HEMATOPOIETIC STEM CELL TRANSPLANTATION (HSCT) vs. ADIPOSE-TISSUE-BASED THERAPY AS A THERAPEUTIC OPTION IN SYSTEMIC SCLEROSIS: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Abstract

Introduction: Systemic sclerosis (SSc) is a multisystem autoimmune disease. Currently, there is no cure for this disease. One of the emerging therapies for SSc includes hematopoietic stem cell transplantation (HSCT) and adipose-tissue-based therapy. A study that compares the usage of HSCT with adipose-tissue-based therapy in SSc has not been made. The objective of this study was to conduct a systematic review and meta-analysis that compared the efficacy of HSCT and adipose-tissue-based therapy in SSc.

Methods: A comprehensive literature search was conducted from inception to 14th June 2023 in PubMed, CENTRAL, EBSCOhost, ProQuest, SAGE, and JSTOR. The inclusion criteria are: (1) Investigated the effects of HSCT or adipose-tissue-based therapy in SSc; (2) Study design is RCT; (3) Is a human study; (4) Written in English; (5) Full-text is available. The quality of evidence was assessed using Cochrane risk of bias 2 (RoB 2). Certainty of evidence was evaluated using Grading of Recommendations, Assessment, Development, and Evaluation (GRADE). The outcomes are mean change in modified Rodnan skin score (mRSS), visual analog scale (VAS), quality of life (QoL), activities of daily living (ADL), and adverse events (AEs).

Results: A total of 1011 articles were obtained after duplicate removal with 32 retrieved for a second screening and nine assessed for eligibility. Five articles were included in the systematic review and four in the meta-analysis. Overall, our study found 170 patients in the intervention group and 158 controls. There was a more significant change in the mean mRSS in those who received HSCT compared to adipose-tissue-based therapy ($P < 0.00001$). HSCT had significantly more SAEs compared to adipose-tissue-based therapy ($P = 0.04$). Two out of three HSCT studies reported two deaths in the HSCT group compared to no deaths in control. In contrast, there was no event of death in both the adipose-tissue-based therapy and control groups. There was a moderate risk of bias for our study and a moderate level of confidence.

Conclusion: In conclusion, this meta-analysis suggested that HSCT might be superior to adipose-tissue-based therapy as therapy in SSc patients. Some of the limitations of our studies are the small number of studies, exclusion of non-English studies, and lack of studies that directly compared HSCT against adipose-tissue-based therapy. Thus, we strongly suggest more research regarding HSCT and adipose-tissue-based therapy in SSc patients to be conducted.

Keywords: Adipose-Tissue-Based Therapy, Hematopoietic Stem Cells, Meta-Analysis, Scleroderma, Stem Cells, Systematic Review

Introduction

Systemic sclerosis (SSc), also known as scleroderma, is a complex multisystem autoimmune disease that affects the skin, visceral organs, musculoskeletal system, and blood vessels. It is characterized by fibrosis of the skin and visceral organs, as well as vasculopathy (1-3). This disease is associated with various complications, including digital ulcer (DU), interstitial lung disease (ILD), pulmonary arterial hypertension (PAH), scleroderma renal crisis, cardiac failure, and dysphagia. SSc is generally classified into two subtypes: limited cutaneous SSc (lcSSc) and diffuse cutaneous SSc (dcSSc) (4-6).

A recent study in 2021 found that SSc had a global prevalence of 17.6 per 100,000 population, with an incidence rate of 1.4 per 100,000 person-years. This study also highlighted the predominance of SSc in women,

with an approximate female-to-male ratio of 1:4 (7). Additionally, SSc has the highest mortality rate among all connective tissue diseases, with a reported mortality ratio of 2.3-3.5, and cumulative survival rates of 75% at 5 years and 62.5% at 10 years (8).

Since one of the characteristic features of SSc is the thickening of the skin, measuring the skin thickness has become a commonly used method for evaluating the severity of the disease as well as therapeutic efficacy. One method to measure skin thickness is by using the modified Rodnan skin score (mRSS). This method involves assessing skin thickness in 17 body areas (fingers, hands, forearms, upper arms, face, anterior chest, abdomen, thighs, legs, and feet) and assigning a score from 0 to 3, where 0 indicates no thickening and 3 indicates severe thickening (9).

Given the systemic nature of SSc, the condition could significantly impact a person's quality of life (QoL) and activities of daily living (ADL). Commonly used tools for evaluating QoL in SSc patients are Health Assessment Questionnaire (HAQ), Scleroderma HAQ (SHAQ), and Patient Global Assessment (PGA) (10). Meanwhile, ADL questionnaire (ADLQ) can be used to evaluate ADL impairment. Evaluation of pain severity using Visual Analogue Scale (VAS) has also been used to evaluate the treatment efficacy (11).

To date, no cure is available for SSc. Traditionally treatment for SSc involves immunosuppression via the administration of steroids and immunomodulators (2, 12). Other emerging and promising therapies include stem cell transplantation, such as hematopoietic stem cell transplantation (HSCT). HSCT has been considered as a therapy in patients with SSc due to its ability to replace the problematic hematopoietic system with a new one, either from a donor (allogenic HSCT) or the patient themselves (autologous), thereby potentially 'correcting' the defective immune system (13). Another emerging therapy is adipose-tissue-based therapy. Adipose tissue contains cells with regenerative and pro-angiogenic properties, such as adipose-derived stem cells (ASCs) and adipose-derived stromal vascular fraction (AD-SVF) (14). These therapies could play a crucial role in cases refractory to conventional therapies or in particularly aggressive disease (3, 15).

Several reviews have attempted to elucidate the effects of HSCT and adipose-tissue-based therapy in SSc patients. However, these reviews have typically focused on only one type of therapy, either HSCT or adipose-tissue-based therapy. A review that compared the effects of these two different therapies in SSc has yet to be conducted. Furthermore, the existing reviews have often utilized a mixture of randomized controlled trials (RCT) and non-RCT studies (16-18). Thus, we conducted this review to summarize and compare the effects of HSCT against adipose-tissue-based therapy in SSc patients. To enhance the quality of this review, only RCTs will be included.

Materials and Methods

This meta-analysis was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020.

Literature search

A comprehensive literature search was conducted from inception to 14th June 2023 to evaluate the effects of HSCT and adipose-tissue-based therapy in SSc patients. The search was performed in several databases, such as PubMed, CENTRAL, EBSCOhost, ProQuest, SAGE, and JSTOR. The search strategy used is as follows: (((Scleroderma) OR ("Scleroderma, Systemic"[Mesh])) OR ("Scleroderma, Localized"[Mesh])) OR (Systemic sclerosis)) AND ((((((Stem cell) OR (Stem cell transplantation)) OR (Cell transplantation)) OR (Hematopoietic stem cell)) OR (HSCT)) OR ((((((Adipose tissue) OR (Adipose-tissue-based therapy)) OR (Adipose-tissue derived stem cells)) OR (ASC)) OR (Adipose-tissue-derived stromal vascular fraction)) OR (AD-SVF))).

Study selection

An article was included if: [1] Investigated the effects of HSCT or adipose-tissue-based therapy in SSc; [2] Study design is RCT; [3] Is a human study; [4] Written in English; [5] Full-text is available. An article was excluded if: [1] Non-RCT study, case report, case series, review, in vivo or in vitro study, letter to editor; [2] Does not have a clear methodology; [3] Lack of available data.

Data extraction

Three authors extracted the data independently and any differences were resolved through a discussion with a fourth author. The extracted data were: First author name, year of publication, country of origin, population (number of patients, gender, age, disease duration), scleroderma sub-phenotype, intervention (type of stem cell, dosage, route of administration), comparative treatment, and results of the study (mRSS, VAS, QoL, ADL, adverse events/AEs and other related parameters).

Definition of outcomes

The primary outcome was the mean change in mRSS. Secondary outcomes were changes in VAS, QoL, ADL, and AEs.

Data synthesis and analysis

Mean difference (MD) was used for continuous outcomes, while risk ratios (RR) with 95% confidence interval (CI) was used for dichotomous outcomes, with RR < 1 being in favor of stem cell therapy. Heterogeneity was evaluated using I^2 and X^2-test. If there was substantial heterogeneity ($I^2 > 50\%$ or $P < 0.1$), a random-effect model was used. If the study was homogenous ($I^2 \leq 50\%$ and $P > 0.1$), a fixed-effect model was be used. If there are > 10 studies included, publication

bias will be assessed using a funnel plot (19). All statistical analyses were conducted using RevMan 5.4.

Quality assessment

Three authors evaluated the risk of bias for each included study using the Cochrane risk of bias 2 (RoB 2) tool. All authors did the assessment independently and any disagreements are resolved through a discussion with a fourth author. The RoB 2 tool consists of five domains regarding bias in the randomization process, deviation from intended intervention, missing outcome data, measurement of outcome, and selection bias. An overall low risk of bias means there is a low risk of bias for all domains while an overall high risk of bias implies some concerns for multiple domains or a high risk of bias for a minimum of one domain (19).

Certainty of evidence

Three authors evaluated the certainty of evidence using Grading of Recommendations, Assessment, Development, and Evaluation (GRADE). Each author did the evaluation independently. Any differences were resolved through a discussion with a fourth reviewer. GRADE contains five domains: risk of bias, indirectness, inconsistency, imprecision, and publication bias (20). Risk of bias will be based on the results from Cochrane RoB 2 (19). If a study had MD = 0 or RR = 1, then it is imprecise (21). If a study had substantial heterogeneity ($I^2 \geq 50\%$), then it is inconsistent. Each outcome will then be graded as having a high, moderate, low, or very low level of certainty. A high level of certainty means that we are very confident that the true effect lies close to the estimate of effect. In contrast, a very low level of certainty means that we have very little confidence that the true effect lies close to the estimate of effect (20).

Results

After removing duplicates, a total of 1011 articles were obtained from inception to 14th June 2023 in the databases PubMed, CENTRAL, EBSCOhost, ProQuest, SAGE, and JSTOR. Of these, 32 articles were selected for further screening, and nine were deemed eligible for assessment. Since four of these articles were not RCT studies, only five articles were finally included in this systematic review. Due to a lack of data in one study, only four studies were ultimately included in this meta-analysis. The PRISMA flow diagram for this study is displayed in Figure 1.

Study characteristics

The five studies included in this review were published between 2011 and 2022, with one originating from the United States of America (USA) and four from Europe. A total of 170 patients in the intervention group and 158 controls were included in this study. Around 67% and 74.6% are female in the intervention group and control group, respectively (22-26). As many as three articles evaluated the effects of HSCT in SSc (22, 25, 26), while the other

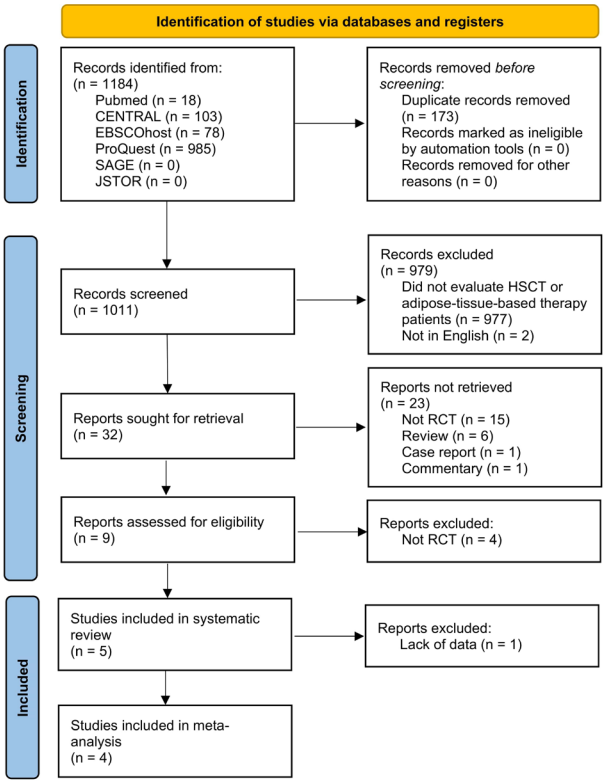

Figure 1: PRISMA flow diagram.

two articles assessed the efficacy of adipose-tissue-based therapy in SSc (23, 24). The follow-up period ranged from four weeks to seven years and the comparator used in the studies were either cyclophosphamide or placebo. The mean or median disease duration ranged from 13.6 months to 18.2 years (22-26). The summary of the findings for this review can be viewed in Table 1.

Change in mRSS

All but one of the included articles assessed the difference in mean mRSS between those who received intervention with those who did not. Out of these four studies, three utilized HSCT, while one employed adipose-tissue-based therapy (22, 23, 25, 26). The three studies investigating the effects of HSCT in SSc patients reported significant improvements in mean mRSS when compared to control (22, 25, 26). Conversely, Daumas et al. (23) found no significant difference in the change of mRSS between the adipose-tissue-based therapy group and the control group (right hand: P = 0.384; left hand: P = 0.591). However, a significant improvement was observed when comparing the change in mRSS at 6 months of follow-up to the baseline (right hand: P = 0.013; left hand: P < 0.001).

Our statistical analysis revealed that HSCT significantly improved mean mRSS compared to cyclophosphamide (MD -11.50 [95% CI -15.09, -7.91], P < 0.00001). In contrast, those who received adipose-tissue-based therapy did not show significant improvement in mean mRSS compared to placebo (MD 2.30 [95% CI -1.18, 5.78], P = 0.19). Additionally, our results suggest that HSCT produced a

Table 1: Summary of findings of the included studies

Reference/ Country	Population	Intervention	Follow-Up Time	Results	Adverse Events
Burt et al. (22) 2011 / USA	Median age 45 years (range 32-58), 10 HSCT (9 F, 1 M) and 9 control (8 F, 1 M), 19/19 dcSSc, median disease duration 13.6 months (range 2-33)	Intervention: Autologous non-myeloablative HSCT IV Comparator: Cyclophosphamide 1 g/m^2 body surface IV monthly for 6 months (patients may switch to HSCT group if there is no improvement after 1 year of follow-up)	2.6 years	1 year of follow-up: Mean mRSS decreased in HSCT group [28 (SD 13.6) to 15 (SD 7.9)] and increased in control group [19 (SD 13.7) to 22 (SD 14.2)] (P = 0.0004). SF-36 score improved in HSCT group [39 to 56, difference=17 (SD 20.59), P = 0.003] and declined in control [50 to 40, difference = -10 (SD 18.03), P = 0.04]. Long-term follow-up (2.6 years): Mean mRSS decreased in HSCT group [29 (SD 13.7) to 12 (SD 8.4), P = 0.0001]. SF-36 score improved in HSCT group [39 to 56, difference = 17 (SD 20.45), P = 0.009]. Those in control group that switched to HSCT (1 year follow-up): Mean mRSS decreased [27 (SD 15.5) to 15 (SD 7.4)]. SF-36 score improved [42 to 78, difference = 36 (SD 27.84), P = 0.04]	During transplantation: infection (2), arrythmia (2), volume overload (2) Long-term follow-up: hypertensive renal crisis (1)
Daumas et al. (23) 2022 / France	Mean age 54 years (SD 12.7), 20 AD-SVF (20 F, 0 M), 20 placebo (19 F, 1 M), 25/40 lcSSc, 15/40 dcSSc, mean disease duration 18.2 years (SD 4.5)	Intervention: AD-SVF IM Comparator: Placebo	6 months	SHAQ improvement in AD-SVF group was similar to placebo group (P = 0.145) but was significant when compared over time (P < 0.001). VAS difference between AD-SVF group and placebo was not significant (P = 0.209) but was significant over time (P < 0.001). Mean mRSS difference between AD-SVF and placebo group was not significant (Right hand: P = 0.384; Left hand: P = 0.591) but was significant over time (Right hand: P = 0.013; Left hand: P < 0.001).	35 AEs were reported in 17 patients (42.5%): 19/35 AEs reported in 8 patients in AD-SVF group and 16/35 reported in 8 patients in placebo group. 8 serious AEs were reported: 1/8 in AD-SVF group and 7/8 in placebo group (P = 0.341).
Del Papa et al. (24) 2019 / Italy	Median age 42 years (range 21-69), 25 AT-G (23 F, 2 M), 13 placebo (13 F, 0 M), 23/36 dcSSc, 15/36 lcSSc, median disease duration 4 years (range 1-10)	Intervention: AT-G IM Comparator: Placebo (patients may switch to AT-G group if there is no improvement after 8 weeks of follow-up)	8 weeks	4 weeks of follow-up: VAS reduced > 50% of baseline in 21/25 in AT-G group and 0/13 in placebo group (P < 0.00001). 8 weeks of follow-up: VAS reduced > 50% of baseline in 25/25 in AT-G group and 0/13 in placebo group.	N/A

Table 1: Summary of findings of the included studies (continued)

Reference/ Country	Population	Intervention	Follow-Up Time	Results	Adverse Events
Sullivan et al (25) 2018 / UK	Mean age 45.9 years (SD 10.6), 36 HSCT (19 F, 17 M), 39 control (29 F, 10 M), mean disease duration 27.1 months (SD 14.6)	Intervention: autologous myeloablative HSCT IV Comparator: Cyclophosphamide 500 mg/m^2 body surface IV initially, then 750 mg/m^2 IV monthly for months	4.5 years	mRSS was more likely to improve in HSCT group compared to control group (EFS: 100% vs. 82%; EFS failure: 71% vs. 29%) [P = 0.03 for EFS, P = 0.1 for EFS failure, P = 0.01 for pooled]. HAQ-DI was more likely to improve in HSCT group compared to control group (EFS: 65% vs. 35%; EFS failure: 29% vs. 0%) [P = 0.06 for EFS, P = 0.6 for EFS failure, P = 0.002 for pooled]. Physical component score of SF-36 was more likely to improve in HSCT group compared to control group (EFS: 73% vs. 35%; EFS failure: 14% vs. 0%) [P = 0.02 for EFS, P = 0.1 for EFS failure, P = 0.003 for pooled]. Mental component score of SF-36 improvement were similar in both HSCT and control group (EFS: 38% vs. 11%; EFS failure: 14% vs. 5%) [PP: P = 0.1 for EFS, P = 0.3 for EFS failure, P = 0.1 for pooled].	7 in HSCT group died: did not receive transplant (3), treatment-related cause (2/7), has history of respiratory, renal, or cardiac failure (2/7) Rate of serious adverse events in person-years: 0.38 in HSCT group and 0.52 in control group (P = 0.08) Percentage of participants who had AEs of grade 3 or higher: 100% in HSCT group and 84% in control group. Event rate of AEs of grade 3 or higher per person-year: 2.0 in HSCT and 1.2 in control group (P < 0.001). Rate of infections (any grade) per person-year: 0.75 in HSCT and 0.79 in control group Rate of infections of grade 3 or more per person-year: 0.21 in HSCT and 0.13 in control group (P = 0.09)
Van Laar et al (26) 2014 / Europe and Canada	Mean age 43.8 years (SD 11.3), 79 HSCT (43 F, 36 M), 77 control (49 F, 28 M), 156/156 dcSSC, mean disease duration 1.4 years (SD 1.3)	Intervention: autologous HSCT IV Comparator: Cyclophosphamide IV monthly for 12 months	7 years	Mean mRSS improved significantly better in the HSCT group (-19.9, SD 10.2) than in the control group (-8.8, SD 12.0) [difference =11.1, 95% CI 7.3-15.0, P < 0.001]. HAQ-DI improved significantly better in HSCT group (-0.58, SD 1.14) than in control group (-0.19, SD 0.79) [0.39, 95% CI 0.051-0.73, P = 0.02]. Physical component score of SF-36 improved better in HSCT (10.1, SD 15.8) compared to control (4.0, SD 11.2) [-6.1, 95% CI -10.9 to -1.4, P = 0.03]. Mental component score of SF-36 difference between HSCT and control group was not significant (-0.3, 95% CI -5.41-6.07, P = 0.3). Index-based utility score of EQ-5D improvement was more significant in HSCT group (0.31, SD 0.50) compared to control group (0.03, SD 0.44) [-0.29, 95% CI -0.45 to -0.12, P < 0.001]. VAS score difference (of EQ-5D) between HSCT and control was not significant (-6.7, 95% CI -21.33-7.87, P = 0.36)	Deaths: 8/8 in HSCT group and 0/8 in control group (P = 0.007) Grade 3 or 4 AEs: 51 patients (62.9%) in HSCT group and in 30 patients (37.0%) in control group (P = 0.002) Infections: detected in 22 patients (27.8%) in HSCT group and in 1 patient (1.3%) in control group (P < 0.001)

AD-SVF: adipose tissue-derived stromal vascular fraction; AE: adverse event; AT-G: adipose tissue grafting; dcSSC: diffuse cutaneous systemic sclerosis; EFS: event-free survival; EQ-5D: EuroQol 5 dimension; F: female; HAQ-DI: health assessment questionnaire-disability index; HSCT: hematopoietic stem cell transplantation; IM: intramuscular; IV: intravenous; lcSSc: limited cutaneous systemic sclerosis; M: male; mRSS: modified Rodnan skin score; N/A: not available; SD: standard deviation; SF-36: short form 36 health survey questionnaire; SHAQ: scleroderma health assessment questionnaire; UK: United Kingdom; USA: United States of America; VAS: visual analog scale.

more substantial change in mean mRSS compared to adipose-tissue-based therapy (P < 0.00001, Figure 2). One study by Sullivan et al. (25) was excluded from the meta-analysis due to lack of suitable data.

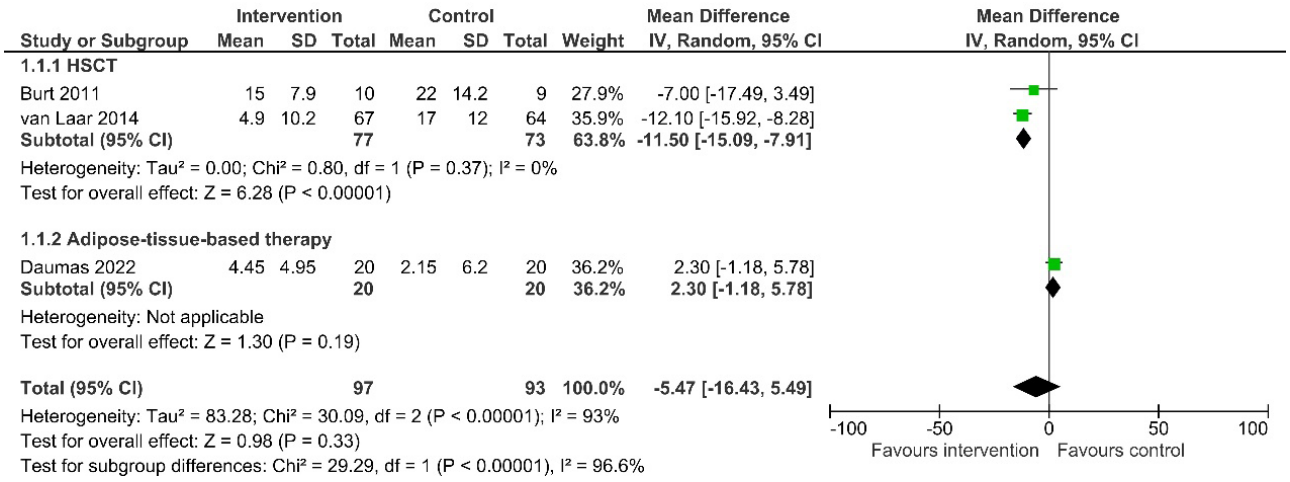

Figure 2: Mean change in mRSS between the different types of therapies (HSCT or adipose-tissue-based therapy) and control. The change in mRSS in HSCT is significantly higher than in control (MD -11.50, [95% CI -15.09, -7.91], P < 0.00001). In contrast, the change in mRSS in adipose-tissue-based therapy is not significant when compared to control (MD 2.30, [95% CI -1.18, 5.78], P = 0.19). Based on the subgroup analysis, HSCT had a more significant change in mRSS compared to adipose-tissue-based therapy (P < 0.00001). Since there was a significant heterogeneity among both groups (I^2 = 93%, P < 0.00001), a random-effect model was used. The box represents the result of each study with the horizontal line representing the 95% CI. The diamond represents the pooled effect of the studies. CI: confidence interval; HSCT: hematopoietic stem cell transplantation; MD: mean difference; mRSS: mean modified Rodnan skin score.

Change in VAS

Three studies, one HSCT and two adipose-tissue-based therapy, evaluated the difference in VAS scores between those the intervention and control groups (23, 24, 26). Del Papa et al. (24) found that more patients in the adipose-tissue-based therapy group had a meaningful improvement in VAS score compared to the placebo group at four weeks of follow-up (84% vs. 0%, P < 0.00001). Furthermore, by eight weeks of follow-up, all patients in the adipose-tissue-based therapy group had achieved > 50% improvement in VAS scores, whereas none in the placebo group reached this threshold. In contrast, Daumas et al. (23) reported no significant difference in VAS scores between adipose-tissue-based therapy and the placebo group (P = 0.209). However, a significant difference was observed when comparing VAS scores six months post-treatment to baseline (P < 0.001). Similarly, van Laar et al. (26) found no significant difference in VAS scores between the HSCT and control groups (P = 0.36). Formal statistical analysis for the change in VAS was not performed due to a lack of suitable data.

ADL and QoL

Four studies evaluated the effects of HSCT or adipose-tissue-based therapy on improving the patient's activities of daily living (ADL) and quality of life (QoL) (22, 23, 25, 26). All three studies that utilized HSCT reported that patients who received HSCT showed significantly greater improvements in both ADL and QoL compared to the control group (22, 25, 26). In contrast, while Daumas et al. (23) found no significant difference between the adipose-tissue-based therapy group and the control group (P = 0.145), a significant improvement was observed in the SHAQ scores when comparing the post-treatment scores to baseline (P < 0.001). Due to the heterogeneity of the extracted data, a statistical analysis of the effects of HSCT or adipose-tissue-based therapy on ADL and QoL was not feasible.

Adverse events

Three HSCT studies and one adipose-tissue-based therapy study also investigated the safety of the interventions in SSc patients (22, 23, 25, 26). Burt et al. (22) reported two cases each of infection, arrhythmia, and volume overload among patients who received HSCT. During long-term follow-up, one patient experienced hypertensive renal crisis. A study conducted by Sullivan et al. (25) identified two treatment-related deaths among the seven fatalities in the HSCT group. This study also found that the incidence of grade 3 or higher AEs per person-year was significantly higher in those receiving HSCT (AEs: 2.0 vs. 1.2, P < 0.001). However, no significant differences were observed between the HSCT and control groups in terms of the rates of serious AEs (SAEs) and infections (SAE: 0.38 vs. 0.52, P = 0.08; infection: 0.21 vs. 0.13, P = 0.09). Similarly, van Laar et al. (26) also found more AEs occurring in the HSCT group compared

to control. All eight deaths reported during the study occurred in the HSCT group. In addition, the HSCT group had significantly higher rates of infections and grade 3 or 4 AEs compared to control (infection: 27.8% vs. 1.3%, P < 0.001; AEs: 62.9% vs. 37.0%, P = 0.002). Daumas et al. (23) observed a slightly higher frequency of AEs in the adipose-tissue-based therapy group compared to the placebo group (54% vs. 45%). However, the difference in the number of SAEs between the adipose-tissue-based therapy group and the placebo groups was not statistically significant (1/8 vs. 7/8, P = 0.341).

Through a statistical analysis, it was revealed that neither HSCT nor adipose-tissue-based therapy resulted in a significantly higher incidence of grade 3 or higher AEs when compared to control (HSCT: RR 1.52, [95% CI 0.42, 5.48], P = 0.52; Adipose-tissue-based therapy: RR 0.78, [95% CI 0.55, 1.12], P = 0.18). Subgroup analysis further indicated no significant difference between HSCT and adipose-tissue-based therapy (P = 0.33), as shown in Figure 3.

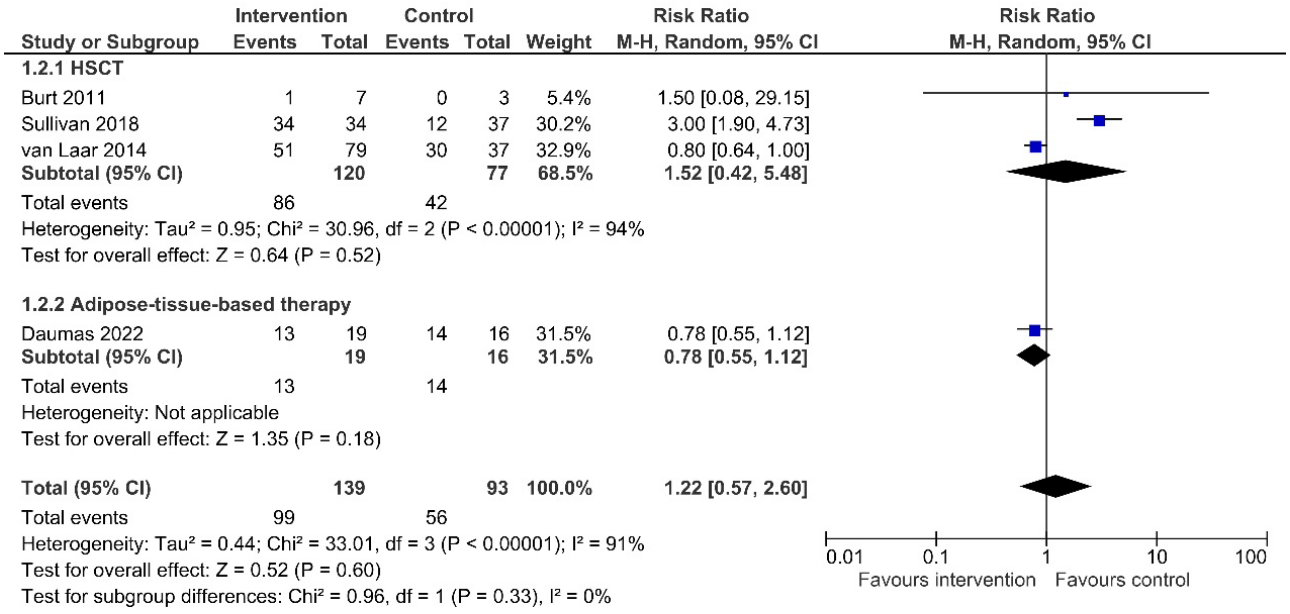

Figure 3: Grade 3 or higher AEs between the different types of therapies (HSCT or adipose-tissue-based therapy) and control. Both HSCT and adipose-tissue-based therapy did not have significantly more grade 3 or higher AEs than in control (HSCT: RR 1.52, [95% CI 0.42, 5.48], P = 0.52; Adipose-tissue-based therapy: RR 0.78, [95% CI 0.55, 1.12], P = 0.18). Based on the subgroup analysis, there was no significant difference between HSCT and adipose-tissue-based therapy (P = 0.33). Since there was significant heterogeneity among both groups (I^2 = 91%, P < 0.00001), a random-effect model was used. The box represents the result of each study with the horizontal line representing the 95% CI. The diamond represents the pooled effect of the studies. AE: adverse event; CI: confidence interval; HSCT: hematopoietic stem cell transplantation; RR: risk ratio.

Neither HSCT nor adipose-tissue-based therapy resulted in a significantly higher number of SAEs compared to the control group (HSCT: RR 1.30, [95% CI 0.94, 1.81], P = 0.12; Adipose-tissue-based therapy: RR 0.28, [95% CI 0.07, 1.20], P = 0.09). However, adipose-tissue-based therapy was associated with significantly fewer SAEs compared to HSCT (P = 0.04, Figure 4).

Infection rates in both the HSCT and adipose-tissue-based therapy groups were not significantly higher than in the control group (HSCT: RR 1.43, [95% CI 0.82, 2.50], P = 0.21; Adipose-tissue-based therapy: RR 0.33, [95% CI 0.02, 5.97], P = 0.46). Additionally, there was no significant difference in infection rates between HSCT and adipose-tissue-based therapy (P = 0.33, Figure 5).

Burt et al. (22) reported no deaths in both HSCT and control group (HSCT: 0/10 [0%]; control: 0/9 [0%]). In contrast, both Sullivan et al. (25) (HSCT: 2/36 [5.5%]; control: 0/39 [0%]) and van Laar et al. (26) (HSCT: 2/67 [2.9%]; control: 0/64 [0%]) reported two deaths in the HSCT group, with no deaths in the control group. Although the HSCT group had more deaths compared to the control group, the difference was not statistically significant (RR 5.08, [95% CI 0.61, 42.67], P=0.13, Figure 6). Similarly, no deaths were reported in either adipose-tissue-based therapy and control (Adipose-tissue-based therapy: 0/20 [0%]; control: 0/20 [0%]). Due to the absence of events in the adipose-tissue-based therapy study, the RR is not estimable and thus, a subgroup analysis was not possible.

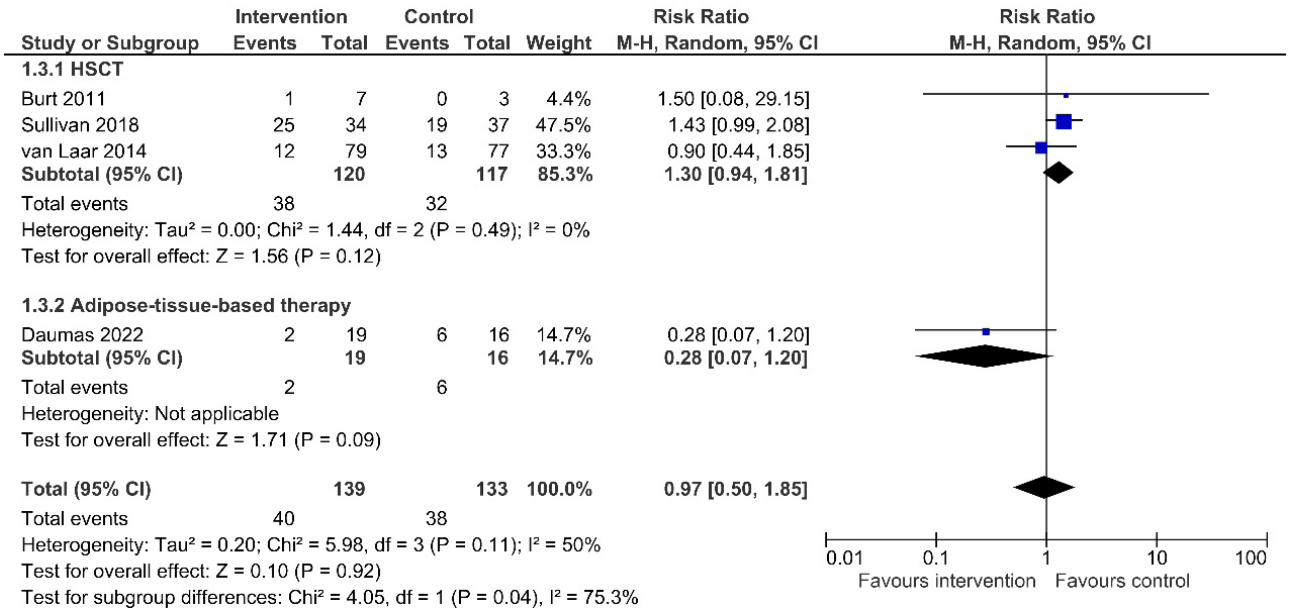

Figure 4: SAEs between the different types of therapies (HSCT or adipose-tissue-based therapy) and control. Both HSCT and adipose-tissue-based therapy did not have significantly more SAEs than in control (HSCT: RR 1.30, [95% CI 0.94, 1.81], P = 0.12; Adipose-tissue-based therapy: RR 0.28, [95% CI 0.07, 1.20], P = 0.09). Based on the subgroup analysis, adipose-tissue-based therapy had significantly fewer SAEs than HSCT (P = 0.04). Since there was significant heterogeneity among both groups (I^2 = 50%, P = 0.11), a random-effect model was used. The box represents the result of each study with the horizontal line representing the 95% CI. The diamond represents the pooled effect of the studies. CI: confidence interval; HSCT: hematopoietic stem cell transplantation; RR: risk ratio; SAE: serious adverse event.

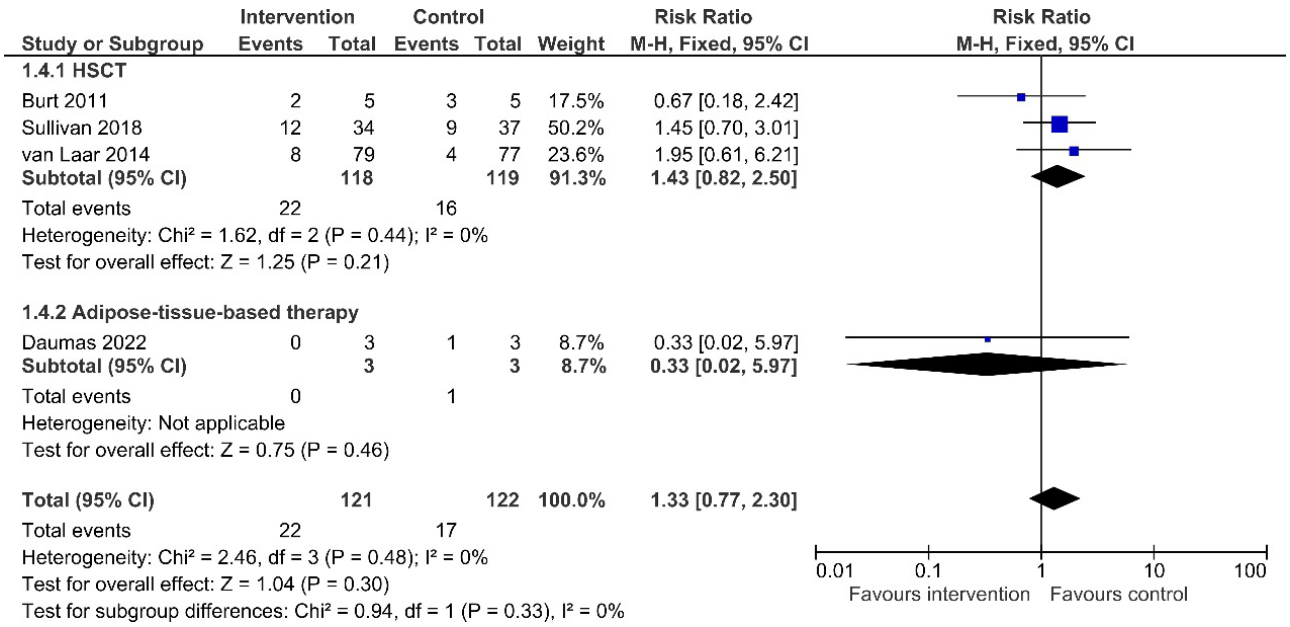

Figure 5: Infections between the different types of therapies (HSCT or adipose-tissue-based therapy) and control. Both HSCT and adipose-tissue-based therapy did not have significantly more infections than in control (HSCT: RR 1.43, [95% CI 0.82, 2.50], P = 0.21; Adipose-tissue-based therapy: RR 0.33, [95% CI 0.02, 5.97], P = 0.46). Based on the subgroup analysis, there was no significant difference between HSCT and adipose-tissue-based therapy (P = 0.33). Since there was no significant heterogeneity among both groups (I^2 = 0%, P = 0.48), a fixed-effect model was used. The box represents the result of each study with the horizontal line representing the 95% CI. The diamond represents the pooled effect of the studies. CI: confidence interval; HSCT: hematopoietic stem cell transplantation; RR: risk ratio.

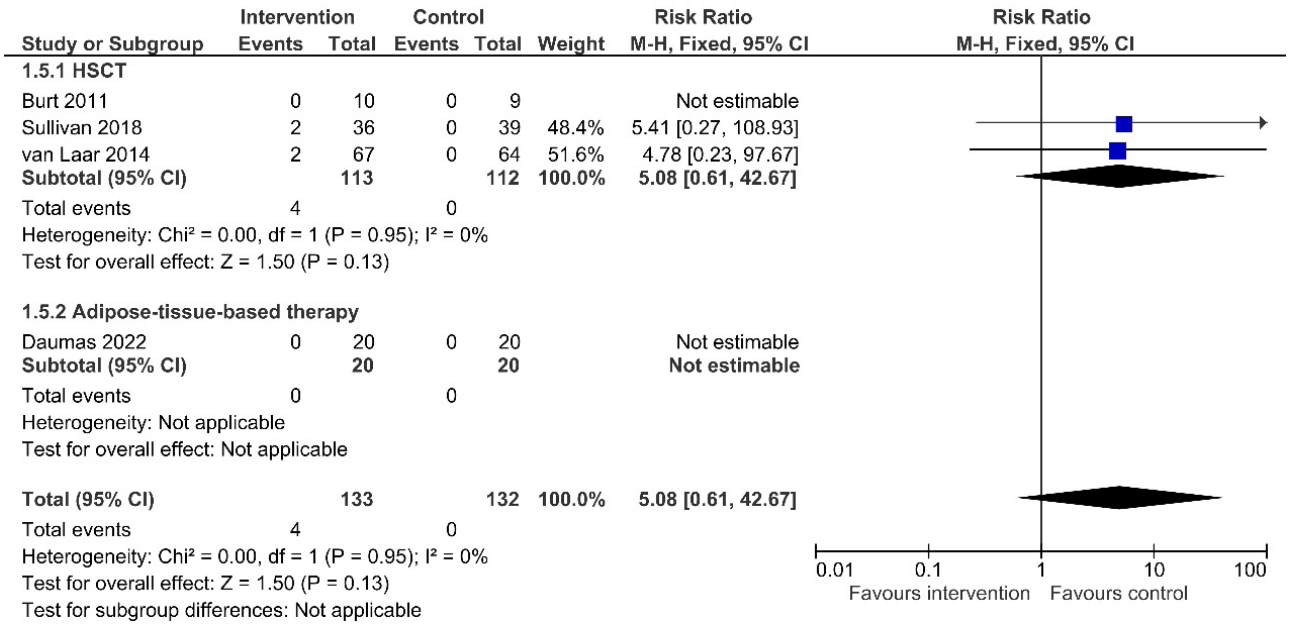

Figure 6: Treatment-related mortality (TRM) between the different types of therapies (HSCT or adipose-tissue-based therapy) and control. HSCT did not have significantly more TRM than in control (RR 5.08, [95% CI 0.61, 42.67], P = 0.13). Due to the lack of events in Daumas et al. (23), the RR is not estimable and thus, a subgroup analysis was also not possible. The box represents the result of each study with the horizontal line representing the 95% CI. The diamond represents the pooled effect of the studies. CI: confidence interval; HSCT: hematopoietic stem cell transplantation; RR: risk ratio; TRM: treatment-related mortality.

Risk of bias

The risk of bias of the included studies have been displayed in Figure 7. The risk of bias was low in three studies, moderate in one study, and high in one study.

Certainty of evidence

As shown in Table 2, the certainty of evidence for mRSS ranged from moderate to high, very low to moderate for grade 3 or higher AEs, and low to moderate for SAEs, infection, and treatment-related mortality (TRM).

Discussion

Several systematic reviews and meta-analyses have examined the effects of HSCT and adipose-tissue-based therapy in SSc. However, these reviews have typically investigated only one type of therapy, either HSCT or adipose-tissue-based therapy, in comparison to control (16-18). To our knowledge, no review has yet compared the efficacy and safety of these two therapies. This review aims to address this gap by being the first to compare these two therapies.

Our qualitative analysis indicated that HSCT resulted in a meaningful change in mean mRSS compared to control. In contrast, adipose-tissue-based therapy did not produce a significant change in mean mRSS. This finding was corroborated by our quantitative analysis, which showed that HSCT led to a significantly greater improvement in mean mRSS compared to adipose-tissue-based therapy. Similarly, HSCT was associated with significant improvements in ADL and QoL, whereas adipose-tissue-based therapy did not produce notable changes. We were unable to draw conclusions about the change in VAS scores due to a lack of sufficient studies. Regarding safety, HSCT was associated with a slightly higher incidence of adverse events compared to adipose-tissue-based therapy.

Our study has several limitations, including the small number of studies available on HSCT and adipose-tissue-based therapy in SSc, the inclusion of only English-language studies, and the absence of studies directly comparing HSCT and adipose-tissue-based therapy in SSc patients. We recommend further research on both therapies, particularly focusing on adipose-tissue-based therapy, to address these gaps.

Conclusion

Our review indicates that HSCT may be superior to adipose-tissue-based therapy for treating patients with SSc. However, HSCT also showed a slightly higher incidence of SAEs and TRM compared to adipose-tissue-based therapy. Overall, the risk of bias was moderate with a moderate level of confidence. We recommend further research to better validate the efficacy and safety of HSCT compared to adipose-tissue-based therapy.

Acknowledgement

We would like to acknowledge St. Carolus Hospital for all the support in making this research.

Figure 7: Risk of bias of the included studies.

Table 2: Certainty of evidence of the included studies

Outcome	No. of studies	GRADE					Certainty of Evidence
		Risk of Bias	Indirectness	Inconsistency	Imprecision	Small-Study Effect	
mRSS							
HSCT	2 studies (150 patients)	Not downgraded	Not downgraded	Not downgraded	Not downgraded	Not downgraded	High
Adipose-tissue-based therapy	1 study (40 patients)	Not downgraded	Not downgraded	Not applicable[†]	Downgraded[§]	Not downgraded	Moderate
Grade 3 or higher AEs							
HSCT	3 studies (225 patients)	Downgraded[*]	Not downgraded	Downgraded[‡]	Downgraded[‖]	Not downgraded	Very low
Adipose-tissue-based therapy	1 study (40 patients)	Not downgraded	Not downgraded	Not applicable[†]	Downgraded[‖]	Not downgraded	Moderate
SAEs							
HSCT	3 studies (225 patients)	Downgraded[*]	Not downgraded	Not downgraded	Downgraded[‖]	Not downgraded	Low

Table 2: Certainty of evidence of the included studies (continued)

Outcome	No. of studies	GRADE					Certainty of Evidence
		Risk of Bias	Indirectness	Inconsistency	Imprecision	Small-Study Effect	
Adipose-tissue-based therapy	1 study (40 patients)	Not downgraded	Not downgraded	Not applicable[†]	Downgraded[||]	Not downgraded	Moderate
Infection							
HSCT	3 studies (225 patients)	Downgraded[*]	Not downgraded	Not downgraded	Downgraded[||]	Not downgraded	Low
Adipose-tissue-based therapy	1 study (40 patients)	Not downgraded	Not downgraded	Not applicable[†]	Downgraded[||]	Not downgraded	Moderate
TRM							
HSCT	3 studies (225 patients)	Downgraded[*]	Not downgraded	Not downgraded	Downgraded[||]	Not downgraded	Low
Adipose-tissue-based therapy	1 study (40 patients)	Not downgraded	Not downgraded	Not applicable[†]	Not applicable[¶]	Not downgraded	Moderate

[*] Downgraded by one level since > 25% of the patients were from a high-risk study
[†] Heterogeneity cannot be assessed since there is only one study
[‡] Downgraded by one level due to presence of substantial heterogeneity ($I^2 \geq 50\%$)
[§] Downgraded by one level due to 95% CI including MD = 0
[||] Downgraded by one level due to 95% CI including RR = 1
[¶] Due to lack of event, the RR and 95% CI is not estimable

AE: adverse event; GRADE: grading of recommendations, assessment, development, and evaluation; HSCT: hematopoietic stem cell transplantation; mRSS: modified Rodnan skin score; SAE: serious adverse event; TRM: treatment-related mortality.

Competing interests

The authors declare that they have no competing interests.

Ethical Clearance

This research did not involve human subjects and therefore was exempt from the ethical clearance.

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