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Fish skin grafts versus standard of care on wound healing of chronic diabetic foot ulcers: A systematic review and meta-analysis

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ABSTRACT

Introduction: This study will explore the effectiveness of fish skin grafts (FSG) in ulcer healing in diabetic foot disease compared to standard of care (SOC).
Methods: The systematic review and meta-analysis were performed following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) standard. The electronic databases of PubMed, EMBASE, and Web of Science (WoS) internet were searched for the outcome rate of complete ulcer healing. The risk of bias assessment was conducted using the tool recommended by the Cochrane Collaboration. Statistical analysis included the individual and combined result of the studies, heterogeneity test, the effect size, sensitivity analysis, and publication bias tests.
Results: Five randomised controlled trials (RCTs) with a total of 411 patients were included in this study. This meta-analysis showed a higher rate of complete ulcer healing in groups receiving fish skin grafts (OR = 3.34, 95% CI 2.14–5.20, $p < 0.01$, $I^2 = 0\%$) compared to control groups.
Conclusion: Fish skin grafts have been shown to be more effective for achieving complete ulcer healing compared to current conventional treatments in diabetic foot disease.

1. Introduction

Diabetes mellitus (DM) has become a serious international health problem. Despite recent global efforts to address the DM pandemic, the prevalence of diabetes in the population continues to rise, reaching 537 million in 2021. Most countries are far from achieving the World Health Organisation's goal of a zero increase in prevalence by 2025 [1]. By 2030, the International Diabetes Federation (IDF) estimates that one in every nine adults will have DM, affecting a total population of 643 million people [2].

DM imposes a substantial economic burden on countries, health systems, people with DM, and their families [3]. The global costs associated with DM have increased by 316% over 15 years, from 232 billion dollars in 2007 to 966 billion dollars in 2021. The IDF estimates that the total health expenditure related to DM will reach 1.03 trillion dollars by 2030, and 1.05 trillion dollars by 2045 [4–9].

Foot complications are one of the leading causes of hospitalisation in patients with DM and often require prolonged stays [10]. Unfortunately, 15% of the diabetic population will develop diabetic foot ulcers (DFU) [11], with 25% of these ulcers leading to lower limb amputation [12, 13]. Lower limb amputations are performed at a frequency that is 15 times higher in the diabetic compared to the non-diabetic population [14], and 83% of lower limb amputations in diabetic patients are preceded by DFU [15].

The current standard hospital treatments for patients with DFU include debridement, antibiotic administration, revascularisation, and the use of offloading orthoses [16]. However, these treatments do not guarantee successful closure of the ulcer [17].

Cell- and/or tissue-based wound treatments (CTPs) have, over the last twenty years, become used increasingly frequently as treatments for non-closing ulcers [18]. Initially, studies used material from the small intestine of pigs. Subsequently, decellularised mammalian membranous organs, cellularised skin equivalents, and freeze-dried amniotic membranes have been studied [19]. In 2013, the US Food and Drug

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Administration approved a new product, decellularised fish skin (Kerecis® Omega3 Wound™, Kerecis, Iceland) [20]. Decellularised fish skin is a sterilised and freeze-dried material. The fish skin graft has the advantage of not having been treated with antibiotics or virus inactivation methods, thus preserving the natural omega-3 fatty acids, and is a by-product of the food industry [21]. Therefore, fish-derived CTP is both ecologically sustainable and rich in soluble molecules and natural omega-3 fatty acids. Omega-3 fats appear to have a multitude of positive effects, including anti-inflammatory functions and, to some extent, antibacterial properties [22]. In clinical use, they have been shown to promote healing of chronic ulcers [23].

The use of this material provides structural protein and lipid content (including omega 3), favouring cell migration in the fish skin graft to create dermal neo-tissue to seal the wound. It promotes a physiologically normal healing process, as the wound moves from the inflammatory phase to the healing phase, [24].

There are several authors who have reviewed this novel treatment, but a meta-analysis has not been performed. The objective of this review was to determine the effectiveness of FSG treatment in promoting DFU healing.

2. Material and methods

The systematic review and meta-analysis were performed following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) standard [25]. In addition, this systematic review and meta-analysis protocol was registered with the international prospective register of systematic reviews (PROSPERO) online database (PROSPERO Identifier: 522989).

2.1. Eligibility criteria

This meta-analysis was based on randomised controlled trials (RCTs) comparing the effectiveness of FSG with SOC, which is collagen alginate dressing, for treatment resistant DFU. Only human studies in English or Spanish were considered.

Articles were included in the meta-analysis if they met the following inclusion criteria: the study was an RCT; the target population was diagnosed with DFU; the intervention programme was based on fish skin graft and standard care as the control; and the study variable was the rate of DFU closure.

Studies that aimed to treat FSG in diabetic foot patients but did not measure ulcer closure rates were excluded. Studies that did not quantitatively report ulcer closure rates in diabetic foot patients were also discarded. Studies lacking a control group were excluded, as were case studies.

The following Population, Intervention, Control and Outcome (PICO) framework was used: P: Adult patients diagnosed with chronic DFU; I: FSG treatment; C: Conventional ulcer treatment; and O: Rate of ulcer closure.

To identify the evidence, the WoS, EMBASE, Cinahl, Scopus and PubMed databases were searched. The last search was performed in September 2023. The search was performed using the keywords "Diabetic foot ulcer", "DFU", "fish skin graft", and "FSG" using the Boolean operators "AND" and "OR": ((Diabetic foot ulcer) OR (DFU)) AND ((fish skin graft) OR (FSG)).

2.2. Selection process, data collection, and data list

Two independent reviewers (F.M.B and A.M.R) conducted a double-blind assessment of titles and abstracts (Cohen's kappa: 0.81) to determine whether each item met the inclusion criteria. In cases of doubt, the full text of the article was evaluated (Cohen's kappa: 0.88). Any disagreements were resolved through discussion and if a consensus could not be reached, the opinion of a third reviewer (M.R.M) was sought. It was also planned, if necessary, to email the original authors for further information regarding study details, but this was not required. The main reviewers independently created two tables for the extraction of data from the eligible articles. First author; year of publication; country of origin; sample size; method; results; and conclusions of each article were recorded. Data were sought for any outcome related to the outcome of interest (ulcer closure rate in DFU) in the experimental and control groups. The risk of bias assessment for each article was conducted separately by the main reviewers using the tool recommended by the Collaboration with Cochrane, Robvis, which identifies five types of bias with their respective domains: selection bias has four domains; performance bias and detection bias have one domain each; attrition bias has two domains; and reporting bias has one domain. This tool allows analysis of the presence of a low risk of bias, high risk of bias, or unclear risk of bias in each domain. If there is incomplete information available for analysis, the study is considered to have an unclear risk of bias [26]. In this study, an intervention was considered to have a low risk of bias if there was a low risk of bias in all key domains; an unclear risk of bias if there was a low risk of bias in one or more key domains; and a high risk of bias if there was a high risk of bias in one or more key domains In addition, the main reviewers conducted a methodological evaluation of the articles using the Critical Appraisal Skills Program in Spanish (CASPe), excluding any article that scored below eight out of a total of eleven points [27].

The statistical analysis was based on the dichotomous method, assuming either a fixed effects or random-effects model to calculate the odds ratio (OR) with a 95% confidence interval (CI = 95%) [28]. The heterogeneity of the studies was assessed using the statistical parameter of heterogeneity I^2 (Dersimonian and Laird's heterogeneity test) [29], with a value ranging between 0% and 100%, where 0% indicates no heterogeneity; 25% indicates low heterogeneity; 50% indicates moderate heterogeneity; and $\geq$ 75% indicates high heterogeneity [28]. If I^2 was equal to or greater than 50%, a random-effects model would be assumed; otherwise, a fixed-effects model would be used. A p-value < 0.05 was considered to be statistically significant [29]. A Galbraith plot was created to assess the extent of heterogeneity between studies in the meta-analysis. The y-axis shows the (log transformed) effect size divided by its standard error (z score) and the inverse of the standard error on the x-axis [30]. A L'Abbé plot was included to summarise the heterogeneity of studies: it shows the risks (or odds) in the exposed or index group (y-axis) against those of the control group [30]. A sensitivity analysis was conducted by replicating the results of the meta-analysis and excluding one study included in the review at each step. This showed whether the results obtained were similar in direction, effect size, and statistical significance, indicating the robustness of the analysis [31]. Publication bias was initially analysed qualitatively by visual examination of a funnel plot. Egger's test (with an Egger graph) and Begg's test [31,32] were performed to more accurately assess possible publication bias. If there was any statistically significant bias ($p > 0.1$), a "trim and fill" analysis [32] Meta-Analyses (PRISMA) SPSS v.28, RevMan v.5.3, and Epidat v.4.2 were used for calculations and statistical analysis.

3. Results

3.1. Study selection

The study selection process was presented using the PRISMA flow diagram (Fig. 1). Initially, a total of n = 45 articles were identified, of which 29 articles were duplicates. Of the remaining 17 articles selected for full text review and eligibility assessment, 11 were excluded: four articles had no control group; five articles were case reports; and two articles had no quantitative data. Finally, n = 5 articles were included in this review (Fig. 1). These articles were assessed for risk of bias, with satisfactory results. Additionally, critical appraisal was conducted using the CASPe tool and indicated high methodological quality (Table 2).

The studies included a total of n = 196 individuals in the

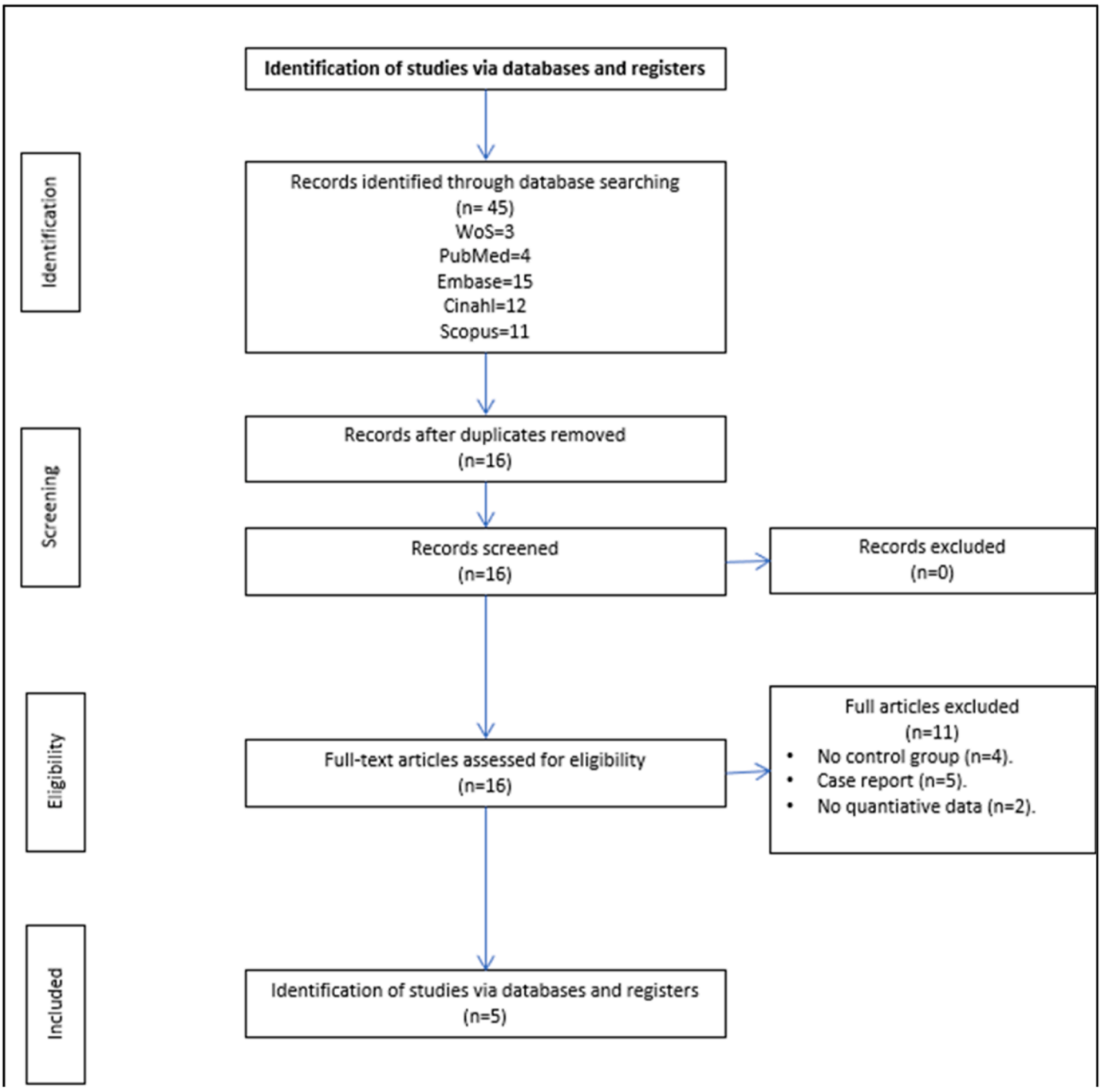


Fig. 1. PRISMA (2020) flowchart detailing information flow throughout the review process.

experimental groups and n = 215 individuals in the control groups, resulting in a total of n = 411 participants (Table 1).

The quality of the studies was assessed using the CASPe tool for critical reading of scientific evidence in the five clinical trials included in this review [33–37]. All studies passed the evaluation, with scores ranging from 10 to 11 out of a total of 11 points (Table 2), indicating high quality. No articles were rejected [27].

The risk of bias assessment was conducted using the tool recommended by the Cochrane Collaboration (Robvis), (Figs. 2 and 3).

3.2. Results of individual studies

Among the five studies included [33–37], Winters et al. [37] contributed the most to the analysis with 34.5% of the total weight, while the article by Kim et al. [33] contributed the least, with 11.3%. The Odds Ratio was used to calculate the effect size, considering the number of cases with ulcer closure and the sample size in each group. The overall odds ratio was 3.34 (2.14, 5.20) (Table 3), favouring the experimental group. In other words, there was an overall 3.34 times greater likelihood of a DFU healing if the intervention is used compared to conventional treatment. Assuming a fixed-effects model, we concluded that there are no differences between the effects estimated by these studies (Table 3).

The heterogeneity test yielded an index where the I2 value was 0% (Table 4), indicating a lack of heterogeneity among the effects calculated from the five studies. A Galbraith plot for analysis of heterogeneity across studies is shown in Table 4. The centre line depicts the regression line and parallel to the regression line, at a distance of two standard

Table 1
Summary of individual trials, by intervention strategy.

First Author, Year of Publication	Country	N	Gender (M/F)	Age (mean/SD)	HbA1c (mean/SD)	BMI (mean/SD)	Treatment strategy	Time treatment	Healing Rate	Conclusions
Kim et al. 2021 [33]	Korea	48	CG = 15/17 EG = 11/5	CG = 42.0 (21.1) EG = 43.3 (25.2)	-	-	CG = SOC EG = FSG	10.1 ± 5.5 days	CG: 53.3%. EG:77.7%.	FSG (Kerecis) is more effective than SOC.
Lantis et al. 2023 [34]	US	77	CG = 15/17 EG = 34/17	CG = 62.8 (13.7) EG = 57.8 (10.8)	CG = 7.8 (1.9) EG = 10.3 (13.0)	CG = 33.4 (8.0) EG = 33.4 (8.5)	CG = SOC EG = FSG	12 weeks	CG: 31.4%. EG:53.3%.	FSG resulted in significantly more HR wounds healed.
Lullove et al. 2022 [35]	US	94	CG = 48 EG = 46	-	-	-	CG = SOC EG = FSG	12 weeks	CG: 31.3%. EG:63%.	HR in favour of the FSG group.
Lullove et al. 2021 [36]	US	89		CG = 60.68 (11.87) EG = 56.67 (11.18)	CG = 7.83 (2) EG = 13.16 (20.42)	CG = 34.59 (6.17) EG = 33.08(8.6)	CG = SOC EG = FSG	12 weeks	CG: 33%. EG:67%.	FSG more HR wounds at 12 weeks than SOC alone.
Winters et al. 2021 [37]	US	118	77/42	CG = 52 EG = 52	-	-	CG = SOC EG = FSG	20 weeks	CG: 63.4%. EG:83.2%.	HR in favour of the FSG group.

N = number of participants; M = male; F = female; SD = standard deviation; CG = control group; EG = experimental group; FSG = fish skin graph; SOC = standard of care; HR = healing rate.

Table 2
Points table by CASPe tool for critical reading of scientific evidence.

Ref.	Author	P1	P2	P3	P4	P5	P6	P7	P8	P9	P10	P11	TOTAL
[33]	**Kim et al.**	YES	YES	YES	-	YES	YES	YES	YES	YES	YES	YES	10/11
[34]	**Lantis et al.**	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	11/11
[35]	**Lullove et al.**	YES	YES	YES	NO	YES	YES	YES	YES	YES	YES	YES	10/11
[36]	**Lullove II et al.**	YES	YES	YES	NO	YES	YES	YES	YES	YES	YES	YES	10/11
[37]	**Winters et al.**	YES	YES	YES	NO	YES	YES	YES	YES	YES	YES	YES	10/11

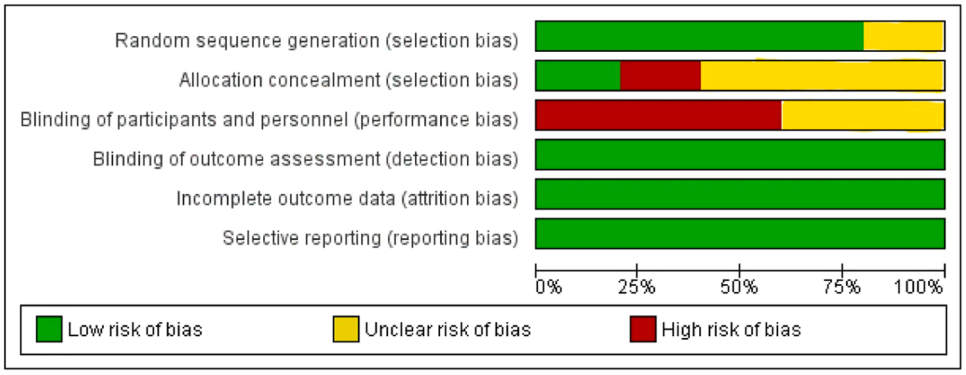


Fig. 2. Risk of bias graph.

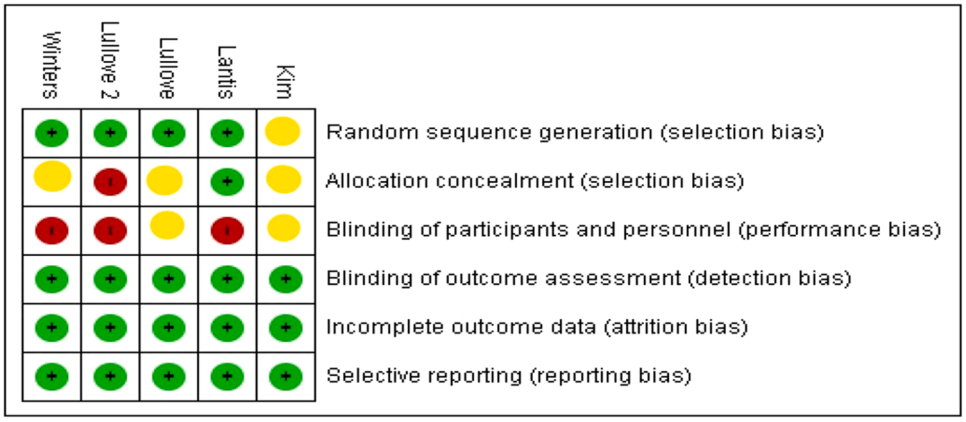


Fig. 3. Risk of bias summary.

Table 3
Individual and combined results.

INDIVIDUAL AND COMBINED RESULTS

Study	Year	n	OR	CI(95,0%)		Weights(%) Fixed eff.	Random eff.
LULLOVE	2021	94	3,7529	1,5961	8,8241	26,8365	26,8365
WINTERS	2021	118	3,1306	1,3273	7,3837	26,6422	26,6422
LULLOVE II	2022	49	4,2500	1,2874	14,0307	13,7518	13,7518
LANTIS	2022	77	3,0316	1,1700	7,8551	21,6403	21,6403
KIM	2023	48	2,6471	0,7018	9,9848	11,1292	11,1292
Fixed effects		386	3,3411	2,1455	5,2028		
Random effects		386	3,3411	2,1455	5,2028		

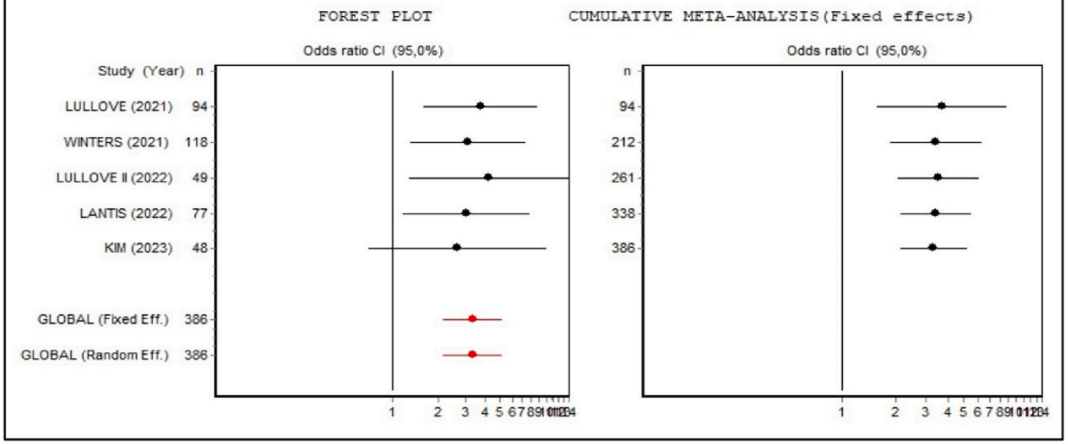


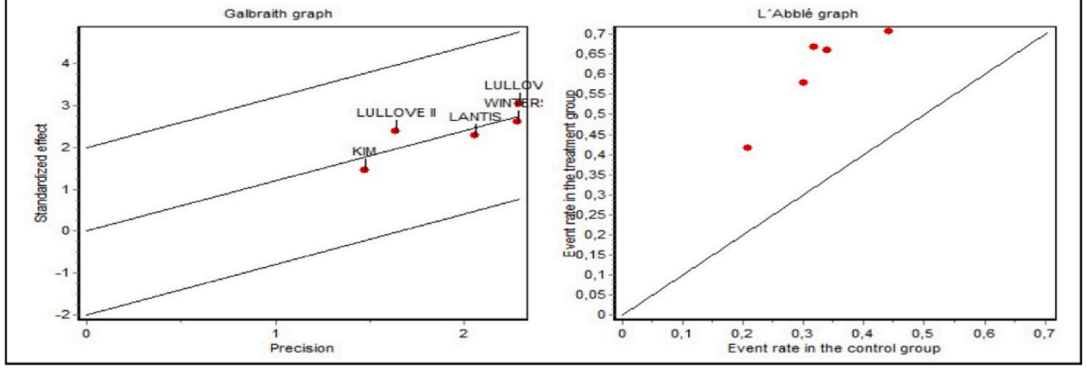
Table 4
Heterogeneity test (Dersimonian and Lairdś heterogeneity test, Galbraith graph and LÁbblé graph.

HETEROGENEITY

Dersimonian and Laird's heterogeneity test

Q statistic (Chi-square)	df	p-value
0,4073	4	0,9819

Heterogeneity statistics	Estimator
Variance between studies	0,0000
Variance within studies	0,2553
Coefficient RI	0,0000
Proportion of total variance due to the variance between studies)	
Variation coeff. between studies	0,0000



deviations, two external lines create an interval into which all five studies (in small red circles) fall, indicating that no inconsistency was found between the studies. A LÁbbé plot (Table 4) shows that all of the studies are well to the upper left of the line of equality, indicating that FSG was more effective than SOC in all trials.

The sensitivity analysis (Fig. 4) and influence graph (Fig. 5)

SENSITIVITY ANALYSIS

FIXED EFFECTS MODEL

Omitted study	Year	n	OR	CI(95,0%) Lower limit	Upper limit	Relative change (%)
LULLOVE	2021	292	3,2016	1,9076	5,3733	-4,17
WINTERS	2021	268	3,4210	2,0397	5,7376	2,39
LULLOVE II	2022	337	3,2153	1,9958	5,1801	-3,76
LANTIS	2022	309	3,4320	2,0809	5,6602	2,72
KIM	2023	338	3,4399	2,1504	5,5028	2,96
GLOBAL		386	3,3411	2,1455	5,2028	

Fig. 4. Sensitivity analysis.

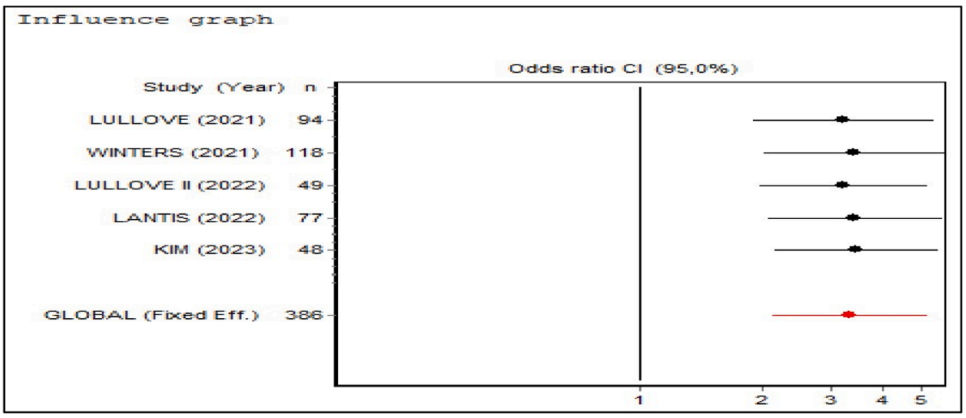


Fig. 5. Sensitivity analysis: Influence graph.

confirmed the robustness of the study findings in terms of direction, statistical significance, and effect size.

The Beggś funnel plot and Egger's plot for publication bias did not show asymmetry of publication bias. As the total number of studies was less than 10, the detection of publication bias was ensured by Egger's regression test. The details are shown in Fig. 6. The two-tailed p-value of $p = 0.8363$ and t-statistic $= -0.225$ (near to 0) means that publication bias was unlikely to have occurred (Fig. 6).

4. Discussion

The objective of this review was to determine on the effectiveness of FSG treatment on ulcer healing in DFU patients compared to SOC treatment. Diabetic foot ulcer (DFU) most often results from the combination of two major complications of diabetes: diabetic neuropathy and angiopathy. It is often complicated by soft tissue and bone infection. Arterial disease carries the most severe prognosis in terms of risk of amputation and mortality [38]. Chronic ulcers are a major public health issue with an annual cost (direct and indirect) estimated at USD 3 billion in the United Kingdom [39] and more than USD 12 billion in the United States [40].

Fish skin graft treatment has been shown to be efficacious in the treatment of DFU wounds. The unique properties of FSG allow it to adhere well to the wound bed, limit the number of dressings needed, promote pro-inflammatory healing, and promote the wound bed, limit the number of dressings required, and promote faster and more complete wound healing. This is more cost-effective than current standard treatments [41–43]. The five studies included in this meta-analysis [33–37] recruited a total of 411 patients diagnosed with DFU. Of the 411, 196 patients were treated with FSG and 215 were treated with SOC. Although few studies were included, despite the study size of 411 patients, the literature indicates that a meta-analysis with this number of articles is feasible [33–37]. Due to the small number of trials of this novel treatment, a meta-analysis will provide the best evidence at the time and should be updated as new trials become available [44]. The use of FSG resulted in significantly higher rates of complete wound healing compared to conventional treatments OR = (3.34 [2.14, 5.20]). The final effect size cannot be compared with other meta-analyses because it is the first to be published. However, there have been some systematic reviews, some of the DFU target population, and others of ulcers with closure problems. These previous reviews have also demonstrated the efficacy of FSG treatments for DFU ulcers. Ibrahim et al. [45] included 10 studies, showing positive results for FGS compared to conventional treatments. However, there was no control group in several of the studies, and others were case studies. Luze et al. [46] included 14 studies and concluded that the novel FSG treatment could represent an effective and low-cost alternative for treatment, as existing evidence indicates accelerated wound healing, a reduction in pain and frequency of dressing changes, as well as improved long-term outcomes. It should be noted, however, that the review included both human and animal studies, as well as case studies, and in several studies there was no control group for comparison. Both reviews concluded that FSG is safe,

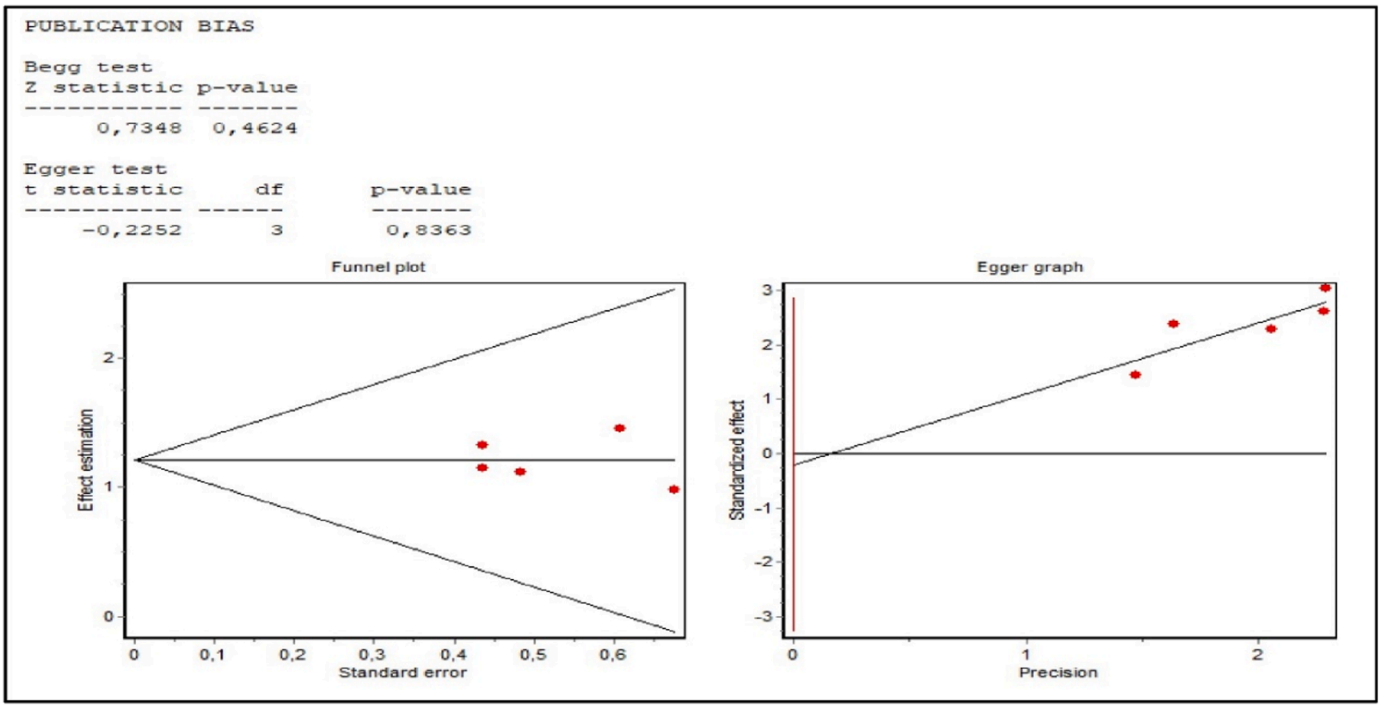


Fig. 6. Publication bias: Begg test, Egger test, Beggś funnel plot and Egger graph.

more effective, and economically efficient than conventional treatments for diabetic ulcers. Regarding assessment of the risk of bias, the blinding of participants and personnel domain was compromised with a high risk of bias due to the absence of blinding in three of the trials [34,36,37]. Blinding is a condition imposed on a specific procedure to preserve the knowledge of the assigned treatment, the course of the treatment, or previous observations [47]. This should be considered in future studies as the number of clinical trials increases and it could be an inclusion criterion for future meta-analyses and reviews. The lack of blinding of participants in clinical trials can introduce biases in physiological responses (depending on the intervention group), including treatment adherence, as well as potential loss to follow-up [48]. Furthermore, the lack of blinding of the research personnel could impact the differential administration of co-interventions, the possibility of adjusting doses, or even the potential to encourage or discourage differential adherence to the study [49].

In this meta-analysis, the selected outcome variable was the ulcer closure rate, as it is currently the most reliable variable for evaluation. Closure rate, along with the reduction in ulcer surface area, are two commonly used variables for reporting the outcomes of FSG treatments in ulcer closure [50]. However, the assessment based on ulcer surface measurement is highly controversial due to the absence of depth measurement and the lack of consensus on the technique to be used for surface measurement [51].

The treatment duration in the included studies ranged from 12 weeks to one study of 20 weeks duration, indicating that the results can be observed between 12 weeks and 20 weeks of treatment. However, further studies are needed to investigate the progression of these healed ulcers over time and to assess potential adverse effects that may occur outside the treatment and observation periods of the included studies.

5. Conclusions

The findings of this meta-analysis, which incorporates recent studies, suggest that current FSG treatments can be considered the first choice for achieving ulcer closure and healing in patients with DFU. These treatments significantly increase the ulcer healing rate compared to existing conventional treatments. In conclusion, the use of FSG as a treatment for ulcer closure in patients with DFU has a higher success rate compared to conventional treatments.

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None.

Conflict of Interest

None.

Declaration of Competing Interest

The authors whose names are listed immediately below certify that they have NO affiliations with or involvement in any organisation or entity with any financial interest (such as honoraria; participation in speakers' bureaus; membership, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

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