Review

DOI: 10.5582/irdr.2025.01032

Secondary musculoskeletal disability and rehabilitation aspects in adults with thalidomide embryopathy: A narrative review

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SUMMARY: To review musculoskeletal disabilities and rehabilitation in adults with thalidomide embryopathy (TE), the authors reviewed the literature related to musculoskeletal disability, quality of life (QOL) and rehabilitation intervention in adults with TE, obtained through a PubMed search, and their experience in clinical practice with Japanese individuals. Through literature search, 25 studies were included for this review. Literature search results and the authors' experiences revealed that, in adults with TE, upper limb disabilities included neuropathy, mainly due to carpal tunnel syndrome; finger pain due to tenosynovitis; and symptoms caused by osteoarthritis, mainly in the shoulders. Disabilities of the trunk and spine included lower back and neck pain. Although disabilities in the lower limbs were uncommon, pain due to hip and knee osteoarthritis were reported. Regarding the health-related QOL in adults with TE, the physical domain of QOL was reduced, which may be related to musculoskeletal disabilities. Reports on rehabilitation approaches for secondary musculoskeletal disabilities in TE, including physical therapy, environmental modification, and alternative medicine, were scarce. This review of musculoskeletal disabilities and QOL in adults with TE revealed that pain is common in the upper limbs and spine, and is associated with reduced physical QOL.

Keywords: limb malformation, rehabilitation approach, health-related quality of life

1. Introduction

Thalidomide embryopathy (TE) is a well-known drug-induced tragedy having affected over 4,000 infants worldwide, born in the late 1950s and early 1960s (*1*). These infants were born to mothers who took thalidomide in their early pregnancy. Thalidomide had sedative property, and compound preparations which combined thalidomide with other drugs were marketed for a wide variety of indications, including asthma, hypertension, and migraine. The most common phenotype of TE is congenital limb malformation. The second most common group of defects involves developmental abnormalities of the ear and eye and abnormalities in the innervation of the external ocular muscles, facial muscles, and tear glands. Other defects include cleft palate, hypoplasia of the external genitalia, anomalies of the internal organs, and neurodevelopmental problems (*2*).

Limb malformations are common in the upper extremities, and most individuals with upper limb malformations have normal lower limbs. Some individuals have defects in all limbs; malformations of the lower limbs with normal upper limbs are rare. The limb malformations were generally symmetrical. Upper limb malformations include amelia, phocomelia, defects in the radius and thumb, and triphalangism or hypoplasia of the thumb. Lower limb malformations include amelia, phocomelia, tibial defects, aplasia or hypoplasia of the femur, and polydactylism. Other lower-limb abnormalities include congenital dislocation of the hip and clubfoot (*2-4*).

Spinal involvement is sometimes confirmed, including congenital partial absence of the sacrum, scoliosis, and abnormalities of the disc and endplate leading to intervertebral fusion (*2,4,5*). An individual with TE in whom an anterior sacral meningocele was recognized in adulthood has also been reported (*6*).

Owing to these congenital musculoskeletal

abnormalities, children with TE had difficulty in performing activities of daily living (ADL). Physical and occupational therapies played a significant role in treating these conditions (*7,8*). In children with amelia or phocomelia in their upper limbs, various types of upper-limb prostheses, including those using electric motors or compressed gases, were used (*9,10*). However, most children discarded their prostheses for functional reasons and preferred to use their feet as they grew. Through rehabilitation with occupational therapists, most children with normal lower limbs have become independent (*11*).

The present age of survivors of TE is approximately 60 years, and additional musculoskeletal disabilities and related decline in quality of life (QOL) in adults with TE have been reported over the past 20 years (*12-15*). However, there exists no previous studies that overview the declined QOL due to musculoskeletal disabilities from the perspective of rehabilitation. This study aimed to review musculoskeletal disabilities and related rehabilitation aspects, including QOL and the rehabilitation approach.

2. Research design and literature search strategy

This study comprised a literature review and the authors' experience in clinical practice with Japanese individuals with TE.

2.1. Literature search

The authors searched PubMed for articles related to musculoskeletal disability, related QOL, and rehabilitation approaches in adults with TE. This search was conducted for literature published between January 1980 and December 2024 because most individuals with TE were born in the late 1950s or early 1960s. The search strategies included "thalidomide AND musculoskeletal", "thalidomide AND pain", "thalidomide AND quality of life", and "thalidomide AND rehabilitation". Among the identified records, studies on novel use of thalidomide, non-English literature, and duplicate records were removed, considering the titles and abstracts. The first author (NH) read the full-text articles of the screened records, and selected studies to be included in this review article. The exclusion criteria were *i*) those with no or partial relation to thalidomide, *ii*) those with no relation to secondary musculoskeletal disability, *iii*) review article, and *iv*) discussion or comment. In addition to the database search, the authors identified records from citation searching.

2.2. Author's experience in clinical practice

The authors provide information on the personal experiences of Japanese individuals with TE regarding secondary musculoskeletal disability and the rehabilitation approach. The provision of information on Japanese individuals with TE was approved by the ethics committees of the National Rehabilitation Center for Persons with Disabilities (approval number 2022-136), Faculty of Medicine, The University of Tokyo (approval number 2373-7), and Shiga University of Medical Science (approval number R2017-267). Written informed consent was obtained, or the opt-out method was applied to obtain consent using descriptions in the websites of the authors' affiliations.

3. Results of literature search and the key findings

3.1. Literature search results

Figure 1 displays the flow diagram for selecting studies for this review. The database search using PubMed identified a total of 1,106 records. After removing 1,025 studies on novel use of thalidomide including medication for cancer, peripheral neuropathy, psoriatic diseases,

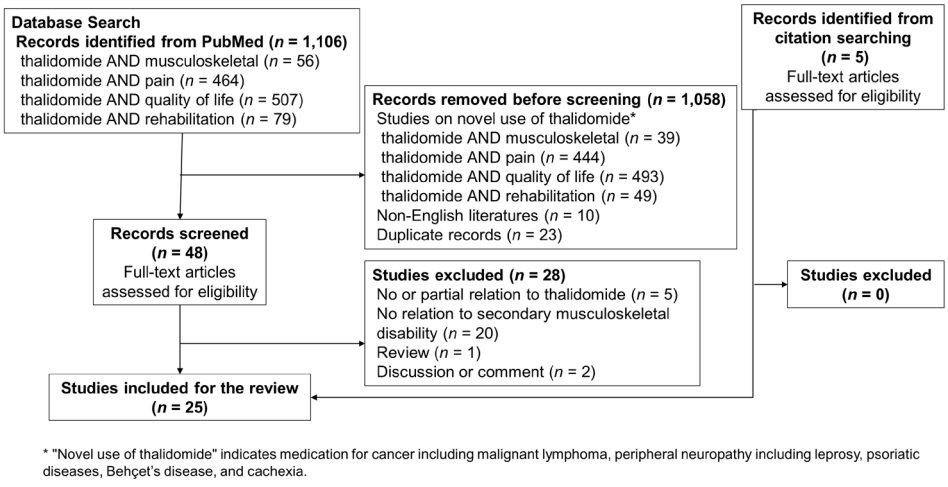

Figure 1. Flow diagram for identifying studies.

Behçet's disease, and cachexia, 10 non-English literature, and 23 duplicate records, 48 records were screened and full-text articles were assessed for eligibility. Among these, 28 studies were excluded according to the criteria described above, and 20 studies remained to be included in this review. In addition, 5 records were identified from citation searching, and none was excluded. Overall, 25 studies were included for this review.

Table 1 shows the subjects and design of studies included for this review. The number of studies from UK was 7, followed by Germany (n = 6), Japan (n = 5), and Sweden (n = 4). Thirteen studies included interview and/or questionnaire, and the sample size exceeded 100 in 7 of them. Eight were report of 1 or 3 cases. There were 3 imaging studies and 2 neurophysiological studies, and each one of them was a case control study. The key findings from these studies are described based on the study subjects in the following sections.

3.2. Aging and musculoskeletal disability in adults with TE

Adults with TE aged 54 to 60 reported significantly greater numbers of musculoskeletal problems and nervous system symptoms, including pain, pins and needles and numbness, than the age-matched controls (*16*).

3.2.1. Disabilities in upper limbs

Adults of TE with upper limb deficiency report a high prevalence of neuropathic pain in the upper limbs (*17*). Neurophysiological testing in adults complaining of numbness or tingling revealed findings of compressive neuropathy. Although many of the results revealed compression of the median nerve at the wrist, other findings (*e.g.*, suggested cervical radiculopathy) have also been observed (*18,19*). In adults with radial deficiency, including those with TE, the development of carpal tunnel syndrome and decompression surgery with good outcomes have been reported (*20,21*). They underwent surgery in their 20s or 30s, and the early development of symptoms may be due to the narrow anteroposterior diameter and small cross-sectional area of the carpal tunnel in patients with radial deficiency (*20*).

Another upper-limb disability is the pain caused by early onset osteoarthritis. Middle-aged adults undergoing shoulder joint replacement have good postoperative results, although pain and limited range of motion due to glenohumeral osteoarthritis do not respond to conservative preoperative treatments (*22,23*). An adult with TE who developed a special form of shoulder osteoarthritis has also been reported. The glenohumeral joint is formed by a convex glenoid and a concave humeral head (*24*). As for the elbow joint, though limited

Table 1. Subjects and design of studies included for the review

First Author (Year) (*Ref.*)	Country	Study Subject	Study Design (Sample Size)
Bent (2007) (*12*)	UK	QOL and health status	Interview (n = 28 among 70) Questionnaire (n = 44 aomng 88)
O'Carroll (2011) (*13*)	Ireland	QOL and health status	Questionnaire (n = 17 among 26)
Ghassemi Jahani (2016) (*14*)	Sweden	QOL and function of limbs	Questionnaire (n = 31 among 84)
Markiewicz (2023) (*17*)	UK	QOL and upper limb disability	Questionnaire (n = 127 among 346)
Ghassemi Jahani (2014) (*25*)	Sweden	Disability in upper and lower limbs	Questionnaire for upper limbs and CT for lower limbs (n = 31 among 84)
Imai (2020) (*27*)	Japan	QOL and pain	Questionnaire (n = 51 among 67)
Newbronner (2019) (*32*)	UK	QOL and health status	Questionnaire (n = 351 among 467)
Niecke (2022) (*33*)	Germany	QOL and health status	Questionnaire (n = 186 among 202)
Hinoshita (2019) (*36*)	Japan	Life situation	Questionnaire (n = 173 among 274)
Sagoe (2024) (*16*)	UK	Comorbid health condition	Questionnaire (n = 392 among 415)
Ghassemi Jahani (2017) (*29*)	Sweden	Physical function and ADL with or without PFFD	Questionnaire (n = 31)
Nippert (2002) (*34*)	Germany	QOL and health status in women	Questionnaire (n = 104 among 166)
Samel (2019) (*35*)	Germany	QOL and health status in women	Physical examination and questionnaire (n = 115 among 206)
Kimura (2001) (*20*)	Japan	Carpal tunnel syndrome	Case report (n = 1)
Oshima (2006) (*21*)	Japan	Carpal tunnel syndrome	Case report (n = 3)
Newman (1999) (*22*)	UK	Shoulder osteoarthritis	Case report (n = 1)
Merkle (2016) (*23*)	Germany	Shoulder osteoarthritis	Case report (n = 3)
Kimmeyer (2021) (*24*)	Germany	Shoulder osteoarthritis	Case report (n = 1)
Fahlbusch (2023) (*30*)	Germany	Knee osteoarthritis	Case report (n = 1)
Morrison (2020) (*37*)	UK	Intervention for fall prevention	Case report (n = 1)
Hodo (2017) (*31*)	USA	Anatomy of lower limb	Case report (n = 1)
Kamimura (2024) (*26*)	Japan	Imaging of upper limbs	CT for upper limbs (n = 5)
Ghassemi Jahani (2016) (*28*)	Sweden	Degenerative changes in cervical spine	Case control study including cervical spine MRI (n = 27)
Nicotra (2016) (*18*)	UK	Peripheral nerve dysfunction of upper and lower limbs	Case control study including neurophysiological testing (n = 17)
Jankelowitz (2013) (*19*)	Australia	Neurological symptoms in upper limbs	Clinical and neurophysiological assessment (n = 16)

range of motion is reported, pain and development of osteoarthritis remain unelucidated (*25*). A Japanese study investigating computed tomography findings of the upper limbs in middle-aged adults with TE revealed abnormal elbow findings, including hypoplasia of the trochlea and/or capitulum of the humerus, coronoid fossa, olecranon, and coronoid processes (*26*). The same study revealed that the carpal bones made contact with the radius or ulna only in a limited area. These anatomical abnormalities may lead to age-related articular surface deformation, resulting in limitations in joint mobility and pain.

3.2.2. Disabilities in trunk and spine

A questionnaire survey of Japanese adults with TE showed that pain in the lower back or neck was relatively common (*27*). On cervical spine MRI, a higher degree of disc degeneration and more foraminal narrowing were observed in middle-aged individuals with TE than in age- and sex-matched healthy controls (*28*).

3.2.3. Disabilities in lower limbs

In a survey of 31 middle-aged adults with TE (*25*), five with proximal femoral focal deficiency (PFFD) and other malformations in the lower limbs showed significantly reduced ambulation, including three individuals using wheelchairs most of the time. Osteoarthritic changes in the hips, knees, and metatarsophalangeal joints have been observed in individuals with PFFD. In some of the remaining 26 adults without major lower limb anomalies, slightly deformed femoral head, knee abnormalities with a hypoplastic lateral femoral condyle, and knee instability were observed. Osteoarthritic changes were observed in the hips, knees, and feet; however most were mild. The same group reports that TE adults with PFFD need more assistive products and support, show lower physical function, and need longer time for ADL in the morning (*29*).

Reports on treatment for lower limb osteoarthritis are scarce. Total knee arthroplasty and patelloplasty was reported in a 59-year-old female with end-stage osteoarthritis of the left knee and phocomelia (*30*). A 54-year-old female experiencing recurrent bilateral foot pain showed dysmorphic and osteoarthritic changes in the ankle and foot on X-ray images, and anatomic abnormalities of tendons on MRI. This patient chose conservative treatment with immobilization of the foot (*31*).

3.3. Musculoskeletal disability and QOL in adults with TE

The health-related QOL (HRQOL), including its relationship with musculoskeletal disabilities, has been investigated in adults with TE across various nations and age groups. In a study of UK individuals aged approximately 40 years (*12*), most of them stated that their bodies were less flexible and that they were less able to carry things than in the past. Regarding HRQOL, the Physical Function scale of the 36-item Short Form Health Survey (SF-36) was below the population norms for this age group, and was lower in more severely affected individuals. In another UK study of individuals in their mid-50s (*32*), the physical health domain of the Short Form 12 Health Survey (SF-12) showed a markedly lower average aggregate score than the general population, whereas the mental health domain showed a slightly lower score. There was a strong negative correlation between lower SF-12 physical health scores and the severity of impairment, indicating that the more severe the thalidomide damage, the poorer the physical HRQOL. In a study from Ireland (*13*), the Illness-Intrusiveness Ratings Scale was used to assess the extent to which disability interferes with HRQOL for individuals with TE in their mid-40s, and the scores were high compared with other physical health conditions. A Swedish study evaluated the effect of limb malformations on HRQOL in individuals in their late 40s (*14*). The Physical Composite Summary (PCS) score of SF-36 was significantly reduced in relation to the national norm. Individuals with major limb deformities had a significantly lower PCS score of the SF-36 compared with those without any major deformities. In particular, those with PFFD reported a considerable reduction in PCS score. The PCS score was correlated with the upper extremity function and pain score for the lower extremities. A study from Germany on individuals aged approximately 50 years (*33*) showed a significantly reduced PCS score of the SF-36 in comparison to an age-adjusted German population with chronic diseases. Individuals with mild pain had higher physical and mental HRQOL than those with severe pain. A study from Germany on women aged 35 to 40 years (*34*) showed lower physical domain score compared with the control group in WHO QOL-BREF, and less satisfied with their QOL. The results of another German study on women aged 48 to 53 years (*35*) indicated ongoing decrease in the health status and QOL. In a study of Japanese individuals in their early 50s (*27*), most complained of physical pain, mainly in their shoulders, lower back, and neck. Significant correlations with pain severity were observed for the PCS scores on the SF-36.

3.4. Rehabilitation approach for secondary musculoskeletal disabilities in TE

There are a few reports on conservative management, including rehabilitation approaches, for secondary musculoskeletal disabilities in individuals with TE. In a survey on the life situations of Japanese individuals with TE (*36*), approximately 30% of those reporting symptoms and/or physical problems utilized massage, acupuncture, moxibustion, or chiropractic. Physical

therapy for a male with TE in his mid-50s has been reported (*37*). He had severe shortening of both upper limbs and an unequal leg length, and complained of low back pain, poor balance, and fear of falling. After wearing an insole for the unequal leg length and 15 physiotherapy treatment sessions, his complaints improved.

4. Author's experience in clinical practice

As for upper limb disability, we have encountered adults with TE who complained of finger pain due to tenosynovitis (Figure 2). Tenosynovitis may be common mechanism for finger pain in malformed upper limbs, but has not been described in previous reports. Abnormalities in carpal bones reported in a CT study (*26*) can be revealed in plain X-rays. Figure 3A shows fusion of the carpal bones and a narrow, deformed radiocarpal joint in a female adult in her early 50s. This individual also showed narrow intervertebral spaces with endplate irregularity and spondylolisthesis in the lumbar spine (Figure 3B). X-ray images sometimes reveal abnormalities in individuals without apparent lower limb malformations. Figure 3C shows inclined knee joint with the hypoplastic lateral femoral condyle, and Figure 4 shows acetabular dysplasia in both hips and narrowed joint space in the right.

Ergonomic improvements, including environmental modifications and the implementation of supportive devices, can be considered to improve and/or prevent the progression of secondary musculoskeletal disabilities from a rehabilitation engineering perspective. Two of the authors (HT and SS) treated a male office worker with TE complaining of numbness and tingling of the neck/shoulder and low back pain. They visited the office and assessed the office environment and his posture. By adjusting the height of the notebook PC display with a base that raised the PC slightly and applying a cushion for seat pressure dispersion and an additional shape-memory seat back that fits his back, he had remission of all the symptoms (Figure 5).

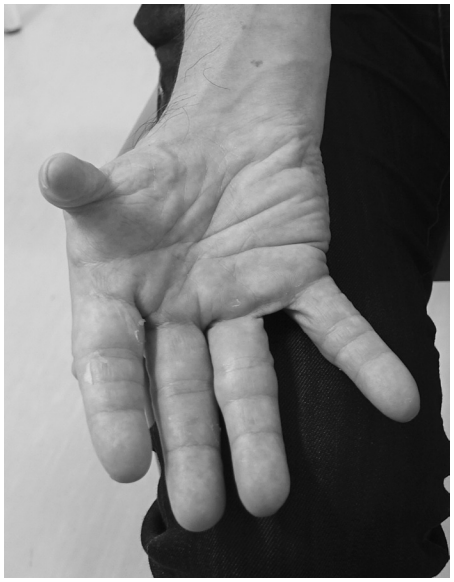

Figure 2. Thumb and thenar hypoplasia. This male adult with thalidomide embryopathy in his late 50s complains pain in fingers due to tenosynovitis.

5. Discussion

This review revealed that many adults with TE experience secondary musculoskeletal disabilities. Table 2 displays the summary of musculoskeletal disabilities, their prevalence, and interventions obtained from this study. Common symptoms include pain from neuropathy and osteoarthritis of the upper limbs, and pain in the lower back or neck. Lower limb symptoms are not

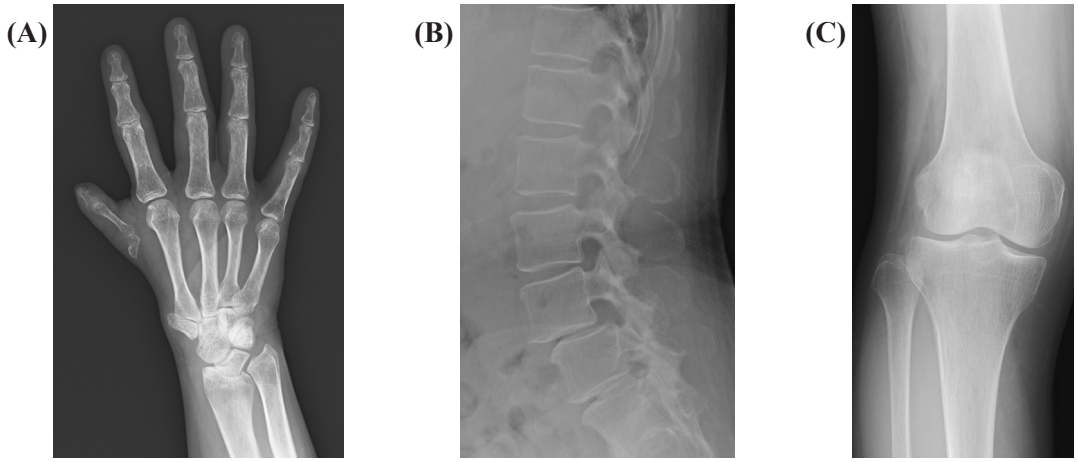

Figure 3. X-ray images of a female adult in her early 50s. In this female adult with thalidomide embryopathy, showing relatively mild upper-limb hypoplasia and no apparent lower-limb malformations, the right hand with thumb hypoplasia shows fusion of the carpal bones and a narrow, deformed radiocarpal joint **(A)**. The lumbar spine shows narrow intervertebral spaces with endplate irregularity and spondylolisthesis **(B)**. The right knee joint is inclined with the hypoplastic lateral femoral condyle **(C)**.

common, but include pain from osteoarthritis of the hip and knee. These disabilities are related to a decreased physical domain of HRQOL, which is particularly low in those with severe limb involvement and pain. HRQOL has been studied in various nations including UK, Sweden, and Germany (Table 1), and the decrease in physical domain was common. However, the care system and the societal support may differ among nations, and these may affect the accessibility to health care service including rehabilitation. As for available intervention, reports on rehabilitation treatment were limited, although orthopedic surgeries have been reported to resolve musculoskeletal symptoms.

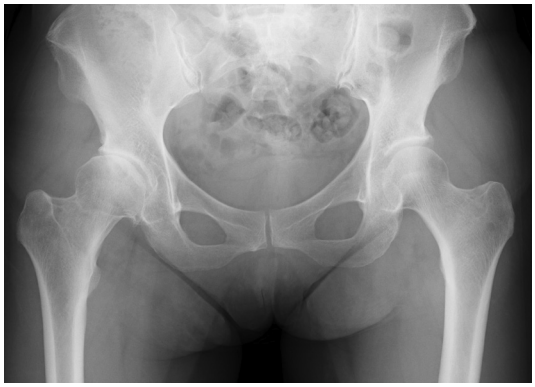

Figure 4. Hip X-ray of a male adult in his late 50s. This male adult with thalidomide embryopathy was affected by hearing impairment but no limb malformations. Both hips show acetabular dysplasia and the joint space in the right is narrow.

We believe that secondary musculoskeletal disabilities occur through the following mechanisms (Figure 6). Individuals with relatively mild upper limb hypoplasia normally use their upper limbs to perform ADL. As age-related changes and stress from repetitive and/or compensatory use accumulate, joint dysfunction including arthropathy, tenosynovitis, and peripheral upper limb neuropathy occur. An example of compensatory use is using index and middle fingers for pinching in an individual with TE and no thumbs. However, individuals with relatively severe upper-limb hypoplasia normally use their lower limbs to carry out their ADL. They develop spinal disorders and lower-limb arthropathy as age-related changes accumulate due to repetitive and/or compensatory use. Those who use their lower limbs to eat and wash their faces must bend their spines, which can cause spinal disorders. However, repetitive and/or compensatory use is not the only causes

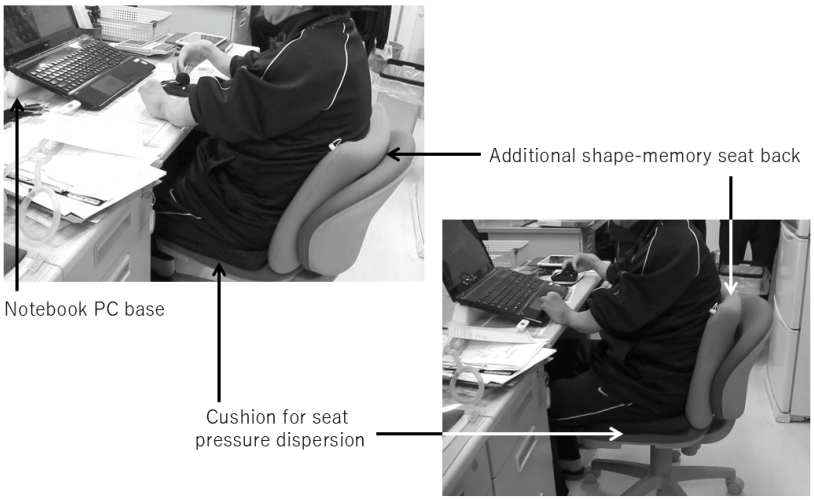

Figure 5. Ergonomic intervention. Sitting posture improved and the symptoms mitigated after ergonomic intervention in a male office worker with thalidomide embryopathy.

Table 2. Summary of musculoskeletal disabilities and interventions

Musculoskeletal Disability	Prevalence	Available Intervention*
Upper Limbs		
neuropathic pain in upper limbs	common	decompression surgery
pain from tenosynovitis	unknown	
pain from osteoarthritis (mainly in the shoulder)	commom	joint replacement surgery
Trunk and Spine		
pain in the lower back or neck	common	ergonomic improvement
Lower Limbs		
pain from osteoarthritis (mainly in the hip and the knee)	unknown	joint replacement surgery
reduced ambulation	common in individuals with PFFD**	physical theray wheelchair

*Alternative medicine was applied to various symptoms in Japanese individuals. **proximal femoral focal deficiency.

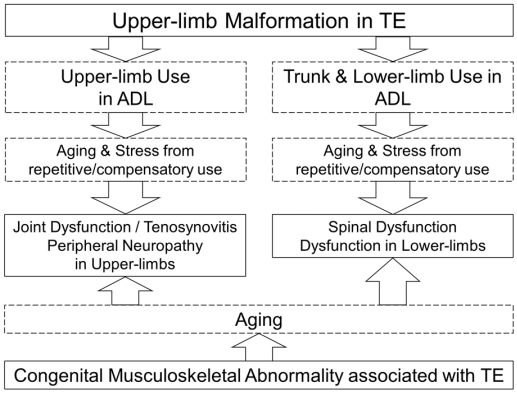

Figure 6. Mechanism of secondary musculoskeletal disabilities related to upper-limb hypoplasia in thalidomide embryopathy.

of these disorders. The above-mentioned congenital limb and spinal malformations may also have contributed to this finding.

Apart from TE, carpal tunnel syndrome and pain in the neck, shoulder, and elbow have been reported to occur more frequently in individuals with unilateral upper limb deficiency, both congenital and acquired (*38*). The authors regarded these symptoms as overuse problems resulting from repetitive and forceful hand-intensive tasks. As for radial deficiency unrelated to TE, carpal tunnel syndrome was reported in an adult with Holt-Oram syndrome (*39*), and grip strength and key pinch were less than the norms in adults with unilateral or bilateral radial deficiencies (*40*). These reports may partially support the mechanism model in Figure 6, though we could find no other literature on the secondary musculoskeletal problems in adults with congenital unilateral or bilateral upper limb deficiencies.

Considering the above-mentioned presumed mechanisms, various rehabilitation approaches could be useful in preventing the development and progression of secondary musculoskeletal disabilities in individuals with TE. The current review identified approaches including physical therapy, environmental modification, and alternative medicine (Table 2). Though physical therapy and environmental modification led to satisfactory outcome, these were case reports with relatively short-term observation. For adults with unilateral upper limb deficiency without TE, Burger *et al*. reported that if an occupational therapist observes and tries to teach a person with upper limb deficiency how to perform an activity without compensatory movements, this can prevent or decrease the extent of the overuse problems (*38*). In addition, we found that individuals with TE sometimes use assistive devices in their ADL, such as buttoning up their shirt, clipping nails, and twisting the plastic bottle open. Appropriate use of self-help devices to avoid stress from repetitive and/or compensatory use of the upper limbs may reduce the risk of secondary musculoskeletal disabilities.

Limitations of this study include reviewing only articles written in English obtained through a PubMed search, and the small number of Japanese individuals with TE that the authors experienced.

In conclusion, this review of musculoskeletal disabilities and QOL in adults with TE revealed that pain is common in the upper limbs and spine, and is associated with reduced physical QOL. Though reports on rehabilitation interventions are scarce and provide little evidence, rehabilitation providers are encouraged to understand the mechanism of secondary musculoskeletal disabilities and select appropriate approaches based on precise evaluation of the physical status of individuals with TE. To establish evidence to support these rehabilitation approaches, the accumulation of personal experience and further studies, preferably interventional studies with control group, are necessary.

Funding: This study was funded by the Ministry of Health, Labor, and Welfare research grant for "Research on various health and living problems of patients with thalidomide embryopathy (Grant Number: 23KC2017)".

Conflict of Interest: The authors have no conflicts of interest to disclose.

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Received May 30, 2025; Revised August 5, 2025; Accepted August 7, 2025.

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Released online in J-STAGE as advance publication August 9, 2025.