applied sciences

MDPI

Review

Minimally Invasive Metatarsal Osteotomies (MIMOs) for the Treatment of Plantar Diabetic Forefoot Ulcers (PDFUs): A Systematic Review and Meta-Analysis with Meta-Regressions

Carlo Biz [1,*], Elisa Belluzzi [1,2,*], Alberto Crimì [1], Nicola Luigi Bragazzi [3,4], Pietro Nicoletti [1,5], Fabiana Mori [1] and Pietro Ruggieri [1]

1 Orthopedics and Orthopedic Oncology, Department of Surgery, Oncology and Gastroenterology (DiSCOG), University of Padova, 35129 Padova, Italy; albe.crim@gmail.com (A.C.); pietronicoletti.ft@gmail.com (P.N.); fabianamori01@gmail.com (F.M.); pietro.ruggieri@unipd.it (P.R.)
2 Musculoskeletal Pathology and Oncology Laboratory, Department of Surgery, Oncology and Gastroenterology (DISCOG), University of Padova, 35129 Padova, Italy
3 Department of Mathematics and Statistics, Laboratory for Industrial and Applied Mathematics, (LIAM), York University, Toronto, ON M3J 1P3, Canada; roberto.bragazzi@gmail.com
4 Leeds Institute of Rheumatic and Musculoskeletal Medicine (LIRMM), University of Leeds, Leeds LS7 4SA, UK
5 Department of Neurosciences, Institute of Human Anatomy, University of Padova, 35128 Padova, Italy
* Correspondence: carlo.biz@unipd.it (C.B.); elisa.belluzzi@gmail.com (E.B.); Tel.: +39-0498213239 (C.B.); +39-0498213348 (E.B.)

Citation: Biz, C.; Belluzzi, E.; Crimì, A.; Bragazzi, N.L.; Nicoletti, P.; Mori, F; Ruggieri P. Minimally Invasive Metatarsal Osteotomies (MIMOs) for the Treatment of Plantar Diabetic Forefoot Ulcers (PDFUs): A Systematic Review and Meta-Analysis with Meta-Regressions. *Appl. Sci.* **2021**, *11*, 9628. https://doi.org/10.3390/app11209628

Academic Editor: Zimi Sawacha

Received: 13 August 2021
Accepted: 13 October 2021
Published: 15 October 2021

Abstract: Plantar Diabetic Foot Ulcers (PDFUs) are frequent injuries affecting and heavily limiting the quality of life in diabetic patients. PDFUs can be treated both conservatively (with a high recurrence rate) or surgically (with a high rate of complication). Recently, minimally invasive surgery (MIS), performed by small incisions, has been increasingly applied on diabetic feet due to their encouraging outcomes and low complication rate. This systematic review with meta-analysis and meta-regression aims to evaluate for the first time the effectiveness of minimally invasive metatarsal osteotomies (MIMOs) in treating PDFUs and reducing their recurrence rate. A literature search of PubMed/MEDLINE, ISI/Web of Science and Scopus databases was carried out with the keywords "(metatarsal osteotom*) OR (metatarsal AND osteotom*) AND diabet* AND (feet OR foot OR forefoot) AND ulcer", covering the period from 1980 until June 2021 following PRISMA guidelines. The JBI critical appraisal tool was used for Quality Assessment. Healing rate/time, infection rate, recurrence rate, non-union rate and complication rate were evaluated. When possible, these values were pooled and expressed in effect size (ES), and their 95% confidence interval (CI) was computed. Meta-regression analysis (both uni- and multivariate) was conducted. Eight studies were included in the review, including 189 patients. The healing rate of these studies ranged between 55.1 and 100%, infection rate from 3.3% to 31.8%, recurrence rate from 0.0% and 13.6% and non-union rate from 4.5–30.0%. Overall complication rate was reported in three studies and ranged from 44.9 to 68.2%. Meta-analysis of the various rates revealed an overall healing rate of 91.9% (range from 74.9 to 97.8%), infection rate of 10.9% (4.2–25.2%), recurrence rate 7.2% (3.6–14.2), non-union rate 16.9% (10.2–26.7) and finally, the complication rate was computed at 53.2%. Satisfactory short- to medium-term clinical and radiographic results were reported by the studies included in this review, supporting that MIMOs represent an effective surgical approach to treat PDFUs. However, poor quality in the methodology of some studies and the lack of long-term data were reported. Therefore, randomized controlled trials, prospective studies and long-term follow-up studies are needed

Keywords: diabetes; diabetic ulcers; foot; foot ulcer; meta-analysis; metatarsal bone; metatarsalgia; minimally invasive surgery; osteotomy; systematic review

1. Introduction

Plantar Diabetic Foot Ulcers (PDFUs) are severe and dreadful complications occurring in diabetic patients, representing even today, a medical and surgical challenge in terms of treatment and a protracted process with high recurrence rates. In diabetic patients, it has been estimated that approximately 25% of hospitalisations are directly related to foot problems [1], and the lifetime risk of developing foot ulcers is around 19–34% [2]. This devastating complication can lead to a substantial number of hospital admissions involving a great deal of medical resources, have a profound negative impact on the quality of life and often result in diabetic foot osteomyelitis and can end up in a lower limb amputation if not recognized and treated promptly on time [3,4]. However, a lower-extremity amputation may not be the most effective solution, as it could be complicated by polymicrobial infections, becoming another serious adverse event with even higher mortality rates [5]. Diabetic patients with pressure ulcers have a 2.5-fold increased risk of death compared with diabetic patients without PDFUs. Further, PDFU development is associated with 5% mortality during the first year and 42% mortality within 5 years [6]. In addition to performing multidisciplinary work, the implementation of a health education program would be important to favour the prevention of diabetic foot ulcers and reduce the risk of amputation [7].

Many factors are involved in PDFU development: for instance, poor glycemic control, peripheral neuropathy, peripheral vascular disease and foot deformity [8]. Trauma, such as ill-fitting shoes and high mechanical pressure resulting from structural deformities in the insensitive diabetic foot, play a significant part in the development of ulceration [9]. Further, duration of diabetes (>10 years), older age, retinopathy, nephropathy, poor foot care habits, barefoot walking and haemoglobin A1c (HbA1c) have been linked to PDFUs [2,9,10]. Other risk factors, especially dyslipidemia, smoking and hypertension, increase the risk of foot problems by altering both blood supply and immune responses to trauma and infection [3]. In these cases, the main therapeutic goal is to promote tissue healing while preserving adequate foot function [11]. It has been shown that infrared thermography could be a useful technique to detect temperature variability in the foot area, allowing diagnosis and prevention of injuries [12,13].

Once a PDFU is observed at the first clinical evaluation, the essential management principles are antibiotic therapy, tissue debridement of superficial skin lesions and off-loading foot pressure until healing is achieved [11]. To reduce the pressure on the affected part and promote wound healing, primary conservative methods remain the restriction of weight-bearing. Several methods of off-loading are available such as total contact casts, removable cast walkers, therapeutic footwear, foot orthoses, custom shoes, custom braces, padding and strapping therapy [14–16]. Nonetheless, there is no consensus in the literature for the optimal off-loading strategy [15,17,18].

It is estimated that about 77% of all PDFUs treated conservatively can initially be healed within 1 year [19]. However, after starting full weight bearing, their recurrence rate is 40% in the following first year after care, 60% within the first 3 years and 65% within 5 years [2]. Further, although PDFUs can heal with appropriate local treatment and shoe modification, a significant number of patients have chronic ulceration despite prolonged treatment, and even when primary healing has occurred, ulcer recurrence is frequent [20].

Hence, surgical treatment is indicated in case of failure of conservative management. The traditional operative methods, including both bone procedures and tendon balancing [20–22], are often correlated with high complication rates, such as infections and wound recurrences [23–25]. For these reasons, a conservative surgery sparing a toe, a metatarsal bone, or a ray would be less traumatic and more acceptable by patients when feasible [26].

Currently, minimally invasive surgery (MIS) represents an innovative approach and is becoming more popular because of lower complication rates [27]. Different minimally invasive and percutaenous osteotomies, at different levels of the distal metatarsal bones, generally by a dorsal approach and without head resection, have been proposed including osteoclasis, a V-shaped cut, a Gauthier osteotomy or oblique cuts such as in a Weil osteotomy or its variants [28,29].

The common goals of these minimally invasive or percutaneous procedures is not only to favor the reduction of bone-induced pressure on the PDFU and consequently promote its healing, but also to restore the metatarsal parabola of the forefoot, preventing recurrent, transfer skin lesions and possible future wound and bone infection [6]. Due to the preserved soft tissue covering and its characteristic stiffness in diabetic foot, the primary stability of these osteotomies is so high that successive osteosynthesis not only is not necessary, but it would also be harmful in preventing the dorsal elevation of the metatarsal bone with respect to the ulcer level. In fact, the patient is asked to walk on the operated foot in the immediate postoperative period to elevate the head dorsally and to release plantar pressure. Technically, the bone cut is usually perpendicular to the metatarsal neck [26].

Recently, some authors reported the outcomes of perpendicular or oblique osteotomies using minimally invasive techniques located at different levels of the metatarsal neck or at the distal diaphysis [27,30]. These include a variant of the most widespread Distal Metatarsal Metaphyseal Osteotomy (DMMO) [31], a percutaneous technique used routinely in the last decade for the treatment of metatarsalgia [27,32].

A recent meta-analysis about the contemporary management of diabetic neuropathic foot ulcerations revealed disappointing functional outcomes [33]. Moreover, the meta-analysis showed that minimally invasive surgery for PDFUs by metatarsal osteotomies is a poorly investigated topic [33], contrary to the several traditional surgical techniques explored in the literature [20–22,33].

The goals of this systematic review with meta-analysis and meta-regressions were to critically evaluate the available literature to establish if there is sufficient evidence demonstrating that minimally invasive metatarsal osteotomies (MIMOs) proposed for PDFU treatment are (1) effective in achieving ulcer healing and (2) effective in preventing recurrence of ulcers, and (3) to summarize their rates of post-operative complications.

2. Materials and Methods

2.1. Study Reporting

The present Systematic Review and Meta-Analysis was conducted using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (PRISMA), which were used to monitor all steps of the research [34]. The study protocol has been registered with the Open Science Framework depository (Identifier code: DOI 10.17605/OSF.IO/NX7CA).

2.2. Search Strategy

From 1 to 30 June 2021, an electronic search was conducted in the three following databases: PubMed/MEDLINE, ISI/Web of Science (WoS) and Scopus. In these databases, an advanced search was carried out using the following specific keywords and Boolean terms: "(metatarsal osteotom*) OR (metatarsal AND osteotom*) AND diabet* AND (feet OR foot OR forefoot) AND ulcer". A date filter was then inserted to cover the period from 1980 until June 2021. The earliest reference found for the use of the procedure in toe deformities in any patient population was dated 1986 [35].

2.3. Selection Criteria

Only studies written in English, which included a minimally invasive metatarsal osteotomy as surgical treatment, were selected. Randomized clinical trials, cohort studies, case-control studies, case series and case reports were considered eligible. Studies reporting outcomes for the hallux and/or lesser toes were included. As PDFUs may be multifactorial, diabetic patient groups with or without neuropathy or peripheral arterial disease were included. Studies were included if they used a concurrent secondary procedure (e.g., flexor, extensor tenotomies of lesser toes).

2.4. Exclusion Criteria

All articles written in languages other than English, were without data or that were off-topic were discarded. Studies were excluded if they involved non-diabetic patients and did not report outcomes of diabetic and non-diabetic patients separately. Letters, commentaries, opinion pieces, book chapters and reviews were also excluded.

2.5. Outcome Measures

The following were selected as the main outcomes for evaluating the effectiveness of metatarsal osteotomies: healing rate, treatment time, revision surgeries and possible complications. The size, the grade with the Texas Classification of Diabetic Foot Wound (if present) and number of ulcers were also compared as outcome measures. If present, pre- and post-intervention AOFAS score values and VAS scale values were taken into account.

2.6. Selection Method

The selection was made by reading the abstracts of all of the articles found. If the abstracts met the inclusion criteria, the full-text manuscript was retrieved and analyzed. A cross-reference search of the selected articles was also performed to obtain other relevant articles for the study.

Finally, the selected articles and references were reviewed and assessed independently by two reviewers (FM and PN) and all queries were discussed and resolved by the supervisory team (CB and EB) in regular meetings. Data extraction was completed independently by assessors (EB and NLB). If there was disagreement among the investigators regarding the inclusion or exclusion criteria, the senior investigator (PR) made the final decision. The level of agreement was high, with a kappa statistic > 0.80.

2.7. Data Extraction

The studies that were selected as includible were ordered in an Excel file in which the data extraction was completed independently. Data were extracted for the various studies, (authors, publication date, study design, level of evidence) and for the patients included: number of patients, sex, age, type of intervention, type of diabetes, number of ulcers, ulcer grade, ulcer age, wound size, diabetes treatment, ankle brachial index (ABI), healing rate, outcomes (AOFAS, VAS) and complications.

2.8. Quality Assessment

Given the study design of the included studies, the Joanna Briggs Institute (JBI) critical appraisal tool [36], consisting of an 11-point checklist, was used to assess the methodological quality of studies retained in the analysis and to recognize any potential risk of bias.

2.9. Statistical Analysis

When possible (in the presence of at least two estimates), findings from the retained investigations were pooled together. More specifically, rates were synthesized and expressed as effect sizes (ES), applying the logit event rate technique, which is one of the available approaches to meta-analyze proportions [37], together with the Freeman–Tukey transformation (or arcsine square root transformation). ESs were computed with their 95% confidence intervals (CIs). Moreover, ESs were pictorially represented and inspected by means of forest plots. When there were enough studies, meta-regression analyses (both uni- and multivariate) were conducted on covariates and moderators of interest.

Heterogeneity among studies was assessed by means of Cochran's Q and I^2 statistics. If the amount of inconsistency across studies was >50.0% and statistically significant, a mixed-effect model was applied instead of a fixed-effect model. Evidence of publication bias was evaluated by conducting the trim-and-fill analysis and visually inspecting the funnel plot. It is worthy stressing that funnel plots were provided for each ES computed, even though findings from the publication bias assessment should be interpreted with caution when the number of available studies retained in the meta-analysis is low.

All statistical analyses were conducted by means of the commercial Comprehensive Meta-Analysis Software version 3.3.070 (Biostat Inc., Englewood, NJ, USA).

3. Results

3.1. Search Yield

The search results and selection process are shown in Figure 1 using the PRISMA flow-chart. In the end, eight research papers met the criteria of selection and thus were included in this review.

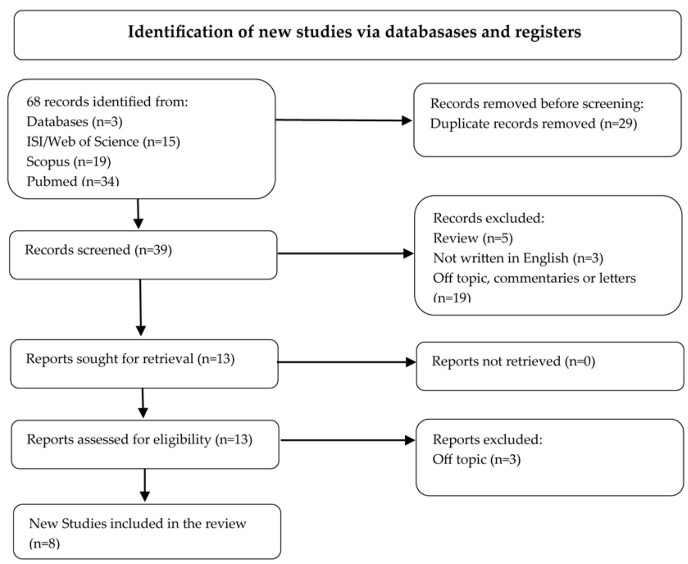

Figure 1. Systematic Reviews and Meta-Analyses (PRISMA) flow chart representing the process for inclusion of papers. For this study, nine articles were assessed for eligibility after screening: among these, 8 new studies were included in the analysis [34].

3.2. Quality assesment

The quality assessment, using the JBI critical appraisal tool [36], of the research included is reported in Table 1.

3.3. Study Characteristics

Study characteristics are reported in Table 2.

3.4. Outcomes of the Selected Studies

Study characteristics are described in Table 3.

Table 1. Quality Assessment with JBI Critical Appraisal Checklist for Case Series.

Checklist	Wray et al., 1986 [35]	Tillo et al., 1990 [29]	Fleischli et al. 1999 [38]	Tamir et al., 2016 [30]	Biz et al., 2018 [27]	Tamir et al., 2020 [39]	Chiu et al., 2020 [40]	Tamir et al., 2021 [41]
Were there clear criteria for inclusion in the case series?	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Was the condition measured in a standard, reliable way for all participants included in the case series?	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Were valid methods used for identification of the condition for all participants included in the case series?	NA	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Did the case series have consecutive inclusion of participants?	NA	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Did the case series have complete inclusion of participants?	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Was there clear reporting of the demographics of the participants in the study?	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Was there clear reporting of clinical information of the participants?	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Were the outcomes or follow up results of cases clearly reported?	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Was there clear reporting of the presenting site(s)/clinic(s) demographic information?	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Was statistical analysis appropriate?	NA	No	No	No	Yes	Yes	Yes	Yes
Total number of NO	7	1	1	1	0	0	0	0

Table 2. Study characteristics.

	Wray et al. 1986 [35]	Tillo et al. 1990 [29]	Fleischli et al. 1999 [38]	Tamir et al. 2016 [30]	Biz et al. 2018 [27]	Tamir et al. 2020 [39]	Chiu et al. 2020 [40]	Tamir et al. 2021 [41]
N° of patients	1	52	20	17	30	21	16	32
Gender (males/females)		(38/14)	(13/7)	(16/1)	(20/10)	(16/5)	(12/4)	(29/3)
Age (mean ± SD)	52	55.4	62 (range 31–82)	57 (range 42–75)	66.7 ± 6.8 (range, 53–75)	64 (range 45–83)	57.81	60.1 ± 7.5
Type of diabetes	NA	27: type I; 25: type II	NA	NA	2 type 1; 28: type II	NA	NA	2
HbA1C	NA	NA	NA	8.1 (median 7.1, range 4.9 to 12.2 g/dL)	7.1% ± 0.8% (range, 5.9–8.4%)	8.1% (range 6.4–13.8)	9.14 (range, 5.2–13.2 g/dL)	7.9% ± 1.7% (63 ± 18 mmol/mol)
Wound Size	NA	NA	NA	NA	16.3 ± 0.6 (range, 5–25) mm	length 21.8 ± 9.0 mm, width 15.8 ± 7.6 mm,	5.72 (cm^2)	mean area 97.9 ±86.6 mm^2 (range 19.6–392.7 mm^2, median 78.5
Ulcer grade	NA	NA	NA	All 1A [1]	IA [2]: 4; IIA: 2; IIB:6; IIC:2; IIIA:2; IIIB:15; IIIC:1; IIID:3	All 1A [1]	NA	A0 [1]: 3; A1:30; A2:1
Ulcer age (months)	NA	NA	NA	19 (median 11, range 1 to 60)	10.3 ± 3.8 (range, 6–19)	NA	NA	median of 1.5 months (range 0.5–18)
Mean follow-up (months)	24	19	17 (range 4–66)	NA	25.3 ± 10.0 (range, 18–71)	19.3 (median 17.6, range 12–34)	15.2 (±3.21)	18.6 months (median: 18.4, range 12.2–27.5)

[1] Texas classification. [2.] UTDWC Classification.

Table 3. Outcomes extracted from the studies retained in the present systematic review and meta-analysis with meta-regressions.

	Wray et al., 1986 [35]	Tillo et al., 1990 [29]	Fleischli et al., 1999 [38]	Tamir et al., 2016 [30]	Biz et al., 2018 [27]	Tamir et al., 2020 [39]	Chiu et al., 2020 [40]	Tamir et al., 2021 [41]
Healing rate	27/49 (55.1%)	1/1 (100.0%)	21/22 (95.5%)	20/20 (100.0%, 17/20, 85.0%, completely healed; 3/20, 15.0%, improved)	30/30 (100.0%)	19/21 (90.5%)	14/16 (87.5%)	31/32 (96.9%)
Healing time	NA	NA	40 days (range of 8 to 113 days)	Six weeks	7.9 ± 4.0 (range 4–17) weeks; ulcers with a diameter 1.5 cm or less required 6.8 ± 4.1 (range 4–17) weeks to heal, while ulcers with a diameter more than 1.5 cm required 9.4 ± 3.6 (range 4–15) weeks	Mean of 3.7 (median 3, range 2–11) weeks; in 13 of the 21 patients, the wound was healed within 3 weeks or less	2.14 (±1.38) months	Mean of 3.7 weeks (SD 4.2, median 3, range 1–23, IQR 2–4)
Peak pressure under the head of the osteotomized metatarsal	NA	NA	NA	NA	NA	NA	NA	Decreased from 338.1 to 225.4 kPa (33%, $p < 0.0001$) following surgery; the pressure time integral under the head of the osteotomized metatarsal decreased as well from 82.4 kPa·s to 65.0 kPa·s (21%, $p < 0.0001$)
AOFAS score preop	NA	NA	NA	NA	55.3 ± 8.3 (range, 42–71)	NA	NA	NA
AOFAS last follow-up	NA	NA	NA	NA	81.4 ± 9.1 (range, 64–100)	NA	NA	NA
VAS (satisfaction) post op	NA	NA	NA	NA	9.8 ± 0.7 (range, 7–10)	NA	NA	NA
Infections	NA	NA	7/22 (31.8%; 3/22, 13.6%, deep wound infections were successfully treated with irrigation and debridement, pin removal, and antibiotics; 4/22, 18.2%, superficial wound infections successfully treated with pin removal	1/20 (5.0%)	1/30 (3.3%, wound infection by *Streptococcus agalactiae*)	3/21 (14.3%, related to the surgery within 1 year, one needing excision of the first metatarsal head, one requiring drainage, and one requiring hospitalization for administration of intravenous antibiotics)	NA	2/32 (6.3%, operative site infections that recovered with parenteral and oral antibiotics, respectively; one was a deep postoperative wound infection and one was a foot infection not related to the surgery)

			and oral antibiotics)					
Wound discharge	NA	NA	NA	NA	NA	5/21 (23.8%, without other signs of infection, which were successfully treated with oral antibiotics)	NA	NA
Necrosis	NA	NA	NA	NA	NA	1/21 (4.8%, necrosis of the fifth toe related to the casting, resulting in the amputation of the toe)	NA	NA
Swelling	NA	NA	NA	NA	18/32 feet (56.3%, persistent moderate swelling of the forefoot for more than 6 weeks without infection, which improved after some months with complete callus formation at the osteotomy levels and without further treatment)	NA	NA	NA
Recurrence/relapse	NA	3/49 (6.1%)	3/22 (13.6%; residual deformity from acute Charcot episode, resulting in plantar midfoot ulcers under bony prominences)	NA	NA	NA	0/16 (0.0%)	1/32 (3.1%, under the callus formed at the osteotomy site)
Acute Charcot	NA	NA	7/22 (31.8%, treated with serial total contact casting until the resolution of the acute inflammatory process and bony consolidation identified on radiographs)	NA	NA	NA	NA	NA
Non-unions	NA	NA	1/22 (4.5%, asymptomatic)	6/20 (30.0%, asymptomatic, 6 months after the procedure, three after osteotomy of the neck and three after osteotomy of the shaft)	NA	3/21 (14.3%, asymptomatic)	NA	4 (12.5%, asymptomatic)
Transfer lesions	NA	13 (26.5%, transfer	2/22 (9.1%, under adjacent metatarsal	2/20 (10.0%; one below the fourth metatarsal head 5	NA	3/21 (14.3%, five transfer lesions in three patients)	2/16 (12.5%, at an average of	4/32 (12.5%; under the heads of adjacent metatarsals)

		ulceration; six patients (12.2%) developed transfer calluses)	heads)	months after an osteotomy of the second metatarsal neck and the other below the second metatarsal head, 10 months after osteotomy of the third metatarsal neck)			7.5 months after the surgical procedure)	
Loss of screw fixation	NA	NA	1/22 (4.5%, with an acceptable metatarsal alignment being maintained)	NA	NA	NA	NA	NA
Redo-surgery	NA	NA	2/22 (9.1%, exostectomy)	NA	NA	NA	NA	3/32 (9.4%, two patients were treated conservatively, while three had further offloading surgery)
Overall complications	NA	22/49 (44.9%)	15/22 (68.2%; major complications occurred in 13/22 cases, 59.1%; minor complications were noted in 6/22 cases, 27.3%)	NA	NA	NA	NA	18/32 (56.3%; 23 adverse events/complications in 18 patients, 16 of which not related to surgery)

3.5. Systematic Review

3.5.1. Healing Rate and Healing Time

Healing rate was reported in eight studies and ranged from 55.1 to 100.0%. In the study by Tamir et al. (2016) [30], 17/20 lesions (85.0%) completely healed, while the remaining 3/20 (15.0%) improved. In six studies [27,30,38–41], the healing rate was greater than 90.0%. Healing time was reported in six studies and ranged from 1 to 2 months [27,30,38–41].

3.5.2. AOFAS and VAS

Preoperative AOFAS score was reported only in one study [27]. It was computed at 55.3 ± 8.3 (range 42–71), whereas AOFAS at last follow-up was 81.4 ± 9.1 (range 64–100). Postoperative VAS for satisfaction was reported in the study by Biz et al. (2018) and was computed at 9.8 ± 0.7 (range 7–10).

3.5.3. Peak Pressure under the Head of the Osteotomized Metatarsal

This outcome was reported only in 1 study [41]. The outcome was found to decrease from 338.1 to 225.4 kPa (33%, $p < 0.0001$) following surgery; the pressure time integral under the head of the osteotomized metatarsal decreased as well from 82.4 kPa to 65.0 kPa·s (21%, $p < 0.0001$).

3.5.4. Infection Rate

Infection rate was reported in five studies and ranged from 3.3–31.8% [27,30,38–41]. All infections were successfully resolved after administration of antibiotics. Wound discharge rate was reported only in one study [39] and was computed at 23.8%. Similarly, necrosis rate was reported only in one study [39] and was 4.8% (one case of necrosis of the fifth toe related to the casting, resulting in the amputation of the toe).

3.5.5. Non-union Rate

Non-union rate was reported in four studies, ranging from 4.5 to 30.0%, and all of them were asymptomatic [30,38,39,41].

3.5.6. Swelling Rate

Swelling rate was reported only in noe study [27], where 18 out of 32 feet were found to be swollen. Swelling rate was computed at 56.3%, and was persistently moderate, affecting the forefoot for more than 6 weeks without infection. It improved after some months with complete callus formation at the osteotomy levels and without further treatment.

3.5.7. Recurrence/Relapse Rate

Recurrence/relapse rate was reported in four studies and ranged from 0.0 to 13.6% [29,38,40,41]. Loss of screw fixation was reported only in 1 study [38], with one case being reported (4.5%, with an acceptable metatarsal alignment being maintained). Redo-surgery rate was reported in two studies, ranging from 9.1 to 9.4%.

3.5.8. Acute Charcot

This adverse outcome was reported only by Fleischli et al. (1999) [38]. Seven cases (31.8%) were reported and treated with serial total contact casting until resolution of the acute inflammatory process and bony consolidation was identified on radiographs.

3.5.9. Transfer Lesion Rate

Transfer lesions rate was reported in six studies and ranged from 9.1 to 26.5% [29,30,38–41].

3.5.10. Overall Complication Rate

Overall complication rate was reported in three studies and ranged from 44.9 to 68.2% [29,38,41].

3.6. Meta-Analysis

3.6.1. Healing Rate

The overall healing rate resulted 91.9%, ranging from 74.9 to 97.8%. Due to the significantly high amount of heterogeneity among studies (I^2 = 80.0%; Q = 30.04), a mixed-effect model was implemented. With the meta-regression analysis, it was found that the age of the recruited populations tended to become older through the years in a significant way (coefficient = 0.2724 (SE = 0.1180), p = 0.0209) (Table 4). The lowest ES was reported in the study by Tillo et al. (1990) [29], who recruited the highest number of diabetes type 1 patients (coefficient = 0.0522 (SE = 0.0102), p = 0.0000) and performed a variety of surgical procedures (Q = 27.24, p = 0.0000). However, these moderators resulted not significant with the multivariate meta-regression analysis. Evidence of publication bias could be detected with visual inspection of the funnel plot (Figure 2) and with the trim-and-fill analysis, resulting in an "adjusted" ES of 70.9%, ranging from 41.0 to 89.5% (four studies were trimmed/removed).

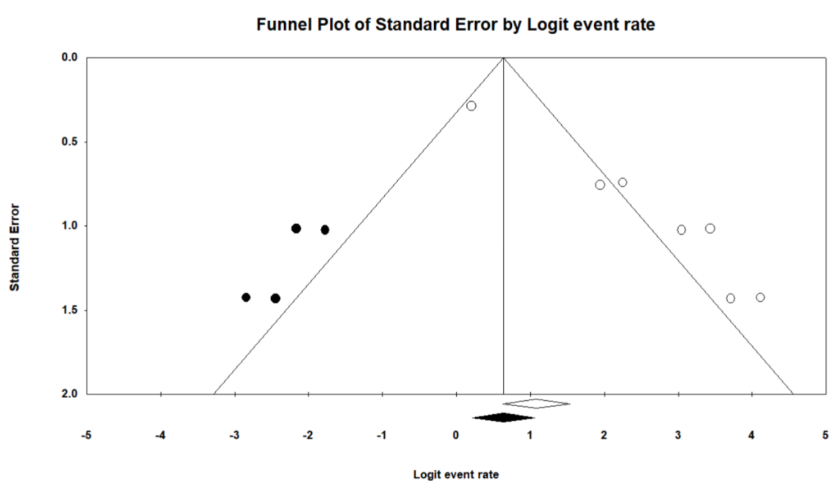

Figure 2. Funnel plot for the effect size of healing rate showing evidence of publication bias with four studies being trimmed/removed. White circles are the effect sizes of the studies included in the present systematic review and meta-analysis, while black circles represent effect sizes not reported by published studies, probably due to publication bias. If the corresponding observed effect sizes are trimmed/removed, the overall effect size (white diamond) becomes the "adjusted" overall effect size (black diamond).

3.6.2. Infection Rate

The overall infection rate was 10.9%, ranging from 4.2 to 25.2%. Due to the significantly high amount of heterogeneity among studies (I^2 = 61.0%; Q = 10.27), a mixed-effect model was applied. With the meta-regression analysis, a significant impact of the type of surgery (Q = 8.90, p = 0.0117) could be found, with the lowest ES reported in the study by Tillo et al. (1990) [29]. Study year (coefficient = −0.0799 (SE = 0.0295), p = 0.0067) was another significant moderator, with infection rates improving (decreasing) throughout years. Follow-up time had a borderline impact on ES estimation (coefficient =

−0.2980 (SE = 0.1529), p = 0.0513). There were not enough studies to perform a multivariate meta-regression analysis. Visual inspection of the funnel plot and the trim-and-fill analysis revealed no evidence of publication bias.

3.6.3. Recurrence/Relapse Rate

The overall recurrence/relapse rate was 7.2% [95%CI 3.6–14.2]. Due to the null amount of heterogeneity among studies (I^2 = 0.0%; Q = 2.57), a fixed-effect model was chosen. No significant moderators could be found with the meta-regression analysis. No evidence of publication bias could be detected, both with visual inspection of the funnel plot and with the trim-and-fill analysis.

3.6.4. Non-Union Rate

The overall non-union rate was 16.9% [95%CI 10.2–26.7]. Due to the low to moderate amount of heterogeneity among studies (I^2 = 38.6%; Q = 4.89), a fixed-effect model was applied. No significant moderators could be found with the meta-regression analysis. No evidence of publication bias could be found, both with visual inspection of the funnel plot and with the trim-and-fill analysis.

3.6.5. Transfer Lesion Rate

The overall transfer lesion rate was 17.4% [95%CI 12.1–24.4]. Due to the low amount of heterogeneity among studies (I^2 = 8.3%; Q = 5.45), a fixed-effect model was conducted. With the meta-regression analysis, diabetes type (coefficient = −0.0206 (SE = 0.0091), p = 0.0241) was significant, whereas age (coefficient = −0.1253 (SE = 0.0706), p = 0.0759), type of surgery: Q = 4.99, p = 0.0825) and study year (coefficient = −0.0286 (SE = 0.0153), p = 0.0610) resulted statistically borderline. They were not significant with the multivariate meta-regression. No evidence of publication bias could be detected both with visual inspection of the funnel plot and with the trim-and-fill analysis.

3.6.6. Redo-Surgery Rate

The overall redo-surgery rate was computed to be 9.3% [95%CI 3.9–20.4]. Due to the null amount of heterogeneity among studies (I^2 = 0.0%; Q = 0.00), a fixed-effect model was conducted. However, there were not enough studies to perform meta-regressions and publication bias analysis.

3.6.7. Overall Complication Rate

The overall complication rate was 53.2% [95%CI 43.4–62.7]. Due to the low to moderate amount of heterogeneity among studies (I^2 = 40.9%; Q = 3.38), a fixed-effect model was applied. There were not enough studies to perform a meta-regression analysis. Evidence of publication bias could be found, both upon visual inspection of the funnel plot (Figure 3) and with the trim-and-fill analysis, which resulted in an “adjusted” effect-size of 44.9% [95%CI 37.2–52.9], with two studies being trimmed/removed.

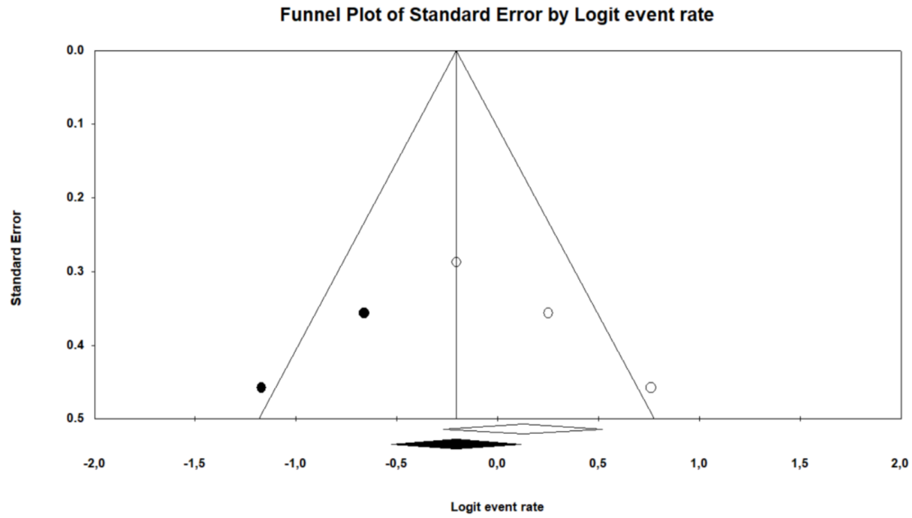

Figure 3. Funnel plot for the effect size of overall complication rate showing evidence of publication bias with two studies being trimmed/removed. White circles are the effect sizes of the studies included in the present systematic review and meta-analysis, while black circles represent effect sizes not reported by published studies, probably due to publication bias. If the corresponding observed effect sizes are trimmed/removed, the overall effect size (white diamond) becomes the "adjusted" overall effect size (black diamond).

Table 4. Outcomes obtained from meta-analysis with meta-regressions, pooling the studies included in the present systematic review.

Outcome	Effect Size	Moderators	Publication Bias
Healing rate	91.9% [95%CI 74.9–97.8] I^2 = 80.0%; Q = 30.04; mixed-effect model	**Univariate Metaregression** Age: coefficient = 0.2724 (SE = 0.1180), *p* = 0.0209 Gender: coefficient = 0.0353 (SE = 0.0708), *p* = 0.6182 Type of surgery: Q = 27.24, *p* = 0.0000 Diabetes type: coefficient = 0.0522 (SE = 0.0102), *p* = 0.0000 Length of diabetes: coefficient = −0.1606 (SE = 0.2705), *p* = 0.5526 Glycated hemoglobin: coefficient = −0.9868 (SE = 0.6758), *p* = 0.1442 Study year: coefficient = 0.0733 (SE = 0.0312), *p* = 0.0189 Follow-up time: coefficient = 0.1664 (SE = 0.2708), *p* = 0.5389 Ulcer's grade: coefficient = −0.0163 (SE = 0.0179), *p* = 0.3646 **Multivariate Metaregression** Age: coefficient = –0.0077 (SE = 0.1954), *p* = 0.9688 Diabetes type: coefficient 0.0576 (SE = 0.0424), *p* = 0.1742 Study year: coefficient = 0.0056 (SE = 0.0627), *p* = 0.9283	"Adjusted" effect-size = 70.9% [95%CI 41.0–89.5]; trimmed k = four studies

Infection rate	10.9% [95%CI 4.2–25.2] I^2 = 61.0%; Q = 10.27; mixed-effect model	**Univariate Metaregression** Age: coefficient = −0.0034 (SE = 0.2100), *p* = 0.9872 Gender: coefficient = −0.0515 (SE = 0.0369), *p* = 0.1630 Type of surgery: Q = 8.90, *p* = 0.0117 Diabetes type: coefficient = 0.2245 (SE = 0.2094), *p* = 0.2837 Length of diabetes: coefficient = −0.3405 (SE = 0.4261), *p* = 0.4242 Glycated haemoglobin: coefficient = 1.2551 (SE = 1.1480), *p* = 0.2743 Study year: coefficient = −0.0799 (SE = 0.0295), *p* = 0.0067 Follow-up time: coefficient = −0.2980 (SE = 0.1529), *p* = 0.0513 Ulcer grade: coefficient = 0.0132 (SE = 0.0130), *p* = 0.3121 **Multivariate Metaregression** Not enough studies	No publication bias; trimmed k = zero studies
Recurrence/relapse	7.2% [95%CI 3.6–14.2] I^2 = 0.0%; Q = 2.57; fixed-effect model	**Univariate Metaregression** Age: coefficient = 0.1129 (SE = 0.1279), *p* = 0.3774 Gender: coefficient = −0.0655 (SE = 0.0462), *p* = 0.1564 Type of surgery: not enough studies Diabetes type: coefficient = 0.0042 (SE = 0.0196), *p* = 0.8291 Length of diabetes: not enough studies Glycated haemoglobin: not enough studies Study year: coefficient = −0.0264 (0.0332), *p* = 0.4266 Follow-up time: coefficient = −0.1327 (SE = 0.3539), *p* = 0.7077 Ulcer grade: not enough studies	No publication bias; trimmed k = zero studies
Non-unions	16.9% [95%CI 10.2–26.7] I^2 = 38.6%; Q = 4.89; fixed-effect model	**Univariate Metaregression** Age: coefficient = −0.1842 (SE = 0.1591), *p* = 0.2470 Gender: coefficient = 0.0529 (SE = 0.0316), *p* = 0.0944 Type of surgery: Q = 1.5676 (SE = 1.1323), *p* = 0.1662 Diabetes type: cannot be performed because of collinearity issues Length of diabetes: not enough studies Glycated haemoglobin: not enough studies Study year: coefficient = 0.0521 (SE = 0.0613), *p* = 0.3947 Follow-up time: not enough studies Ulcer	No publication bias; trimmed k = zero studies

		grade: not enough studies	
Transfer lesions	17.4% [95%CI 12.1–24.4] $I^2 = 8.3\%$; Q = 5.45; fixed-effect model	**Univariate Metaregression** Age: coefficient = −0.1253 (SE = 0.0706), *p* = 0.0759 Gender: coefficient = −0.0226 (SE = 0.0266), *p* = 0.3963 Type of surgery: Q = 4.99, *p* = 0.0825 Diabetes type: coefficient = −0.0206 (SE = 0.0091), *p* = 0.0241 Length of disease: coefficient = 0.0042 (SE = 0.2281), *p* = 0.9854 Glycated haemoglobin: coefficient = 0.0034 (SE = 0.7250), *p* = 0.9962 Study year: coefficient = −0.0286 (SE = 0.0153), *p* = 0.0610 Follow-up time: coefficient = 0.2248 (SE = 0.1964), *p* = 0.2523 Ulcer grade: not enough studies **Multivariate Metaregression** Age: coefficient = 0.0397 (SE = 0.1313), *p* = 0.7622 Diabetes type: coefficient = −0.0364 (SE = 0.0291), *p* = 0.2122 Study year: coefficient = 0.0210 (SE = 0.0390), *p* = 0.5898	No publication bias; trimmed k = zero studies
Redo-surgery	9.3% [95%CI 3.9–20.4] $I^2 = 0.0\%$; Q = 0.00; fixed-effect model	Not enough studies	Not enough studies
Overall complications	53.2% [95%CI 43.4–62.7] $I^2 = 40.9\%$; Q = 3.38; fixed-effect model	Not enough studies	"Adjusted" effect-size = 44.9% [95%CI 37.2–52.9]; trimmed k = two studies

4. Discussion

In the recent literature, PDFU healing is still described as a challenging and protracted process with high recurrence rates, negatively affecting the patients' quality of life and potentially leading to amputation [42–44]. A normal wound closure follows a dynamic process comprising four sequential phases: hemostasis, inflammation, proliferation and remodeling [45]. However, the process of wound healing is affected negatively in patients with diabetes. Specifically, the process starts with a decrease of fibrinolysis with an imbalance of cytokines affecting wound healing. Moreover, angiogenesis is decreased by hyperglycemia. Cell migration (keratinocytes and fibroblasts) is decreased with a negative impact on extracellular matrix production and thus causing a deficient re-epithelialization [46].

Several methods have been proposed to treat PDFUs [20–22,24]. However, the current crucial issue is to relieve the pressure because the wound never heals until the pressure is off-loaded. There are many methods to relieve it [47] including body weight reduction, total contact casts [48], corrective shoes with customized insoles [49] and even surgical correction, such as metatarsal head resection and ray amputation [20–22,33]. In this context, MIS has been proposed as an effective intervention [24]. Its main objectives are primarily the healing of PDFUs by relieving the pressure on them; secondarily, the prevention of ulcer recurrence, transfer lesions and local infections [6].

Many reports showed the more traditional surgical procedures (metatarsal head resection, metatarsal osteotomy and exostectomy, metatarsal head resection, arthrodesis) and tendon balancing (Achilles' tendon lengthening, gastrocnemius recession, and/or plantar fascia release) can achieve good to excellent results on diabetic ulcer healing, regardless of their grade severity and dimensions [1–3]. However, open surgical bone procedures are often correlated with high complication rates, such as wound recurrence or postoperative infection, while tendon balancing presents risks of tendon overlengthening, rupture and plantar flexion weakness [21,38,50].

To the best of our knowledge, no previous systematic review has provided quantitative evidence synthesis regarding the mere efficacy of MIMOs for diabetic foot ulcerations.

The goal of the present systematic review and meta-analysis was to identify the available body of evidence of these MIMOs regarding their effectiveness in promoting PDFU healing and in preventing their recurrence and to summarize the rates of post-operative complications.

4.1. MIMOs for PDFU Healing and Prevention (1986–2021)

From 1986 to the present, in different decades, relatively few original studies regarding MIMOs for PDFUs have been published. In the eight original articles included in this review, different osteotomy shapes have been proposed [27,29,30,35,38–41]. Despite the heterogeneity of the surgical methods, a systematic, common approach to the diabetic foot was found: all osteotomies were performed in a minimally invasive way carried out by an incision less than 3 cm performed by a dorsal foot approach, predominantly at the level of the lesser distal metatarsal bones, drawn down in oblique slide shape and without fixation or only temporary. Among the different authors, none used fixation except for the surgical procedures described by Fleischli et al. (1999) [38]. More commonly, as originally proposed by Wray et al. (1986), a metatarsal neck osteotomy of the metatarsal bones, osteotomized obliquely, starting proximally on the dorsum but proceeding distally and plantar-ward at an angle of 45°, was described [35]. With some differences, Tillo et al. (1990) proposed four different types of distal metatarsal bone osteotomies: osteoclasis of the head, V-osteotomy, shortening colectomy and oblique slide osteotomy [29]. Later, Fleischli (1999) was the only one to suggest a dorsally based, closing wedge metaphyseal osteotomy at the base of the metatarsal bones, temporarily fixed in most cases with K-wires [38].

In the 21st century, Tamir et al. in 2016 used a perpendicular or short oblique osteotomy performed at the neck or diaphysis of the metatarsal bone, with healing of the plantar lesion being reported in most of the cases [30]. More recently, Biz et al. (2018) treated a series of 30 patients by distal metatarsal diaphyseal osteotomies, performed with an angle of approximately 45° with respect to the long axis of the metatarsal bone in a dorsal-distal to proximal-plantar direction [27]. Similarly, in 2020 Tamir et al. [39] treated another series of 21 patients using a mini-invasive osteotomy without fixation, perpendicular to the first metatarsal bone metaphysis, similar to that described by Giannini et al. for Hallux Valgus (HV) percutaneous correction [51]. In the same year, Chiu et al. (2020) proposed a diaphyseal ostectomy proximal to the level of the metatarsal neck to preserve metatarsophalangeal joint function [40]. However, in the case of the metatarsophalangeal joint, severe destruction or stiffness was reported; even the joint was removed with the osteotomized bone segment [40]. In 2021, Tamir et al. treated 32 patients with metatarsal distal oblique osteotomies without fixation, described as minimally invasive floating distal metatarsal osteotomy [41].

In this review, only single series, case series, study design, level IV of evidence, some with poor methodological quality and different outcome measures were examined. The studies included used heterogeneous outcome evaluation parameters, and only the study by Biz et al. [27] evaluated the patients' AOFAS and VAS scores, both pre-operatively and at the last follow-up. Only Tamir et al. (2021) used the reduction of pressure under the metatarsal head after osteotomy as a measure of clinical outcome (from 82.4 kPa preoperatively to 65 kPa in the follow-up measures) [41]. The inclusion criteria of these studies consisted of participants with diabetes of both types (1 and 2) or not specified and at different stages of disease progression, further increasing the difficulty in comparing the different studies. Finally, some studies included people with no sensory neuropathy, while other studies included participants with sensory neuropathy, in both cases associated to previous foot ulceration.

Reliable scientific evidence is essential to guide the use of MIS in clinical practice applied to the diabetic feet for the management of PDFUs. Overall, the studies analyzed in this review report encouraging and promising results following MIMOs with regard to ulcer healing (range 55.1–100.0%), mean healing time (range from 1 to 2 months) and recurrence rates (range 0.0–13.6%). In the study by Tamir et al. (2016), 17/20 lesions (85.0%) completely healed, while the remaining 3/20 (15.0%) improved [30]. Thus, if we consider the other six studies (case report excluded), the healing rate was greater than 90.0% [27,30,38–41]. Healing time was reported in six studies and ranged from 1 to 2 months [27,30,38–41].

Hence, the most important finding of this review is that MIMOs are an effective intervention in PDFU management, not only for promoting healing but also for reducing their recurrence by achieving a better distribution of plantar pressure on the metatarsal bone with a low incidence of complications.

Relating to the severity of the ulcers, based on their clinical experience [6,27], the authors strongly believe that MIMOs can be an alternative valid treatment also for PDFUs with chronic infection, ulcers penetrating deep structures (IIIB), and ulcers with osteomyelitis of the metatarsal bones or the proximal phalanx. These challenging feature presentations, or evolution of diabetic feet, becoming increasingly frequent, in association to other vascular complications, such as ankle brachial index below 0.5 or flat pulse volume recording at the ankle level, should be considered as relative, but not absolute, contraindications for MIMOs [6,52]. As the PDFU represents the main access door for the bacteria causing foot osteomyelitis, resolving the first promotes the healing of the second, avoiding long-term antibiotic therapy, which causes progressive bone damage in diabetic patients [53]. However, the few absolute contraindications of these percutaneous procedures must be well known by clinicians and surgeons: severe ischemia and gangrene, insufficient vascular perfusion and extensive soft tissue infection presenting as cellulitis of the foot or toe.

Finally, it is the opinion of the authors, that the best approach to diabetic foot ulcers remains multidisciplinary, with a team that should include endocrinologists, podiatrists, wound care nurses, vascular, general and orthopedic surgeons, and infectious disease specialists. For this reason, in particular for PDFU management, referral to a diabetic care clinic is advised for the most appropriate indication of treatment [6].

4.2. MIMO Complications

This review showed an overall complication ranged between 44.9 and 68.2%. The most frequent complications were swelling (56.3%) reported in one study [27], radiographical nonunion (4.5–30.0%), infections (3.3–31.8%), transfer lesions (9.1–26.5%) and ulcer recurrences (0–13.6%). Radiographical non-union, although very frequent, was reported in four studies (range 4.5–30.0%) and in all cases described as asymptomatic [29,38,40,41], probably because of sensory neuropathy. Only in Fleischli's study, a fixation was used to prevent nonunion, using temporary K-wires or cancellous bone screws [38]. However, as expected by the presence of metalwork, the technique was burdened by a higher infection rate (31.8%) compared to the other studies.

Infections often adversely affect the healing of PDFUs. Infection rate was reported in five out of 8 studies and ranged from 4.2 to 25.2% [27,30,38–41]. They were mainly treated successfully with oral or intravenous antibiotics. Only six cases, reported in three studies [27,38,41], required subsequent surgical treatment to eradicate a deep infection. Wound discharge rate was reported only in one study and was computed at 23.8% [39]. Similarly, necrosis rate was reported only in one study and was 4.8% (one case of necrosis of the fifth toe related to the casting, resulting in the amputation of the toe) [39].

Transfer lesions were reported in six studies (range 9.1–26.5%) and usually described under the heads of the adjacent metatarsals [29,30,38–41]. These lesions occur when a correct metatarsal parabola is not re-established in the forefoot [6]. In two studies, transfer lesions were reported to appear at a mean of 10 and 7.5 months, respectively, (after the osteotomy procedures) [30,40]. This is probably due to the resumption of patients' normal walking and incorrect overloading of the lateral metatarsal bones. The highest transfer lesion rate (26.5%) was found in the report by Tillo et al. (1990) [29] (excluding the case report of Wray (1986) [35]), but considering all of the other papers, the transfer lesion rate was 17%.

The recurrence/relapse pooled rate of the ulcers was 7.2%. It has to be considered that this rate is higher in the first studies related to the 90s [29,38], while thereafter only 1 case was described by Tamir et al. 2021 [41]. Only four patients needed an off-loading redo -surgery; the only other cases that required further surgery are the six patients who had deep infections.

Swelling rate was reported only in one study, where 18 out of 32 feet were found to be swollen [27]. Swelling rate was computed to be 56.3% and was persistently moderate, affecting the forefoot for more than 6 weeks without infection, which improved after some months with complete callus formation at the osteotomy levels and without further treatment.

Finally, acute Charcot foot, the most fearsome complication, was reported only by Fleischli et al. (1999) in seven cases (31.8%), who were traditionally treated by serial total contact casting until the resolution of the acute inflammatory process and bony consolidation identified by radiographs [38].

The eight studies considered had a total population of 189 patients; however, regarding the clinical outcomes and complications, statistical analysis presented a heterogenicity that was not statistically significant (except in the case of the healing rate and overall complication rate analysis). Although the outcome measures of the eight papers included in this review presented an outstanding healing rate of 91.9% (ranging from 74.9 to 97.8%), in the 1990s, Tillo et al. [26], who recruited the highest number of diabetes type 1 patients (coefficient = 0.0522 (SE = 0.0102), $p = 0.0000$) and performed a variety of surgical procedures (Q = 27.24, $p = 0.0000$) reported the lowest healing rate. However, these moderators were not significant with the multivariate meta-regression analysis. Further, the results of the meta-analysis showed that age of the recruited populations tended to become older through the years in a significant way (coefficient = 0.2724 (SE = 0.1180), $p = 0.0209$). This may reflect a better glycemic control of the disease due to pharmacological improvements, which resulted in the occurrence of complications, including ulcers, at a later age [54].

The meta-analysis revealed a significant impact of the type of surgery (Q = 8.90, $p = 0.0117$) on the infection rate, with the study of Tillo et al. [29] reporting the lowest ES. The infection rates decreased as the year of publication of the study increased (Q = −0.0799 (SE = 0.0295), $p = 0.0067$), likely due to the progress in clinical management of the patients and for the better glycemic control obtained. The other factor to be considered is that among the older studies, the one by Fleischli et al. [38] is the only study where fixation tools (K-wires and screws) were used. This technique led to a higher rate of deep and superficial wound infections compared to other more modern techniques. All of the other authors did not perform internal fixation or pinning after osteotomy. Regarding recurrence/relapse rate, non-union rate and redo-surgery rate, no significant moderators were identified. Meta-regression analysis of overall complications was not possible due to the low number of studies. Importantly, the diabetes type was found to be a moderator of transfer lesion rate (Q = −0.0206 (SE = 0.0091), $p = 0.0241$), but the statistical significance was lost with the multivariate meta-regression. However, it must be underlined that only three studies specified diabetes type of the patients [27,29,41]. Thus, further studies are needed to verify this point.

4.3. Strengths and Limitations

This systematic review has several strengths. It included all studies published to date on the topic since 1975. Extensive search strategies were employed with detailed, careful and critical assessment to identify risk of bias in compliance with the PRISMA guidelines. Moreover, meta-regressions were conducted, both uni- and multivariate. However, the review is limited mainly by the methodological deficiencies of included studies. All eight publications described in this review are retrospective case series and are therefore vulnerable to bias. The absence of randomization and a control group means that any changes observed are the result of an uncontrolled pre-post analysis instead of a comparative analysis with control subjects who received an alternative treatment such as current standard conservative care. The small sample size of each study poses a further difficulty in generalizing the findings. Only one study performed an a priori power analysis of the minimum sample size required [41]. The other limitation of this review is the heterogeneity of study design and outcome measures of the studies included. Several surgical procedures in the included studies were carried out at different levels of metatarsal bones by surgeons with different levels of experience; hence, there may be potential bias. Further, the different patients' outcomes scores used by the authors may have contributed to the observed significant heterogeneity among studies, impairing comparability and assessment of the merits of each technique. Further, only studies published in English were included; however, our review did not lose much data from studies published in other languages, as only one was in German [55]. Finally, another limit of this review is the large time frame taken into consideration. As already mentioned, the difference over time regarding the clinical management of diabetic patients has played a fundamental role in the improvement of PDFU outcomes. Better results found in most recent articles can be explained by looking at the improvement of the management of diabetic patients in a multidisciplinary way. In the future, it would be interesting to investigate the specific role of the healing of PDFUs in terms of lengthening the prognosis quo ad vitam of diabetic patients and its economic impact on National Health Services.

5. Conclusions

Satisfactory short- to medium-term clinical and radiographic results were reported by the studies included in this systematic review and meta-analysis with meta-regressions, suggesting that MIMOs performed at the different level of the metatarsal bones and without fixation may be an effective surgical treatment option for achieving healing of PDFUs, even when they are chronic, and preventing their recurrence in the forefoot of both type-1 and type-2 diabetic patients. However, these results should be interpreted with caution due to the poor quality and methodological deficiencies identified in some included studies, their limited evidence in providing appropriate functional and radiographic outcome measures (all level IV) and the complete lack of data concerning long-term follow-ups.

For these reasons, randomized controlled trials and prospective, longitudinal research studies, recruiting an adequate number of participants, investigating the combination of foot-loading factors, good glycemic control, and their interaction on PDFU healing are needed. Certainly, higher quality evidence would better support and promote the use of the MIMOs as a treatment option for achieving and maintaining healing of PDFUs in people with diabetic and neuropathic feet.

Author Contributions: Conceptualization, C.B.; methodology, C.B., E.B. and N.L.B.; validation, C.B. and E.B.; formal analysis, N.L.B.; investigation, C.B., E.B., P.N. and F.M.; data curation, C.B., E.B, N.L.B., P.N. and F.M; writing—original draft preparation, C.B., E.B., N.L.B., P.N. and F.M.; writing—review and editing, C.B., E.B, A.C., N.L.B. and P.N.; visualization, E.B.; supervision, P.R.; project administration, C.B. and E.B. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: All data are available in the main text.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Batista, F.; Magalhães, A.A.; Nery, C.; Baumfeld, D.; Monteiro, A.C.; Batista, F. Minimally invasive surgery for diabetic plantar foot ulcerations. *Diabet. Foot Ankle* **2011**, *2*, 10358, doi:10.3402/dfa.v2i0.10358.
2. Armstrong, D.G.; Boulton, A.J.M.; Bus, S.A. Diabetic Foot Ulcers and Their Recurrence. *N. Engl. J. Med.* **2017**, *376*, 2367–2375, doi:10.1056/NEJMra1615439.
3. Ahmad, J. The diabetic foot. *Diabetes Metab. Syndr.* **2016**, *10*, 48–60, doi:10.1016/j.dsx.2015.04.002.
4. Lavery, L.A.; Davis, K.E.; Berriman, S.J.; Braun, L.; Nichols, A.; Kim, P.J.; Margolis, D.; Peters, E.J.; Attinger, C. WHS guidelines update: Diabetic foot ulcer treatment guidelines. *Wound Repair Regen.* **2016**, *24*, 112–126, https://doi.org/10.1111/wrr.12391.
5. Hoffstad, O.; Mitra, N.; Walsh, J.; Margolis, D.J. Diabetes, lower-extremity amputation, and death. *Diabetes Care* **2015**, *38*, 1852–1857, doi:10.2337/dc15-0536.
6. Biz, C.; Ruggieri, P. Minimally Invasive Surgery: Osteotomies for Diabetic Foot Disease. *Foot Ankle Clin.* **2020**, *25*, 441–460, doi:10.1016/j.fcl.2020.05.006.
7. Astasio-Picado, Á.; Cobos-Moreno, P.; Gómez-Martín, B. Self-Care Planning and Sanitary Education in the Prevention of the Diabetic Foot. *Appl. Sci.* **2021**, *11*, 7281.
8. Pendsey, S.P. Understanding diabetic foot. *Int. J. Diabetes Dev. Ctries.* **2010**, *30*, 75–79, doi:10.4103/0973-3930.62596.
9. Schaper, N.C.; van Netten, J.J.; Apelqvist, J.; Bus, S.A.; Hinchliffe, R.J.; Lipsky, B.A.; Board, I.E. Practical Guidelines on the prevention and management of diabetic foot disease (IWGDF 2019 update). *Diabetes/Metab. Res. Rev.* **2020**, *36*, e3266, https://doi.org/10.1002/dmrr.3266.
10. Hwang, D.J.; Lee, K.M.; Park, M.S.; Choi, S.H.; Park, J.I.; Cho, J.H.; Park, K.H.; Woo, S.J. Association between diabetic foot ulcer and diabetic retinopathy. *PLoS ONE* **2017**, *12*, e0175270, doi:10.1371/journal.pone.0175270.
11. Bandyk, D.F. The diabetic foot: Pathophysiology, evaluation, and treatment. *Semin. Vasc. Surg.* **2018**, *31*, 43–48, doi:10.1053/j.semvascsurg.2019.02.001.
12. Astasio-Picado, Á.; Escamilla Martínez, E.; Gómez-Martín, B. Comparative thermal map of the foot between patients with and without diabetes through the use of infrared thermography. *Enferm. Clin.* **2020**, *30*, 119–123, doi:10.1016/j.enfcli.2018.11.002.
13. Astasio-Picado, Á.; Martínez, E.E.; Gómez-Martín, B. Comparison of Thermal Foot Maps between Diabetic Patients with Neuropathic, Vascular, Neurovascular, and No Complications. *Curr. Diabetes Rev.* **2019**, *15*, 503–509, doi:10.2174/1573399815666190206160711.
14. Bus, S.A.; Valk, G.D.; van Deursen, R.W.; Armstrong, D.G.; Caravaggi, C.; Hlaváček, P.; Bakker, K.; Cavanagh, P.R. The effectiveness of footwear and offloading interventions to prevent and heal foot ulcers and reduce plantar pressure in diabetes: A systematic review. *Diabetes/Metab. Res. Rev.* **2008**, *24*, S162–S180, https://doi.org/10.1002/dmrr.850.
15. Elraiyah, T.; Prutsky, G.; Domecq, J.P.; Tsapas, A.; Nabhan, M.; Frykberg, R.G.; Firwana, B.; Hasan, R.; Prokop, L.J.; Murad, M.H. A systematic review and meta-analysis of off-loading methods for diabetic foot ulcers. *J. Vasc. Surg.* **2016**, *63*, 59S–68S. e1-2, doi:10.1016/j.jvs.2015.10.006.
16. Mohammedi, K.; Potier, L.; François, M.; Dardari, D.; Feron, M.; Nobecourt-Dupuy, E.; Dolz, M.; Ducloux, R.; Chibani, A.; Eveno, D.F.; et al. The evaluation of off-loading using a new removable oRTHOsis in DIABetic foot (ORTHODIAB) randomized controlled trial: Study design and rational. *J. Foot Ankle Res.* **2016**, *9*, 34, doi:10.1186/s13047-016-0163-4.
17. Burns, J.; Begg, L. Optimizing the offloading properties of the total contact cast for plantar foot ulceration. *Diabet. Med. J. Br. Diabet. Assoc.* **2011**, *28*, 179–185, doi:10.1111/j.1464-5491.2010.03135.x.
18. Götz, J.; Lange, M.; Dullien, S.; Grifka, J.; Hertel, G.; Baier, C.; Koeck, F. Off-loading strategies in diabetic foot syndrome-evaluation of different devices. *Int. Orthop.* **2017**, *41*, 239–246, doi:10.1007/s00264-016-3358-1.

19. Prompers, L.; Schaper, N.; Apelqvist, J.; Edmonds, M.; Jude, E.; Mauricio, D.; Uccioli, L.; Urbancic, V.; Bakker, K.; Holstein, P.; et al. Prediction of outcome in individuals with diabetic foot ulcers: Focus on the differences between individuals with and without peripheral arterial disease. The EURODIALE Study. *Diabetologia* **2008**, *51*, 747–755, doi:10.1007/s00125-008-0940-0.
20. Dayer, R.; Assal, M. Chronic diabetic ulcers under the first metatarsal head treated by staged tendon balancing: A prospective cohort study. *J. Bone Jt. Surg. Br. Vol.* **2009**, *91*, 487–493, doi:10.1302/0301-620x.91b4.21598.
21. Cychosz, C.C.; Phisitkul, P.; Belatti, D.A.; Wukich, D.K. Preventive and Therapeutic Strategies for Diabetic Foot Ulcers. *Foot Ankle Int.* **2016**, *37*, 334–343, doi:10.1177/1071100715611951.
22. Willrich, A.; Angirasa, A.K.; Sage, R.A. Percutaneous tendo Achillis lengthening to promote healing of diabetic plantar foot ulceration. *J. Am. Podiatr. Med. Assoc.* **2005**, *95*, 281–284, doi:10.7547/0950281.
23. Dallimore, S.M.; Kaminski, M.R. Tendon lengthening and fascia release for healing and preventing diabetic foot ulcers: A systematic review and meta-analysis. *J. Foot Ankle Res.* **2015**, *8*, 33, doi:10.1186/s13047-015-0085-6.
24. La Fontaine, J.; Lavery, L.A.; Hunt, N.A.; Murdoch, D.P. The role of surgical off-loading to prevent recurrent ulcerations. *Int. J. Low. Extrem. Wounds* **2014**, *13*, 320–334, doi:10.1177/1534734614555002.
25. Hamilton, G.A.; Ford, L.A.; Perez, H.; Rush, S.M. Salvage of the neuropathic foot by using bone resection and tendon balancing: A retrospective review of 10 patients. *J. Foot Ankle Surg. Off. Publ. Am. Coll. Foot Ankle Surg.* **2005**, *44*, 37–43, doi:10.1053/j.jfas.2004.11.001.
26. Yammine, K.; Assi, C. Conservative Surgical Options for the Treatment of Forefoot Diabetic Ulcers and Osteomyelitis: An Evidence-Based Review and a Decision-Making Tool. *JBJS Rev.* **2020**, *8*, e0162, doi:10.2106/jbjs.rvw.19.00162.
27. Biz, C.; Gastaldo, S.; Dalmau-Pastor, M.; Corradin, M.; Volpin, A.; Ruggieri, P. Minimally Invasive Distal Metatarsal Diaphyseal Osteotomy (DMDO) for Chronic Plantar Diabetic Foot Ulcers. *Foot Ankle Int.* **2018**, *39*, 83–92, doi:10.1177/1071100717735640.
28. Finestone, A.S.; Tamir, E.; Ron, G.; Wiser, I.; Agar, G. Surgical offloading procedures for diabetic foot ulcers compared to best non-surgical treatment: A study protocol for a randomized controlled trial. *J. Foot Ankle Res.* **2018**, *11*, 6, doi:10.1186/s13047-018-0248-3.
29. Tillo, T.H.; Giurini, J.M.; Habershaw, G.M.; Chrzan, J.S.; Rowbotham, J.L. Review of metatarsal osteotomies for the treatment of neuropathic ulcerations. *J. Am. Podiatr. Med. Assoc.* **1990**, *80*, 211–217, doi:10.7547/87507315-80-4-211.
30. Tamir, E.; Finestone, A.S.; Avisar, E.; Agar, G. Mini-Invasive floating metatarsal osteotomy for resistant or recurrent neuropathic plantar metatarsal head ulcers. *J. Orthop. Surg. Res.* **2016**, *11*, 78, doi:10.1186/s13018-016-0414-x.
31. Laffenêtre, O.; Perera, A. Distal Minimally Invasive Metatarsal Osteotomy ("DMMO" Procedure). *Foot Ankle Clin.* **2019**, *24*, 615–625, doi:10.1016/j.fcl.2019.08.011.
32. Biz, C.; Corradin, M.; Kuete Kanah, W.T.; Dalmau-Pastor, M.; Zornetta, A.; Volpin, A.; Ruggieri, P. Medium-Long-Term Clinical and Radiographic Outcomes of Minimally Invasive Distal Metatarsal Metaphyseal Osteotomy (DMMO) for Central Primary Metatarsalgia: Do Maestro Criteria Have a Predictive Value in the Preoperative Planning for This Percutaneous Technique? *BioMed Res. Int.* **2018**, *2018*, 1947024, doi:10.1155/2018/1947024.
33. Yammine, K.; Assi, C. Surgical Offloading Techniques Should be Used More Often and Earlier in Treating Forefoot Diabetic Ulcers: An Evidence-Based Review. *Int. J. Low. Extrem. Wounds* **2020**, *19*, 112–119, doi:10.1177/1534734619888361.
34. Page, M.J.; Moher, D.; Bossuyt, P.M.; Boutron, I.; Hoffmann, T.C.; Mulrow, C.D.; Shamseer, L.; Tetzlaff, J.M.; Akl, E.A.; Brennan, S.E.; et al. PRISMA 2020 explanation and elaboration: Updated guidance and exemplars for reporting systematic reviews. *BMJ* **2021**, *372*, n160, doi:10.1136/bmj.n160.
35. Wray, C. The Helal osteotomy in a diabetic patient. *Pract. Diabetes Int.* **1986**, *3*, 156–156.
36. Moola, S.; Munn, Z.; Tufanaru, C.; Aromataris, E.; Sears, K.; Sfetcu, R.; Currie, M.; Qureshi, R.; Mattis, P.; Lisy, K. Chapter 7: Systematic reviews of etiology and risk. In *Joanna Briggs Institute Reviewer's Manual*; The Joanna Briggs Institute: Adelaide, Australia, 2017; Volume 5.
37. Khan, S. Meta-analysis on One Proportion. In *Meta-Analysis: Methods for Health and Experimental Studies*; Khan, S., Ed.; Springer: Singapore, 2020; pp. 119–137, doi:10.1007/978-981-15-5032-4_6pp.
38. Fleischli, J.E.; Anderson, R.B.; Davis, W.H. Dorsiflexion metatarsal osteotomy for treatment of recalcitrant diabetic neuropathic ulcers. *Foot Ankle Int.* **1999**, *20*, 80–85, doi:10.1177/107110079902000203.
39. Tamir, E.; Smorgick, Y.; Ron, G.Z.; Gilat, R.; Agar, G.; Finestone, A.S. Mini Invasive Floating Metatarsal Osteotomy for Diabetic Foot Ulcers Under the First Metatarsal Head: A Case Series. *Int. J. Low. Extrem. Wounds* **2020**, , doi:10.1177/1534734620934579.
40. Chiu, W.K.; Yang, T.F.; Wang, H.J.; Chen, C. Assessment of Outcomes of a Metatarsal Bone Ostectomy for Chronic Plantar Ulcers: A Preliminary Study. *Ann. Plast. Surg.* **2020**, *84*, S112–S115, doi:10.1097/sap.0000000000002174.
41. Tamir, E.; Tamar, M.; Ayalon, M.; Koren, S.; Shohat, N.; Finestone, A.S. Effect of Mini-invasive Floating Metatarsal Osteotomy on Plantar Pressure in Patients with Diabetic Plantar Metatarsal Head Ulcers. *Foot Ankle Int.* **2021**, *42*, 536–543, doi:10.1177/1071100720976099.
42. Mavrogenis, A.F.; Megaloikonomos, P.D.; Antoniadou, T.; Igoumenou, V.G.; Panagopoulos, G.N.; Dimopoulos, L.; Moulakakis, K.G.; Sfyroeras, G.S.; Lazaris, A. Current concepts for the evaluation and management of diabetic foot ulcers. *EFORT Open Rev.* **2018**, *3*, 513–525, doi:10.1302/2058-5241.3.180010.
43. Peter-Riesch, B. The Diabetic Foot: The Never-Ending Challenge. *Endocr. Dev.* **2016**, *31*, 108–134, doi:10.1159/000439409.
44. Hoban, C.; Sareen, J.; Henriksen, C.A.; Kuzyk, L.; Embil, J.M.; Trepman, E. Mental health issues associated with foot complications of diabetes mellitus. *Foot Ankle Surg. Off. J. Eur. Soc. Foot Ankle Surg.* **2015**, *21*, 49–55, doi:10.1016/j.fas.2014.09.007.

45. Wilkinson, H.N.; Hardman, M.J. Wound healing: Cellular mechanisms and pathological outcomes. *Open Biol.* **2020**, *10*, 200223, doi:10.1098/rsob.200223.
46. Perez-Favila, A.; Martinez-Fierro, M.L.; Rodriguez-Lazalde, J.G.; Cid-Baez, M.A.; Zamudio-Osuna, M.d.J.; Martinez-Blanco, M.d.R.; Mollinedo-Montaño, F.E.; Rodriguez-Sanchez, I.P.; Castañeda-Miranda, R.; Garza-Veloz, I. Current Therapeutic Strategies in Diabetic Foot Ulcers. *Medicina* **2019**, *55*, 714.
47. Singh, N.; Armstrong, D.G.; Lipsky, B.A. Preventing foot ulcers in patients with diabetes. *JAMA* **2005**, *293*, 217–228, doi:10.1001/jama.293.2.217.
48. Wukich, D.K.; Motko, J. Safety of Total Contact Casting in High-Risk Patients with Neuropathic Foot Ulcers. *Foot Ankle Int.* **2004**, *25*, 556–560, doi:10.1177/107110070402500808.
49. Rizzo, L.; Tedeschi, A.; Fallani, E.; Coppelli, A.; Vallini, V.; Iacopi, E.; Piaggesi, A. Custom-made orthesis and shoes in a structured follow-up program reduces the incidence of neuropathic ulcers in high-risk diabetic foot patients. *Int. J. Low. Extrem. Wounds* **2012**, *11*, 59–64, doi:10.1177/1534734612438729.
50. Lin, S.S.; Lee, T.H.; Wapner, K.L. Plantar forefoot ulceration with equinus deformity of the ankle in diabetic patients: The effect of tendo-Achilles lengthening and total contact casting. *Orthopedics* **1996**, *19*, 465–475.
51. Giannini, S.; Cavallo, M.; Faldini, C.; Luciani, D.; Vannini, F. The SERI distal metatarsal osteotomy and Scarf osteotomy provide similar correction of hallux valgus. *Clin. Orthop. Relat. Res.* **2013**, *471*, 2305–2311, doi:10.1007/s11999-013-2912-z.
52. Lipsky, B.A.; Uçkay, İ. Treating Diabetic Foot Osteomyelitis: A Practical State-of-the-Art Update. *Medicina* **2021**, *57*, 339, doi:10.3390/medicina57040339.
53. Aragón-Sánchez, J.; Lázaro-Martínez, J.L.; Alvaro-Afonso, F.J.; Molinés-Barroso, R. Conservative Surgery of Diabetic Forefoot Osteomyelitis: How Can I Operate on This Patient Without Amputation? *Int. J. Low. Extrem. Wounds* **2014**, *14*, 108–131, doi:10.1177/1534734614550686.
54. White, J.R. A Brief History of the Development of Diabetes Medications. *Diabetes Spectr.* **2014**, *27*, 82–86, doi:10.2337/diaspect.27.2.82.
55. Mehlhorn, A.T.; Harrasser, N.; Walther, M. Treatment of plantar, neuropathic and metatarsal ulcers by minimally invasive metatarsal osteotomy. *Orthopade* **2020**, *49*, 625–631, doi:10.1007/s00132-019-03848-w.