相対的に減少しつつある。理由は、外用薬、bFGF 製剤などの薬剤の進歩、人工真皮により従来は植皮術が不可能だった状況でも植皮術が可能になったこと、NPWT の強力な肉芽化作用・潰瘍縮小効果、などが挙げられる。一方、皮弁手術の利点としてはその他の治療では閉鎖にまで至れない潰瘍の閉鎖が得られることや、厚さを持った良好な皮膚軟部組織で閉鎖できること、治療期間の短縮、などが挙げられる。

① 肘潰瘍： 肘頭は骨突出が強いこと、肘の屈曲伸展運動のために柔軟性に富む軟部組織が必要であることに加え、ウェルナー症候群の肘潰瘍は関節腔が露出していることが多いことなどから、植皮術よりも皮弁術が適切であるケースが多いかもしれない。皮弁術では、radial recurrent flap[5]、尺側手根屈筋皮弁[6], 橈側前腕皮弁[7]などの報告がある。その他、植皮術[8]、骨部分切除[9]の報告がある。

② 膝潰瘍： 膝関節腔が露出するような潰瘍は皮弁術の適応が高い。前脛骨動脈皮弁、縫工筋弁、遊離広背筋皮弁[10,11]の報告がある。

③ 踵潰瘍： 骨髄炎を伴った踵潰瘍に対して遊離前鋸筋弁の報告がある[12]。

④ アキレス腱部潰瘍: X 線でみられるアキレス腱部の火焔様石灰化はウェルナー症候群の特徴的な所見である。石灰の感染からアキレス腱部潰瘍を生じることがしばしばある。Lateral supramalleolar flap による治療の報告がある[13]。

(エ) 切断術： 難治性潰瘍により患部の切断術が避けられない場合もある。和文報告で足部切断 1 例、足趾切断 1 例、英文報告で膝下切断 1 例、足趾切断 1 例がある。また、踵骨骨肉腫による膝下切断 1 例の報告がある[1]。

F) その他

(ア) 高気圧酸素療法： 踵骨骨髄炎を伴う踵部潰瘍に対して高気圧酸素療法を行った報告がある[14].

(イ) 腰部交感神経ブロック： 足潰瘍および疼痛に対して腰部交感神経ブロックを行った報告がある[15,16].

G) 皮膚ケア

(ア) 保湿： ウェルナー症候群では皮膚乾燥がみられることが多く、下腿や足では特に顕著である。皮膚乾燥は胼胝や皮膚潰瘍の発生要因や増悪因子になると考えられる。皮膚乾燥により落屑、発疹などがある状態は手術創のコンタミネーションなどを招き創傷治癒を阻害すると考えられる。保湿剤塗布が有効である可能性がある。

CQ11. 胼胝に対するマネージメントは必要か?

A11. 必要である。

ウェルナー症候群の足では胼胝が高率に存在し（図 1B）、皮膚潰瘍や踵骨などの骨皮質破綻、骨髄炎などを誘発する可能性がある(図 2)。ウェルナー症候群ではひとたび潰瘍や骨髄炎が発生すると極めて難治であり、胼胝の段階で予防が図られることが望ましい。よっ

て、胼胝に対して積極的に介入することは有意義と考えられる。

A) 胼胝の予防： 胼胝は過剰な圧が長期間加わることによって発生する。過剰な圧が加わることを防ぎ、胼胝発生を予防することが重要である。

(ア) 適切な足底装具、靴形装具の使用： 個々の患者の足に合わせて作成した足底装具、靴形装具により胼胝や潰瘍発生を予防できる可能性がある。文献ではウェルナー症候群 2 例に対して足底装具、靴形装具を行った報告がある [17)]。報告では 2 例とも装具製作の難易度が高かったが、1 例では患者満足が得られた。自験例においては積極的に靴形装具を作成している（図 4）。室外履き型、室内履き型があり、患者ライフスタイルに応じて義肢装具士が作成している。市販の健常人用靴と比較して履き心地が良く疼痛が軽減するようである。筆者らは現在、これら装具による胼胝･潰瘍予防効果を検証中である。問題点としては、ウェルナー症候群では足趾変形が急速に進行することがあり、作成した装具が短期間で適合しなくなることがしばしばおこることが挙げられる。

B) 胼胝の治療： ウェルナー症候群では、発生した胼胝に対して積極的に治療することが望ましい。胼胝は過剰な圧が加わり続けるという原因が解消されない限り再発することに留意し、治療を継続して行う必要がある。具体的な方法としては以下が挙げられる。

(ア) 胼胝削り： カミソリ等を用いて胼胝の厚みを減らすことができる。また、胼胝形状をなだらかにすることができる。これらにより、皮膚の狭い範囲に極端に強い圧が加わることを防止できる。

(イ) サリチル酸製剤貼付： 角質を侵軟させ用手的剥離を可能にする。

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表 1 ウェルナー症候群における部位別皮膚潰瘍報告数

部位	和文報告症例数 (n = 63)	英文報告症例数 (n = 56)
肘	11 (17%)	1 (2%)
膝	1 (2%)	2 (4%)
下腿	2 (3%)	4 (7%)
アキレス腱部	4 (6%)	5 (9%)
足関節内果・外果	2 (3%)	6 (11%)
足底	4 (4%)	3 (5%)
踵	6 (10%)	4 (7%)
足趾	4 (6%)	3 (5%)
足	1 (2%)	1 (2%)

表 2 下肢潰瘍の原因となりうる基礎疾患

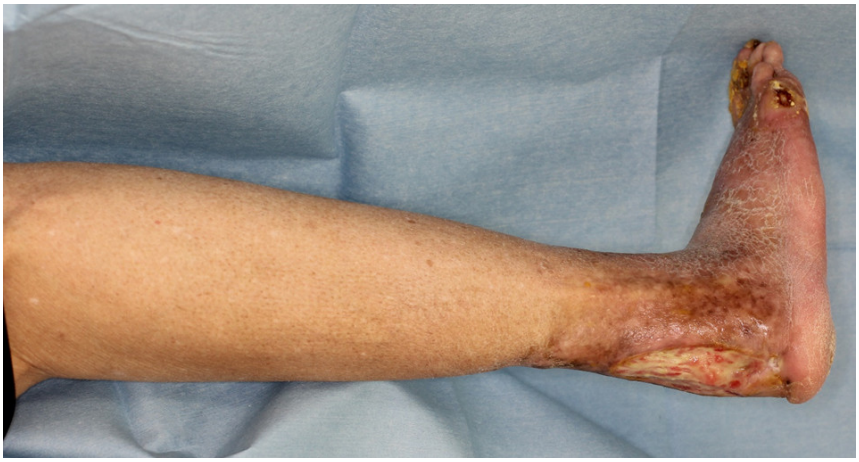
	和文報告 (n = 63)	英文報告 (n = 56)
糖代謝異常	27 (43%)	22 (39%)
高血圧	3 (5%)	1 (2%)
下肢虚血	1 (2%)	2 (4%)

表 3 Critical colonization を疑う兆候*

英文	意味
N: Non healing wounds	治療抵抗性の潰瘍
E: Exudative wounds	多量の浸出液
R: Red and bleeding wound surface and granulation tissue	赤色で出血のみられる肉芽
D: Debris	壊死組織などの存在
S: Smell or unpleasant odor	悪臭

*頭文字をとって、NERDS とよばれる。(文献[4]から引用)

A



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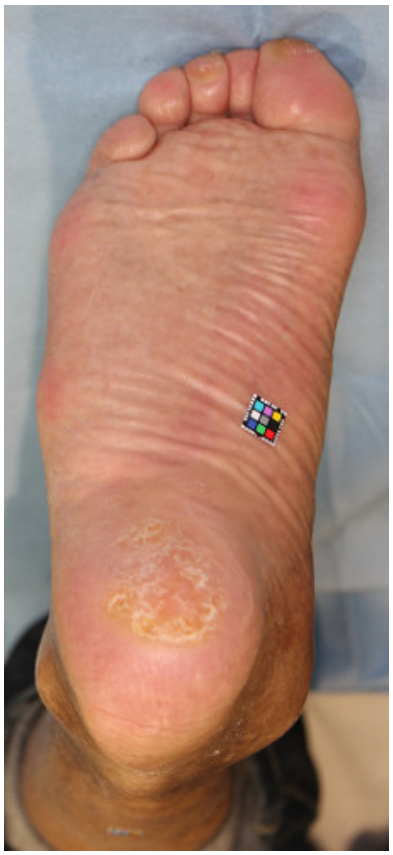
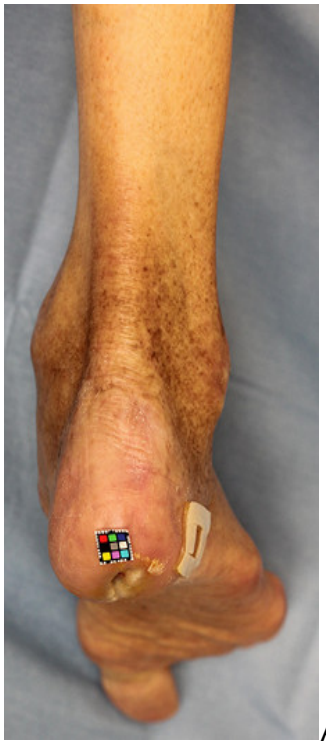


図 1 ウェルナー症候群の下肢典型像。(A) 皮膚軟部組織の硬化・萎縮は下腿遠位 1/3 以遠で著しい。（B）潰瘍のない比較的良好な状態の足であるが、踵部には胼胝がみられる。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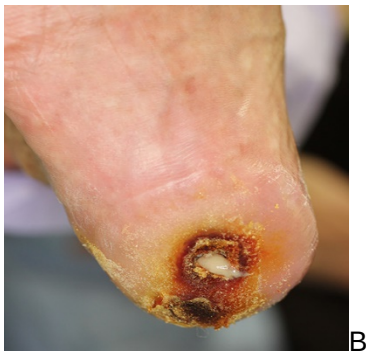
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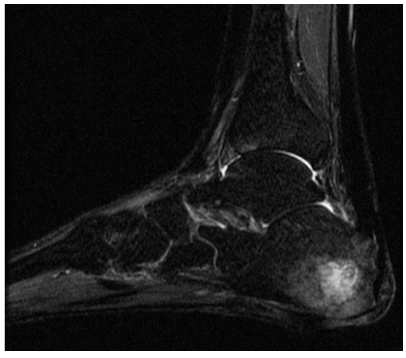

C

図 2 踵部胼胝から踵骨骨髄炎に至った可能性がある症例

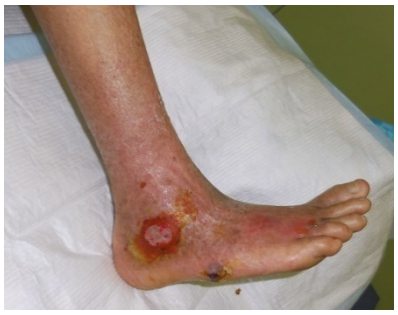
（上）下腿遠位 1/3 から足部にかけての皮膚の状態は全体的に良好である。

（中）踵部に潰瘍から排膿がみられる。

（下）足部 MRI 矢状断 T2 強調脂肪抑制像。踵骨骨髄は high intensity であり、骨髄炎を反

映している。

A



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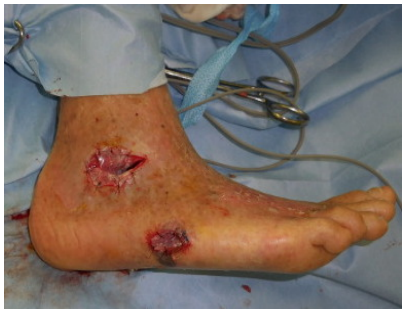

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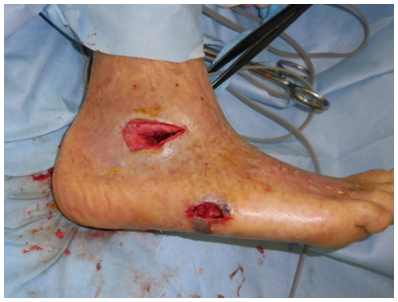

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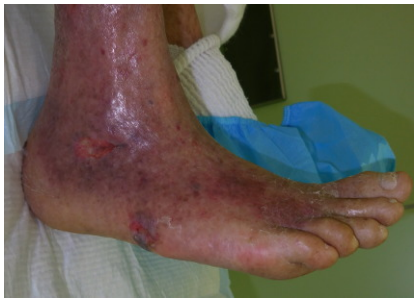

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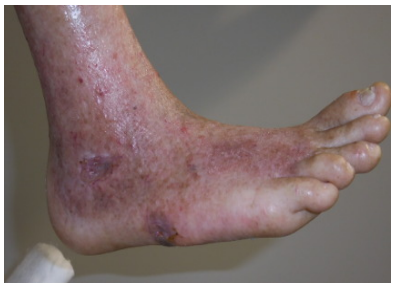

図 3 . (A)足関節外果と足外側に潰瘍がみられる。(B)デブリードマン後。麻酔は下腿中央やや遠位よりの皮膚が柔らかい部位にて腓腹神経ブロックで行った。外果潰瘍は骨髄内に、足外側潰瘍は第五中足骨に達している。(C)人工真皮を貼付した後、陰圧閉鎖療法(NPWT)を開始した。(D)NPWT 後。潰瘍の肉芽化、縮小がみられる。植皮可能な状態と判断し、網状分層植皮術を行った。(E)植皮後。植皮は生着し潰瘍閉鎖が得られている。

図 4 靴形装具の作成例。(A)室外履き型　(B)室内履き型

８．ウェルナー症候群のアキレス腱石灰化

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はじめに

ウェルナー症候群患者では靭帯や腱の非対称性の石灰化が報告されてきたが、メカニズムは不明である[1)]。関節包や腱付着部の石灰化は手、手関節、足、膝及び肘に多発性にみとめられることもある[2)]。アキレス腱に石灰化が生じることもあり[3)]、広範囲で特徴的な形状の石灰化を認めることがある[4)]。過去に異所性石灰化が 3 分の 1 に認められたとする報告があったが[5)]、近年では 85.3%に認められたとする報告がある 6)。ウェルナー症候群患者の皮膚組織の線維芽細胞では燐酸の取り込みに関与する Na-Pi cotransporter(Pit-1) が上昇している[6)]

CQ1. ウェルナー症候群患者のアキレス腱石灰化は非ウェルナー症候群患者のアキレス腱石灰化と異なるか。
A1. ウェルナー症候群患者におけるアキレス腱石灰化は多発性かつ広範囲で濃淡が強く認められ、火焔様とも表現される石灰化様式を示している。この石灰化は非ウェルナー症候群患者の石灰化とは明らかに異なっている。

アキレス腱の石灰化と混同する恐れのあるアキレス腱踵骨停止部における骨棘は、近年の調査の結果アキレス腱付着部表層における線維軟骨成分のアポトーシスと、その後におこる enchondral ossification によるものであり、アキレス腱の石灰化とは異なることが証明された[7)]。

アキレス腱の腱内石灰化はアキレス腱症やアキレス腱付着部症において認めたとする報告[8)9)]や、アキレス腱断裂の術後に認められたという報告[10)]が散見される。ウェルナー症候群患者におけるアキレス腱石灰化は多発性かつ広範囲で濃淡が強く認められ、火焔様とも表現される石灰化様式を示している。この石灰化は非ウェルナー症候群患者の石灰化とは明らかに異なっている。

CQ2. 単純 Xp におけるアキレス腱の石灰化はウェルナー症候群の診断に有用か。
A2. ウェルナー症候群患者におけるアキレス腱石灰化の出現頻度は非ウェルナー症候群患者と大きく乖離しており、アキレス腱実質部での石灰化はウェルナー症候群の診断基準に組み入れることは有用である。

ウェルナー症候群患者のアキレス腱の石灰化は出現頻度や範囲、出現様式に関して非ウェ

ルナー症候群患者のものとは明らかに異なる。2010 年度に「ウェルナー症候群の病態把握、診療指針作成と新規治療法の開発を目的とした全国研究」が行った全国二次アンケート調査に回答を得たウェルナー症候群症例の中で、アキレス腱の石灰化について回答が得られた 92 例のうち 70 例(76.1%)で石灰化を認めた。2004 年～2015 年にかけて奈良県立医科大学整形外科にて足部・足関節の手術を行った非ウェルナー症候群患者 1853 例 2151 足の単純 Xp で、アキレス腱の石灰化が認められたのは 19 足(0.88%)に過ぎず、長径 9.7mm～63.2mm の石灰化が 1～4 個存在した。

ウェルナー症候群患者におけるアキレス腱石灰化の出現頻度は非ウェルナー症候群患者と大きく乖離しており、アキレス腱実質部での石灰化はウェルナー症候群の診断基準に組み入れることは有用である。

まとめ

アキレス腱石灰化として

1)単純 Xp にて長さが 2cm 以上で踵骨と連続性を持たない石灰化が存在する(単独で大きな分節型石灰化)(図 1)

2)長さが 2cm 未満だが踵骨と連続性を持たない石灰化が 2 つ以上存在する(複数の小さな分節型石灰化)(図 2)

3)アキレス腱実質部に明らかに異常で広範囲にわたる火焔様石灰化(図 3)が存在する

以上のいずれかに該当する場合には特異的なウェルナー症候群患者のアキレス腱石灰化を疑って診断を進めていく必要がある。

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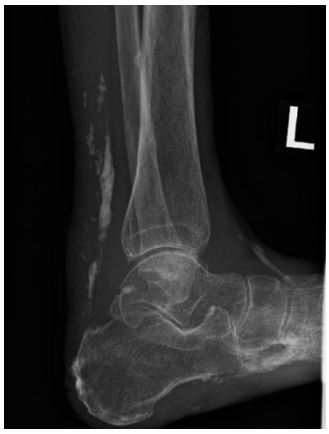

図 1. アキレス腱に 2cm を超える石灰化が存在する。(単独で大きな分節型石灰化)

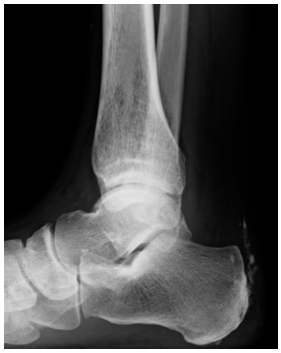

図 2. 2cm 以下の小さな石灰化ではあるが、複数個存在する。(複数の小さな分節型石灰化)

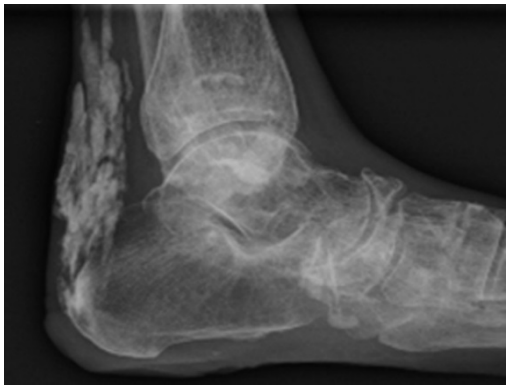

図 3. アキレス腱の停止部に広範囲に火焔様の石灰化が存在する。(火焔様石灰化)

Management guideline for Werner syndrome

-2018-

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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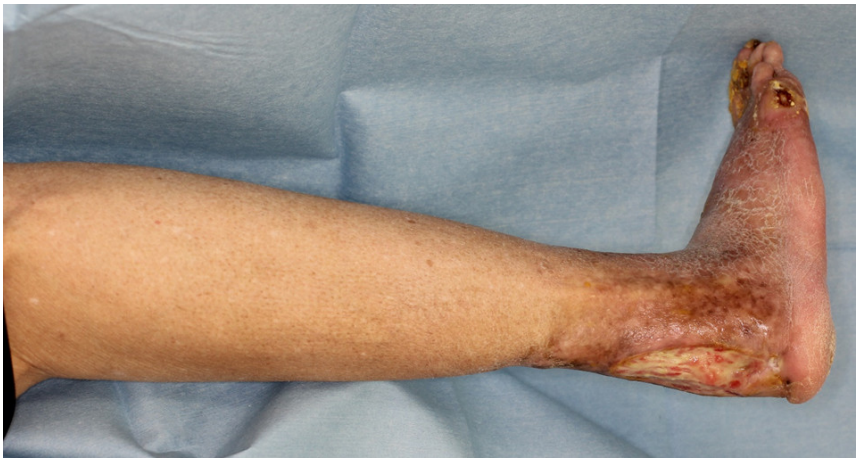

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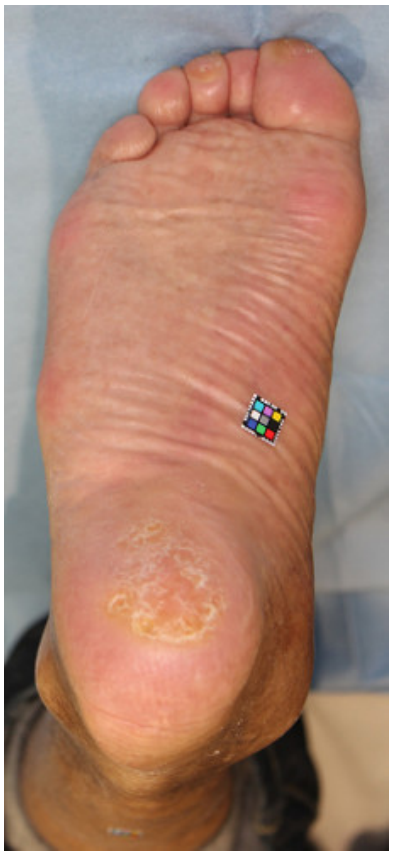
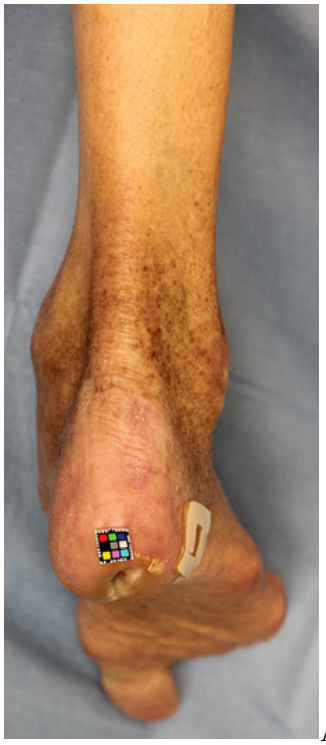


Figure 1. (A) Typical images of lower limbs in Werner syndrome. Significant hardening and atrophy of the skin and soft tissue are observed below the distal one-third of the lower extremities. (B) The foot is in relatively good condition without ulcers yet with a callosity on the heel region.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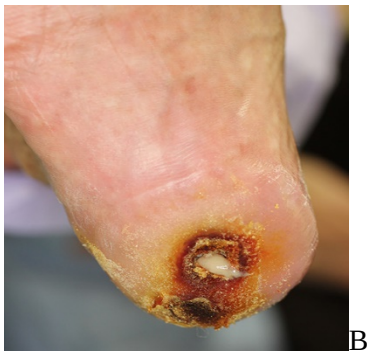
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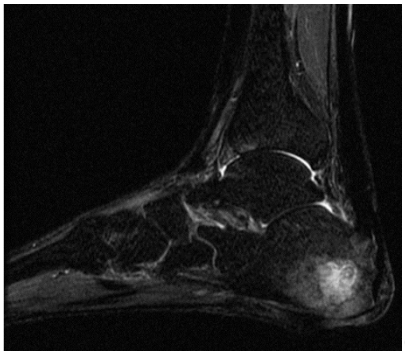
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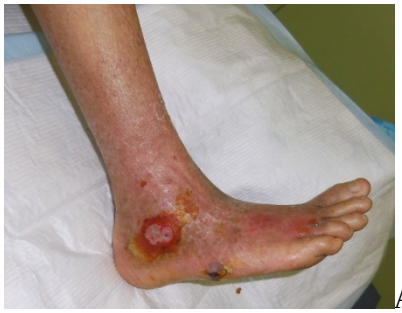
Figure 2. A case of a calcaneal callosity developing into possible calcaneal bone osteomyelitis
(Top) The skin is generally in good condition from the distal one-third of the lower extremities to the foot region.
(Center) Pus from the ulcer on the heel region

(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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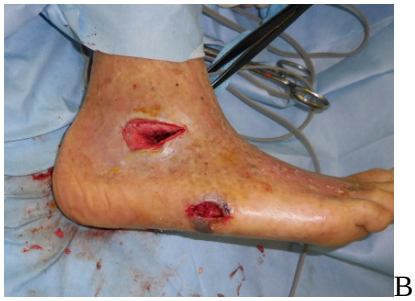
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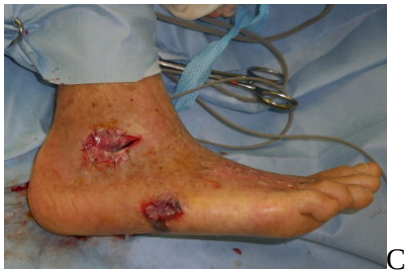
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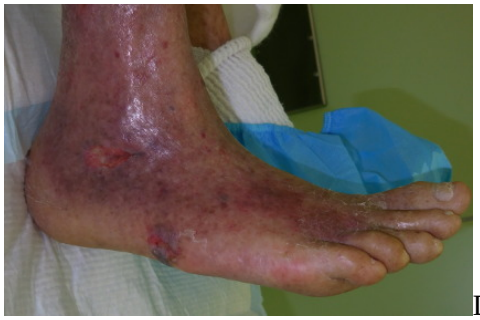
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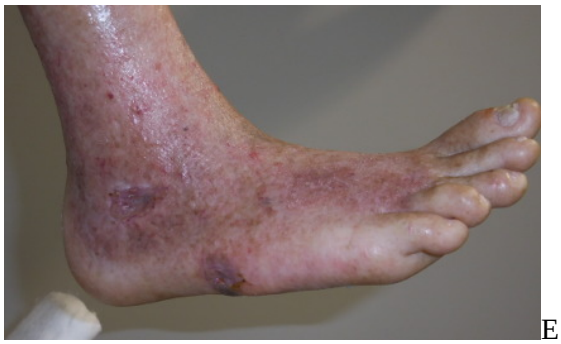
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Figure 3. (A) Ulcers are observed on the lateral malleolus in the ankle and the lateral aspect of

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.

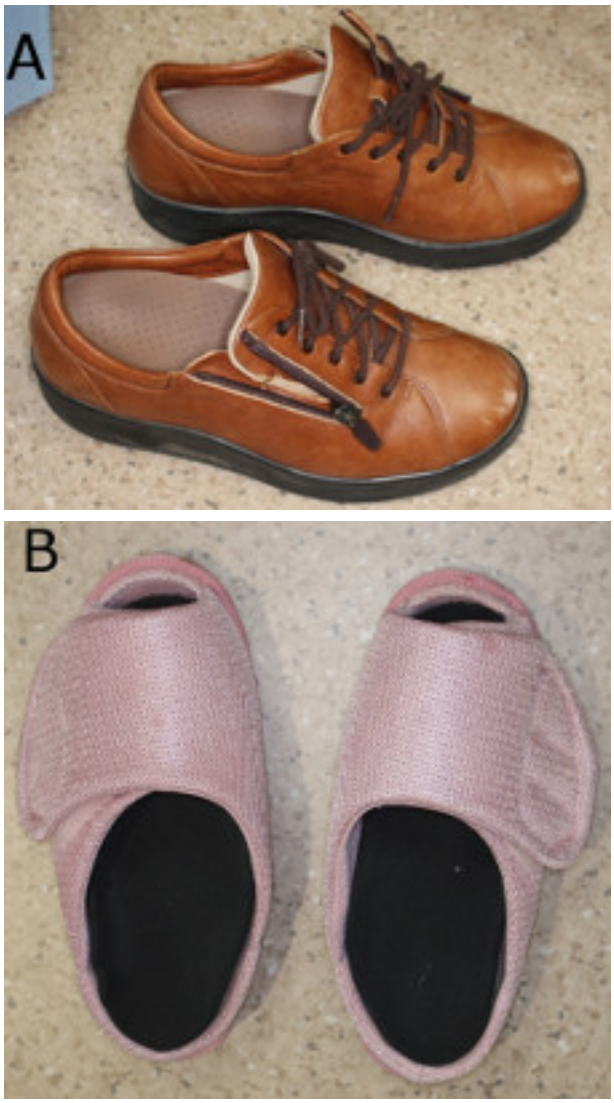

Figure 4. Samples of shoe-shaped orthoses: (A) Outdoor type shoes; (B) Indoor type shoes

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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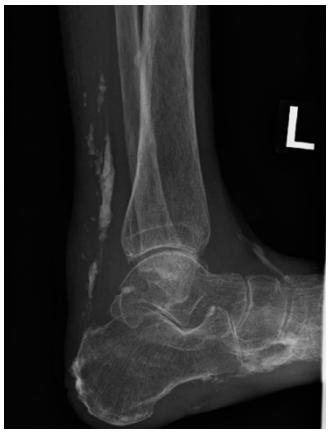
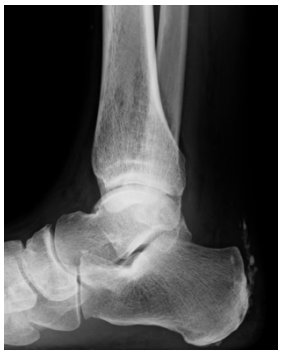
Figure 1



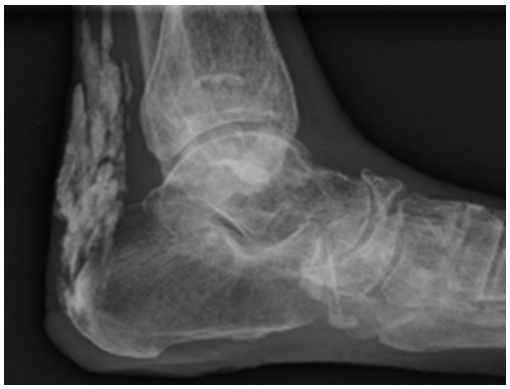
Calcification exceeding 2 cm is observed in the Achilles tendon (a single large segmental calcification)

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).

as exercise training, might be effective for recovering serum BDNF level with resultant improvement of cognitive dysfunction, dementia and long-term prognosis in CHF patients.

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Disclosure statement

The authors declare no conflict of interest.

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Femoral osteoporosis is more common than lumbar osteoporosis in patients with Werner syndrome

Dear Editor,

Werner syndrome (WS) is a rare autosomal recessive genetic disorder characterized by early onset of the normal aging processes and its associated complications, including osteoporosis. Mutations in the human *WRN* gene, encoding a member of the RecQ family of DNA helicases, result in this disorder.[1] We aimed to elucidate the clinical characteristics of osteoporosis in WS. A total of 10 patients (5 men and 5 women; mean age 50 years, range 40–60 years) were included. A diagnosis of WS was made based on the presence of the cardinal signs and symptoms of the disease, which include progeroid changes in hair, bilateral cataracts, intractable skin ulcers, soft-tissue calcification, bird-like face and abnormal voice, and was subsequently confirmed by genetic testing (Table 1).[2] Bone mineral density (BMD) was measured by dual-energy X-ray absorptiometry using the same machine for all the patients, and osteoporosis was diagnosed based on the Japanese diagnostic criteria for primary osteoporosis (BMD ≤70% of young adult mean or *t*-score ≤−2.5 SD).[3] As judged by lumbar ($L_{2–4}$) BMD, only one of 10 patients (case 1) was diagnosed with osteoporosis (Table 1). In contrast, based on the femoral BMD, six of 10 patients (cases 1, 2, 3, 5, 7 and 10) were diagnosed with osteoporosis (Table 1). Examination of thoracolumbar (T_4–L_4) radiographs showed that none of the patients sustained morphological vertebral fracture, any deformity of lumbar spine and calcification of abdominal aorta. Our present observation indicates that

Table 1 Bone mineral density of 10 patients with Werner syndrome

Case	Sex	Age (years)	*WRN* mutation[a]	Lumbar spine BMD ($L_{2–4}$)			Femoral neck BMD		
				g/cm^2	*T*-score (SD)	%YAM	g/cm^2	*T*-score (SD)	%YAM
1	M	57	6/6	0.730	−2.7[c]	70[d]	0.601	−2.1	70[d]
2	F	60	6/6	0.804	−2.1	78	0.452	−3.1[c]	57[d]
3	F	57	4/6	0.790	−1.9	78	0.351	−4.0[c]	45[d]
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[d]
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[c]	59[d]
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/– [b]	0.901	−1.1	85	0.606	−2.0	70[d]

[a]*WRN* mutation 4: IVS25–1 G > C, mutation 6: 1105 C > T (R369X), mutation 7: 3446delA (Q1148 fsX 1161), mutation 11: 2959 C > T (R987X). [b]Compound heterozygote with mutation 4 and another mutation that remains to be determined. [c]*T*-score ≤−2.5 SD. [d]Less than 70% of young adult mean (YAM; age 20–44 years). BMD, bone mineral density; F, female; M, male.

femoral osteoporosis, but not lumbar osteoporosis, is common in patients with WS.

To our knowledge, this is the first study in which BMD was measured by dual-energy X-ray absorptiometry in patients with WS. It has been reported that patients with WS exhibit osteoporosis[4,5] with possible impaired osteoblastic bone formation,[6] but normal osteoclastic bone resorption.[7] A target of the WRN protein is telomeric DNA, but long telomeres and abundant telomerase in mice minimize the need for WRN, and thus *WRN* knockout mice are relatively healthy.[8] However, in a model of accelerated aging that combined a *WRN* mutation with the shortened telomeres of telomerase (*TERC*) knockout mice, the simultaneous loss of *WRN* and *TERC* genes produced a low bone mass phenotype, and age-related osteoporosis resulted from impaired osteoblast differentiation.[9] Although there is no evidence to date for the expression and function of the WRN protein in human bone cells including osteoblasts, this, along with a subsequent report,[10] suggests that defective osteoblast differentiation as a result of telomere dysfunction is an important cellular mechanism that could partly explain the early onset of osteoporosis in patients with WS. It is unclear why femoral bone is more susceptible to osteoporosis than lumbar vertebral bone is, in this patient population, but it might be the case that mechanical offloading of the femur as a result of muscle atrophy and intractable leg ulcers could contribute to skeletal atrophy of the lower extremities in patients with WS.

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Disclosure statement

The authors declare no conflict of interest.

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Effect of sex on the association of isokinetic quadriceps strength with hypertension among older Americans

Dear Editor,

Few studies have examined whether muscle strength is associated with hypertension (HTN).[1–5] We tested this hypothesis in a cross-sectional analysis of data from a USA national sample National Health and Nutrition Examination Survey (NHANES) 1999–2002.[6–9] Participants were adults aged ≥50 years with no history of cardiovascular disease (n = 2335**)**. HTN was either a reported HTN diagnosis or blood pressure measurement of ≥140/90 or the use of HTN medication. Isokinetic muscle strength was measured by dynamometer.

Our sample size of 2266 (37 % aged ≥65 years, 52% women, 82% white) represented 42 225 702 persons in the USA after the sampling rate; oversampling of certain groups and non-response were taken into account by weighting. Mean quadriceps strength (Newtons) was significantly higher in normal individuals: undiagnosed HTN (n = 355, mean 355, 95% CI 337–374), diagnosed HTN (n = 1007, mean 357, 95% CI 346–367) and no HTN (n = 904, mean 393, 95% CI 379–406).

There was a significant effect modification by sex; therefore, sex-specific analyses are presented. Table 1 shows multivariate analyses. Model 1 controlled for the variables of age, race, body mass index and HTN status. Model 2 included model 1 plus blood relatives with a history of heart attack (yes/no) and smoking status (never/former/current). In model 1, the results showed that men aged ≥65 years had significantly lower quadriceps strength (P = 0.00) than men aged 50–64 years. In addition, men with a high body mass index also had lower quadriceps strength in comparison with persons with a healthy body mass index (P = 0.01). As with model 1, the results of model 2 also showed that quadriceps strength was significantly lower in diagnosed HTN (P = 0.02) than in those with no HTN. Quadriceps strength was lower in undiagnosed HTN than in normal individuals, but this difference was not significant. Women did not show such an association (Table 1).

In adults, limb muscle strength declines while HTN increases with aging.[10] In the present study we found that among adults aged ≥50 years without a history of cardiovascular disease, isokinetic quadriceps strength was significantly lower in men with diagnosed and undiagnosed HTN than in men with no HTN. No such association was seen in women. Previous studies have not reported an effect modification by sex. This and other findings should be confirmed in follow-up studies. A greater understanding of the role of muscle strength and mass in hypertension pathogenesis might clarify the role of resistance versus dynamic physical activity in hypertension prevention.

Disclosure statement

The authors declare no conflict of interest.

Table 1 Linear regression of hypertension status and quadriceps strength in persons aged 50 years and older: National Health and Nutrition Examination Survey 1999–2002

Hypertension status	β coefficient model 1	*P*-value	β coefficient model 2	*P*-value	β coefficient model 1	*P*-value	β coefficient model 2	*P*-value
	Men				Women			
Diagnosed hypertension	–21.79	0.02	–23.77	0.01	5.15	0.52	4.83	0.54
Undiagnosed hypertension	–0.34	0.98	0.25	0.98	6.25	0.45	5.67	0.48
No hypertension	1.00		1.00		1.00		1.00	

Recent Trends in *WRN* Gene Mutation Patterns in Individuals with Werner Syndrome

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OBJECTIVES: To determine recent trends in mutation patterns in the *WRN* gene, which cause Werner syndrome (WS), a rare, inheritable progeroid syndrome in Japan.

DESIGN: Retrospective cohort.

SETTING: Longitudinal survey of WS and literature search for case reports.

PARTICIPANTS: Individuals whose genetic testing their facilities had requested between 2009 and October 2016 (N = 67).

MEASUREMENTS: A nationwide epidemiological study was conducted from 2009 to 2011 to improve understanding of the pathology of WS and develop therapeutic guidelines. Since 2009, Chiba University Hospital consecutively evaluated the *WRN* gene in 67 individuals throughout Japan who had requested genetic testing. A literature search was also conducted for case reports on Japanese WS reported since 1997.

RESULTS: A definitive diagnosis of WS was confirmed genetically in 50 of 67 participants. Through the literature search, 16 individuals diagnosed genetically with WS were identified. Of these 66 individuals with WS, 42 were homozygous for a *WRN* mutation, and 21 were compound heterozygotes. One novel mutant allele was identified in an individual with the compound heterozygous genotype. The proportion of compound heterozygotes (31.8%) was significantly greater than reported previously (14.2%), indicating that the incidence of consanguineous marriage of parents has decreased.

CONCLUSION: The increased frequency of individuals with WS with the compound heterozygous genotype is a recent trend in Japan. A long-term follow-up study on *WRN* homozygotes and compound heterozygotes will allow the relationship between *WRN* genotype and clinical severity of WS to be evaluated in the future. **J Am Geriatr Soc 65:1853–1856, 2017.**

Key words: Werner syndrome; Werner gene; gene mutation; ReqQ DNA helicase

Werner syndrome (WS), also known as adult progeroid syndrome, is an autosomal-recessive disorder caused by a mutation in the gene encoding the RecQ DNA helicase[1], with a high incidence in Japan[2]. In 2009, a nationwide study aimed at understanding the pathology and development of therapeutic guidelines for WS was launched as intractable disease research supported by Health, Labour and Welfare Sciences Research grants from the Ministry of Health. The study remains ongoing in a form of research on rare and intractable diseases. Since 2009, Chiba University Hospital has conducted genetic testing of WS as requested by facilities across Japan. A literature search was also conducted for cases of WS in Japanese individuals reported since 1997. A summary of the results of the genetic testing conducted and the literature search is reported.

MATERIALS AND METHODS

Subjects

Participants were 67 individuals whose genetic testing their facilities had requested between 2009 and October 2016. The present study was conducted in accordance with the ethical principles of the Declaration of Helsinki and was approved by our ethical committee before its inception. All participants understood the study aims and methods and provided written informed consent.

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Literature Search

A literature search was conducted using the medical online database (http://mol.medicalonline.jp/library/) for articles written in Japanese and the PubMed (https://www.ncbi.nlm.nih.gov/pubmed/) archives with the following terms: "Werner syndrome" [All Fields] AND {Case Reports (ptyp) AND ["1996/01/01"(PDAT): "3000/12/31"(PDAT)]} from 1997. Multiple reports on the same individuals and those on individuals whose genetic testing the authors performed were excluded.

Genotyping

Genomic deoxyribonucleic acid (DNA) was extracted from anonymized blood samples collected using ethylenediaminetetraacetic acid 2Na (QIAamp DNA Blood Mini Kit, QIAGEN, Hilden, GERMANY). In the genetic testing, the exons were amplified individually, as described previously[3]. The amplified DNA fragments were subjected to direct sequencing for the analysis; 11 mutations common in Japanese subjects were examined. Additional genetic analysis was conducted in some participants.

Statistical Analysis

Comparisons between two groups were conducted using the chi-square test. $P < .05$ was considered statistically significant. Statistical analyses were performed using JMP Pr012 software (SAS Institute Japan, Tokyo, Japan).

RESULTS

Sixty-seven individuals were genotyped. Genotyping in these cases was requested from facilities in 26 of 46 prefectures in Japan. Internal medicine (32.8%) and dermatology (19.4%) departments frequently requested the genetic testing. WS was the genetically definitive diagnosis in 50 cases. The literature search identified 186 reports describing WS, and 49 of these were Japanese WS case reports from the medical online database. In these 49 reports, genotypes were reported in six individuals, three of which the authors had genetically diagnosed and excluded from the study. Of 151 reports of WS identified from PubMed, 51 were Japanese, and genotypes were reported in 15. Multiple reports of the same individuals and those of individuals in whom the authors had performed genetic testing were excluded, leaving 13 individuals for evaluation. In total, 16 individuals genetically diagnosed with WS were identified from the literature.

Table 1 shows the breakdown of the frequency of genotypes. There were 41 homozygotic, 21 compound heterozygotic, and four heterozygotic (only one allele has a mutation) participants. The frequency of compound heterozygosity was significantly higher (31.8%) than reported previously (14.2%) ($P = .02$) (Table 1). Sixteen individuals who underwent genotyping in Chiba University Hospital were free of the mutations. One novel allele mutation, such as the type 6 mutation (c.1105C>T)/c.2772delA (Table 1), was identified in 18 compound heterozygotes who also underwent genotyping in our facility.

Table 1. Breakdown of the Frequency of *WRN* Genotypes in This Report Compared to Previous Report

Mutation	Participants from This Report	Participants from Previous Reports	*P*-Value
	n (%)		
Homozygote	42 (63.6)	41 (73.2)	.19
Mut 1/1	0 (0)	1 (1.8)	.80
Mut 4/4	31 (47.0)	26 (46.4)	.95
Mut 5/5	0 (0)	1 (1.8)	.28
Mut 6/6	9 (15.1)	9 (16.1	.71
Mut 7/7	1 (1.5)	1 (1.8)	.91
Mut 8/8	0 (0)	1 (1.8)	.28
Mut 9/9	0 (0)	1 (1.8)	.28
Mut 10/10	0 (0)	1 (1.8)	.28
Compound heterozygote	21 (31.8)	8 (14.2)	.02
Mut 4/6	6 (9.1)	3 (5.4)	.43
Mut 4/7	5 (7.6)	0 (0)	.04
Mut 1/4	2 (3.0)	5 (8.9)	.16
Mut 4/11	3 (4.5)	0 (0)	.11
Mut 4/ IVS 14+1 G>A	1 (1.5)	0 (0)	.36
Mut 1/11	1 (1.5)	0 (0)	.36
Mut 1/6	1 (1.5)	0 (0)	.36
Mut 1/ 3030–3033delAACG	1 (1.5)	0 (0)	.36
Mut 6/ 2772delA (novel mutation)	1 (1.5)	0 (0)	.36
Heterozygote	4 (6.1)	7 (12.5)	.22
1/?	2 (3.0)	2 (3.6)	.87
4/?	2 (3.0)	4 (7.1)	.30
6/?	0 (0)	1 (1.8)	.28
Total	66	56	

Frequency of each genotype in the study was compared with that in a previous report[5].

Mut 1: c.3913C>T, Mut 4: c.3139–1G>C, Mut 5: c.3915dupA, Mut 6: c.1105C>T, Mut 7: c.3446delA, Mut 8: c.3460–7T>A, Mut 9: c.1389T>A, Mut 10: c.502_503delAA, Mut11: c.2959C>T.

The genotype–phenotype relationship between homozygotes and compound heterozygotes was also analyzed. In this analysis, the clinical signs and symptoms listed in the diagnostic criteria were compared. Twenty-six homozygotic and 14 compound heterozygotic individuals aged 40 and older were selected, because most clinical symptoms do not appear until the age of 40. Parental consanguinity was observed frequently in homozygotes but not in compound heterozygotes (Table 2). There were no differences in major clinical signs and symptoms between the two groups.

DISCUSSION

Previous studies in Japan in 1978 and 1981 revealed that WS is inherited as an autosomal-recessive trait[4]. Approximately 1,200 cases of WS have been reported worldwide. The genetic epidemiology of the Japanese population with WS was reported previously in 1997, and approximately 1,000 cases have been found in Japan[5]. According to a report of a genetic assessment of 1,000 general inhabitants in Kanagawa Prefecture, six residents had heterozygous mutations in the *WRN* gene, which would mean that,

Table 2. Genotype–Phenotype Relationship Between Homozygotes and Compound Heterozygotes

	Homozygote		Compound Heterozygote		
	Positive Signs	Negative Signs	Positive Signs	Negative Signs	
	n				*P*-Value
Cardinal signs and symptoms					
Progeroid changes of hair	22	1	12	1	.68
Cataract	26	0	14	0	N/A
Skin changes, intractable skin ulcers	25	1	14	0	.35
Soft-tissue calcification	18	0	11	0	N/A
Bird-like face	19	3	9	1	.77
Abnormal voice	16	5	9	1	.34
Other signs and symptoms					
Abnormal glucose or lipid metabolism	16	11	12	2	.07
Deformation and abnormality of the bone	13	3	9	0	.09
Malignant tumors	7	14	1	9	.14
Parental consanguinity	14	11	0	12	.001
Premature atherosclerosis	3	11	4	4	.17
Hypogonadism	1	8	1	4	.65
Short stature and low body weight	13	13	6	6	>.99

Clinical signs and symptoms, which were listed in the diagnostic criteria, of 26 homozygotes and 14 compound heterozygotes aged 40 and older were compared.

The number of patients is indicated. For instance, 22 of 26 homozygotic participants had progeroid changes of the hair, and one had no change. The clinical findings have not always been described well in published case reports. Therefore, the total number of participants with each clinical sign differed.

N/A=not available.

mathematically, approximately 23 homozygote individuals would be born every year[2].

There are 83 types of *WRN* gene mutations, including nonsense, splicing, and frameshift mutations, which have been reported recently[1,6,7]. In Japan, the type 4 mutation (mut4), in which G, the base immediately preceding exon 26, is mutated to C (c. 3139–1G>C) is the most common (50.4%), followed by the type 6 mutation (mut6) (c.1105C>T) (17.5%)[5]. These mutation names (mut4, mut6) are used in Japan. The frequency of mut4 (48%) was also highest in the 50 cases in which the present genetic testing led to the definitive diagnosis—similar to the percentage in the previous report. Such a development due to homozygosity is seen frequently in consanguineous marriages. In nonconsanguineous marriage, WS develops because of compound heterozygosity, such as mut4 (c.3139–1G>C)/mut6 (c.1105C>T). According to a previous report, the rate of development of WS from consanguineous marriage was 70%, whereas that from compound heterozygosity was as rare as 14.2%[5]. According to a Japanese nationwide epidemiological survey of WS conducted in 2009, the incidence from consanguineous marriage was 43%, which was lower than in the previous report[7]. The increase in incidence from compound heterozygosity to 31.8% in the present examination reflects this, supporting that development of WS from nonconsanguineous marriage is increasing in Japan. Greater numbers of compound heterozygotes indicates that people with the *WRN* heterozygote mutation have spread widely throughout Japan, probably because of the development of transportation network. The current study also provided information on how rare diseases (in this case, WS) spread genetically on large islands such as Japan. Autozygosity, the genomic signature of consanguinity, has declined because of globalization and urbanization[8]. In addition to these influences of demographic factors on inherited rare diseases, recent improvement in genomic sequencing technique might also have affected the results, because there were more heterozygotes in previous studies (7 of 56 cases) than in the current study (4 of 66 cases), although the difference was not statistically significant (Table 1).

Few reports have indicated relationships between WS genotype and its clinical severity[9]. The current study attempted to determine the difference in phenotypes between homozygotes and compound heterozygotes. Although it was not possible to detect any differences in phenotypes, further analyses should be performed before any conclusions are drawn. The clinical findings of these individuals have not always been well described in published case reports, and some characteristic phenotypes in each genotype may appear later in life. For that reason, whether there is a difference in phenotype between homozygotes and compound heterozygotes is a matter for future examination and will require long-term follow-up. Therefore, a registry for Japanese with WS has been started, which The Japan Agency for Medical Research and Development has supported (http://www.m.chiba-u.jp/class/clin-cellbiol/werner/index.html).

This examination allowed one novel gene mutation to be identified. Relationships between these novel mutations and phenotypes are interesting. In addition, of the cases suspected clinically to be progeria, 16 had no mutation in the *WRN* gene. For these cases, additional genes, including the *LMNA* gene[10], will be analyzed, which also may lead to identification of a novel type of progeria.

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Author Contributions: Yamaga, Takada-Watanabe, Koizumi: analysis and interpretation of data, acquisition of subjects and data. Takemoto: interpretation of data, preparation of manuscript. Kitamoto: analysis and interpretation of data. Sakamoto, Ishikawa, Koshizaka, Maezawa: interpretation of data. Yokote: discussion, review, editing of manuscript.

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改訂版　ウェルナー症候群の重症度分類

1 度	皮膚の硬化や萎縮が四肢のいずれかにみられるが、日常生活への影響はまだ極めて軽微。
2 度	皮膚の硬化や萎縮が四肢のいずれかにみられるが、まだ障害は軽く、日常生活は多少の不自由はあっても従来通り可能であり、歩行障害はないか、あっても軽微である。
3 度	**日常生活は自立しているが、皮膚潰瘍[注1)]または皮下の石灰化による疼痛のために日常生活の制約をうけている。**
4 度	下肢に強い症状があり、自立歩行は不可能。介助により歩行や外出を行う。日常生活でも部分的介助を要する。
5 度	ベッドまたは車椅子の生活でほとんど寝たきり。全面的介助を要する。もしくは悪性腫瘍を発症している。[注3)]

注１）皮膚潰瘍（治療後瘢痕を含む）：ウェルナー症候群は、四肢末梢における皮膚の硬化・萎縮に伴い、下腿や足部、肘部に皮膚潰瘍を好発する。皮膚の萎縮、線維芽細胞の老化による再生能力の低下や血行障害のため、保存的にも観血的にも治癒の困難な場合が多い。疼痛や関節可動域の低下により、下肢潰瘍は歩行障害をもたらし、肘部潰瘍は食事や洗顔に支障をきたすなど、日常生活動作が著しく制限される。潰瘍部への感染併発により、しばしば四肢切断に至る。

注２）難治性潰瘍のため四肢切断に至った場合は 4 度以上に分類される。

注３）ウェルナー症候群では、若年より悪性腫瘍（固形ならびに造血器腫瘍）を高率に発症し、その日常生活活動度と生命予後を左右する。

International Meeting on RECQ Helicases and Related Diseases 2018

国際シンポジウム「早老症と関連疾患」

アジア初開催

February 16(Fri.) - 18(Sun.)

Kazusa Akademia Hall　かずさアカデミアホール

Chair of the Organizing Committee: Koutaro Yokote（Chiba University）

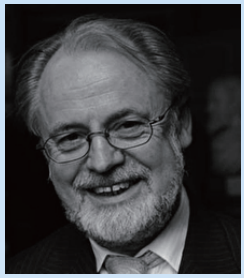
早老症およびその類縁疾患として知られるRECQヘリカーゼ病（ウェルナー、ブルーム、ロズムンドトムソン症候群）やハッチンソン・ギルフォード症候群、コケイン症候群、色素性乾皮症の病態と治療について論じる日本で初めての国際シンポジウムです。早老症の克服に向けて、細胞老化やゲノム、ミトコンドリア、疾患iPS細胞など関連領域から第一線の基礎、臨床研究者をお招きし、新たな発見やトランスレーショナルリサーチを生み出す機会を目指します。

Plenary Speakers

George Martin
University of Washington

Vilhelm Bohr
National Institute of Aging

Yoshihide Hayashizaki
Riken



Jan Hoeijmakers
Erasmus University

Speakers

Leslie B. Gordon Brown University
Ray Monnat University of Washington
Nathan Ellis University of Arizona
Lisa Wang Texas Children' s Hospital
Deborah Croteau National Institute of Aging
Sagar Sengupta National Institute of Immunology, India
Joannna Groden Ohio State University
Junko Oshima University of Washington
Makoto Goto Toin University of Yokohama
Guanghui Liu Chinese Academy of Science
Yasuhiro Furuichi GeneCare Research Institute
Tomoo Ogi Nagoya University

Eiji Hara Osaka University, Cancer Institute
Kohjiro Ueki Tokyo University, National Center for Global Health and Medicine
Emi Nishimura Tokyo Medical and Dental University
Ichiro Manabe Chiba University
Wado Akamatsu Juntendo University
Kaoru Sugasawa Kobe University
Chikako Nishigori Kobe University
Shigeru Yanagi Tokyo University of Pharmacy and Life Sciences
Masato Fujioka Keio University
Kenji Ihara Ooita University
Koutaro Yokote Chiba University

国内外の患者さんやご家族と研究者の交流機会も設ける予定です。幅広い皆様のご参加をお待ちしています。

ポスター演題を募集しています。ふるってご応募下さい！

お問い合わせ　http://www.jtbw-mice.com/recq2018/
E-mail：recq2018@west.jtb.jp

主催　RecQ2018実行委員会
公益財団法人 難病医学研究財団

Tentative Program

Day1 Feb 16th (Fri)

12:30-12:40 **Opening Remarks**
Koutaro Yokote (Chiba University, Chiba, Japan)

12:40-13:30 **Plenary Lecture 1**
George Martin (University of Washington, Seattle, USA)

Session 1 Clinical features and genetics of Werner Syndrome
13:30-14:00 Makoto Goto (Toin University of Yokohama, Yokohama, Japan)
14:00-14:30 Ray Monnat (University of Washington, Seattle, USA)
14:30-15:00 Junko Oshima (University of Washington, Seattle, USA)

Session 2 Bloom Syndrome and Stem cell aging in Skin
15:10-15:40 Nathan Ellis (University of Arizona, Tucson, USA)
15:40-16:10 Joanna Groden (The Ohio State University, Columbus, USA)
16:10-16:40 Emi Nishimura (Tokyo Medical and Dental University, Tokyo, Japan)

16:40-17:40 **Patients and Families Session**
17:40-19:10: **Poster session**

Welcome Reception

Day2 Feb 17th (Sat)

08:30-09:20 **Plenary Lecture 2**
Vilhelm Bohr (National Institute of Aging, Bethesda, USA)

09:20-11:20 **Session 3 Young Investigators Travel Award Presentation**
10min x several good presentation and 1 minutes presentation for all poster presenters

11:30-12:20 **Luncheon Seminar**
Chair: Shigeki Kuzuhara (Suzuka University of Medical Science, Mie, Japan)
Koutaro Yokote (Chiba University, Chiba, Japan)

Session 4 Rothmund Thomson Syndrome, Mitochondrial Dysfunction and Aging
12:30-13:00 Lisa Wang (Texas Children's Hospital, Baylor College of Medicine, Houston, USA)
13:00-13:30 Deborah Croteau (National Institute on Aging, Bethesda, USA)
13:30-14:00 Sagar Sengupta (National Institute of Immunology, New Delhi, India)
14:00-14:30 Shigeru Yanagi (Tokyo University of Pharmacy and Life Sciences, Tokyo, Japan)

14:30-15:20 **Plenary Lecture 3**
Yoshihide Hayashizaki (Riken, Wako, Japan)

Session 5 Aging related Diseases and Hutchinson Gilford Progeria Syndrome
15:40-16:10 Yasuhiro Furuichi (GeneCare Research Institute, Kamakura, Japan)
16:10-16:40 Kohjiro Ueki (Tokyo University, National Center for Global Health and Medicine, Tokyo, Japan)
16:40-17:10 Ichiro Manabe (Chiba University, Chiba, Japan)
17:10-17:40 Kenji Ihara (Ooita University, Ooita, Japan)
17:40-18:30 **Special Lecture:** Leslie Gordon (Brown University, Providence, USA)
Photo

Dinner

Day3 Feb 18th (Sun)

08:00-08:50 **Morning Seminar**
Chair: Yoichi Nabeshima (Foundation for Biomedical Research and Innovation, Kobe, Japan)
Eiji Hara (Osaka University, Cancer Institute, Osaka and Tokyo, Japan)

09:00-09:50 **Plenary Lecture 3**
Jan Hoeijmakers (Erasumus University, Rotterdam, Netherland)

Session 6 Xeroderma Pigmentosa and Cockayne syndrome

09:50-10:20 Kaoru Sugasawa (Kobe University, Kobe, Japan)
10:20-10:50 Chikako Nishigori (Kobe University, Kobe, Japan)
10:50-11:20 Tomoo Ogi (Nagoya University)

Session 7 Can iPS cells be a Future therapeutics?

11:30-12:00 Guanghui Liu (Institute of Biophysics, Chinese Academy of Science, Beijing, China)
12:00-12:30 Masato Fujioka (Keio University, Tokyo, Japan)
12:30-13:00 Wado Akamatsu (Juntendo University, Tokyo, Japan)

13:00-13:10 **Closing Remarks**
Koutaro Yokote (Chiba University, Chiba, Japan)

研究成果の刊行に関する一覧表

雑誌

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amaga M, Takemoto M, Takada-Watanabe A, Koizumi N, Kitamoto T, Sakamoto K, Ishikawa T, Koshizaka M, Maezawa	Recent Trends in WRN Gene Mutation Patterns in Individuals with Werner Syndrome	J Am Geriatr Soc	65	1853-1856	2017