# Different Surgical Modalities for Reconstruction of Soft Tissue Defects in Diabetic Foot Ulcers; A Metaanalysis: A Systematic Review/Meta-Analysis

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**Abstract: Background:** Foot ulceration is a very common complication in diabetic patients. It is well established that about 25% of people with diabetes develop a foot ulcer during their lifetime and 20% of all diabetic patients who enter the hospital are admitted for foot problems. **Aim of the Work:** This study aimed at comparing different surgical modalities used for soft tissue coverage of the diabetic foot wounds highlighting the success rates, postoperative mortality and morbidity. **Patients and Methods:** Twenty one clinical trials or case series studies that discuss different reconstructive surgical techniques for coverage of diabetic foot ulcers from 1998 to 2018and fulfilled the inclusion and exclusion criteria and were included in the review. **Results:** The pooled average success rate was 92%for free tissue transfer, 90% for regional flaps, 95% for intrinsic muscle flaps, 96.7% for local random fasciocutaneous flaps and 74% for STSG. The minor complications rate such as wound infection, marginal flap necrosis/ graft loss, haematoma, successfully revised arterial/venous anastomosis failure and dehisence pooled across the studies was 13.5%. A more detailed description reveals the rate being highest with local intrinsic muscle flaps and local random flaps (19.6% and 19.3% respectively) and lowest with STSG (7.5%) whilst the rate is 18.5% with regional flaps and 14% with free tissue transfer. The major complications rate e.g. major flap necrosis/graft loss and amputations (TMA, below knee and above knee amputation) was 13.1% (9.2-16.7, CI 95%). A deeper review shows that skin grafting was associated with the highest incidence rate of major complications (26%), specifically major graft loss (24% of all operated cases) requiring additional reconstructive procedure, while the lowest incidence of major complications was associated with local random and intrinsic muscle flaps (3.2% and 3.9% respectively). Finally, Incidence rate of major complications following regional flaps and free tissue transfer was 8.6% and 7.2% respectively. In-hospital mortality was reported in 4 studies only. In all of these studies, free tissue transfer was the reconstructive modality utilized. 30-day mortality was 2.9%. No postoperative mortality was reported in the remaining studies where other surgical modalities were used. Taken in consideration the preoperative associated comorbidities in the diabetic patients e.g. ischemic heart disease or uremia which commonly complicate the disease, and are significantly higher among patient underwent free flap reconstruction of the foot wound, the postoperative mortality rate must be cautiously interpreted as these comorbidities contribute to the risk of postoperative mortality. **Conclusion:** Reconstruction of the diabetic foot ulcers should be based on the patient's overall medical status and local wound condition.

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**Key words:** Surgical modalities, reconstruction, soft tissue defects, diabetic foot ulcers

## 1. Introduction

Diabetic patients' feet are prone to development of dreadful complications including infected simple ulcers and up to osteomyelitis and gangrene. Improvements in the diagnosis and treatment of diabetes mellitus and its complications have allowed the patients to have better quality of life. It is well established that about 25% of people with diabetes develop a foot ulcer during their lifetime and 20% of all diabetic patients who enter the hospital are admitted for foot problems ***(Colen, 1994)***.

The etiology and risk factors of a diabetic wound is generally attributable to the triad of neuropathy, Ischemic changes and increased susceptibility to infections. Neuropathy plays the major role in the development of diabetic foot ulcers through decreased protective pain sensation and impaired balance secondary to poor proprioception resulting from sensory neuropathy as well as decreased trophic factors. Motor neuropathy causes intrinsic muscle wasting in the foot, while autonomic neuropathy causes alteration of the blood flow with arteriovenous shunting and distended foot veins. Minor traumas to the foot (e.g. ill- fitting shoes) which are repetitive due to foot deformities caused by joint stiffness and decreased range of motion attributed to glycation of soft tissues worsen the condition as they pass unnoticed due to loss of the protective sensation and

poor vision because of retinopathy and also abnormal foot arches with changes in pressure points ***(Reiber et al., 1999)***.

The evaluation and classification of diabetic foot ulcers are essential in order to organize the appropriate treatment plan and follow up. During the past years, several foot-ulcer classification methods have been proposed, however, none of the proposals have been universally accepted. The University of Texas system grades the ulcers by depth and then stages them by the presence or absence of infection and ischemia. More specifically, grade 0 in the Texas System classification represents a pre- or postulcerative site. Grade 1 ulcers are superficial wounds through either the epidermis or the epidermis and dermis without penetrating to tendon, capsule or bone. Grade 2 wounds penetrate to tendon or capsule, but the bone and joints are not involved. Grade 3 wounds penetrate to bone or into a joint. Each wound grade is subdivided into 4 stages: clean wounds (A), non ischemic infected wounds (B), ischemic wounds (C), and infected ischemic wounds (D) ***(Armostrong et al., 1998).***

Similarly, the International Working Group on the Diabetic Foot has proposed the PEDIS classification which grades the wound on a 5-feature basis: perfusion, extent, depth, infection, and sensation. Finally, according to the Infectious Diseases Society of America guidelines, the infected diabetic foot is subclassified into the categories of mild (restricted involvement of only skin and subcutaneous tissues), moderate (more extensive or affecting deeper tissues), and severe (accompanied by systemic signs of infection or metabolic instability) ***(Lipsky et al., 2012)***.

Treatment cornerstones for diabetic foot ulcers include general measures done in all patients as pressure offloading, cleanliness of the feet and keeping them dry, avoiding excessive trimming of the nails, wearing comfortable, well fitting or custom made shoes in addition to control of diabetes keeping random blood sugar below 200mg / dl and glycated hemoglobin (HBA1c) less than 6 mg /dL as well as using antiplatelet medications. Surgical management includes debridement (the most important measure in wound bed preparation) and wound closure according to the reconstructive ladder beginning from simple dressings till wound healing by secondary intention, split thickness skin grafts, local fasciocutaneous flaps (advancement, rotational or transpositional flaps), regional flaps (e.g. reversed hemisoleus muscle flap, distally based sural flap & medial plantar artery flap) ending with free tissue transfer. ***(Attinger et al., 2006).***

Also the role of vascular surgery is of vital importance for correcting arterial ischemia resulting from the co-existing PAD in diabetic patients. Hence, improving healing power and lowering the risk for further foot ulceration or recurrence. This may include angioplasty & vascular stenting as well as arterial bypass procedures ***(Norgren et al., 2007).***

**Aim of the Work**

The aim of this study is to compare between different surgical options for reconstruction of soft tissue losses in the feet of diabetic patients. Highlighting the effectiveness, postoperative complications and mortality.

## 2. Patients and Methods

**Criteria for considering studies for this review**

**Types of studies**

The review will be restricted to clinical trials or case series studies that discuss different reconstructive surgical techniques for coverage of diabetic foot ulcers from 1998 to 2018.

**Types of participants**

Adult Diabetic patients who developed foot ulcers with soft tissue defects managed by any of the available reconstructive surgical modalities.

**Types of interventions:**

Different surgical techniques used for closure of diabetic foot wounds including split thickness skin grafts, local flaps, intrinsic muscle flaps, regional flaps, perforator flaps and free tissue transfer.

**Types of outcome measures**

***Outcome will be measured in terms of:***

1. Success rate, where success is defined as achievement of complete healing and wound closure without development of any major complication or the need for additional reconstructive procedure.
2. Types and numbers of early postoperative complications encountered.
3. Average time to complete wound healing.
4. Average hospital stay.
5. Post operative mortality rate.

**Search strategy for identification of studies**

- A systematic review of literature was performed to find all studies related to the different surgical techniques used for reconstruction of diabetic foot wounds. The search was conducted using the following electronic data bases: Web-science, EMBASE, Medline/Pubmed, Scopus and Ovid.
- The following search terms were used: Diabetes, foot, wounds, ulcers, neuropathy, skin grafts, local random flaps, intrinsic muscle flaps, pedicled flaps, regional flaps, perforator flaps, free tissue transfer. Other studies were identified from the cited references during bibliography search of reviewed articles. The reviewers then compared the collected articles for application of inclusion and exclusion criteria. The flow diagram in (figure 20) illustrates the search algorithm.

**Inclusion criteria**

Studies in English language., Clinical trials and case series studies done on human subjects., Studies published from 1998 to 2018 (inclusive of the last 20 years)., Patients with diabetes mellitus treated for foot wounds., Use of any reconstructive surgical modality to achieve coverage., Documentation of the healing rates, complications and the need for revisional surgeries., Follow up period of 6 months or more.

**Exclusion criteria**

1. Studies that were entirely literature reviews, technical descriptions or case report studies.
2. Cadaveric studies.
3. Studies involving non human subjects.
4. Studies of reconstruction of foot wounds in non-diabetic patients.
5. Studies of reconstruction of lower leg ulcers.

**Methods of the review**

**Locating and selecting studies:**

Abstracts of articles identified using the search strategy above will be reviewed, and articles that appear to fulfill the inclusion criteria will be retrieved in full data on at least one of the outcome measures must be included in the study. When there will be a doubt, a second reviewer will assess the article and a consensus will be reached and the process will be presented in a PRISMA flow chart and according to the PRISMA statement.

**Data extraction:**

Two review authors will independently extract the data from eligible studies using a standardized data extraction form. Any duplicated studies will be removed.

**Table (1):** Studies included in the review showing authors, years and reconstructive modalities used (ALT = Antero-lateral thigh, DIEP = deep inferior epigastric perforator flap, STSG = split thickness skin graft)

| No. | Study | Reconstructive modality |
|---|---|---|
| 1 | Cohen et al 1999 | Med. Plantar a. flap |
| 2 | Attinger et al 2002 | Abd. Digiti minimi, Abd. Hallucis, Flexor digitorum brevis, Extensor digitorum brevis and Extensor digiti minimi M. flaps |
| 3 | Moucharrafieh et al 2003 | Free Rectus abdominis M., radial forearm and Latissimus dorsi M. flaps |
| 4 | Yetkin et al 2003 | Bilobed flap |
| 5 | Verehelle et al 2004 | Free radial forearm, Latissimus dorsi M, serratus Ant. M, Tensor fascia lata M. and temporal fasciocutaneous flaps |
| 6 | Ozkan et al 2005 | Free ALT, radial forearm, Tensor fascia lata M., Gracilis M., Lat. Arm, parascapular and DIEP flaps |
| 7 | Demirie et al 2006 | Med. Plantar a., Lat. supramalleolar and reverse sural a. flaps |
| 8 | Hong et al 2006 | Free ALT. flap |
| 9 | Kim et al 2007 | Free ALT. flap |
| 10 | Mahmoud et al 2008 | STSG. |
| 11 | Randon et al 2009 | Free Rectus abdominis M., ALT., Latissimus dorsi M., Serratus Ant. M., and Lat. arm flaps |
| 12 | Ramanujam et al 2010 | STSG. |
| 13 | Roukis et al 2010 | V-Y advancement flap |
| 14 | Alexandru V et al 2012 | Peroneal a., Post. Tibial a. and Ant. Tibial a. perforator flaps |
| 15 | Altindas et al 2013 | Abd. Digiti minimi M. flap |
| 16 | Rose et al 2014 | STSG. |
| 17 | Shirol et al 2014 | Abd. Digiti minimi M flap |
| 18 | Lin et al 2015 | Bipedicled flap |
| 19 | Sato et al 2015 | Med. Plantar a. flap |
| 20 | Carvaggi et al 2016. | Square random fasciocutaneous flap |
| 21 | Rodriguez et al 2017 | Abductor Hallucis M. flap |

**Statistical considerations:**

Outcomes from included trials will be combined using the Review Manager software ®. Data will be abstracted from every study in the form of a risk estimate and its 95% confidence interval (CI). Pooled risk estimate will be obtained by weighing each study by the inverse variance of the effect measure on a logarithmic scale. When a risk estimate and its 95%

confidence interval were not available from the article, we calculated unadjusted values from the published data of the article, using SPSS ver. 20.0. This approach to pooling the results assumes that the study populations being compared are similar and hence corresponds to a fixed effect analysis. The validity of pooling the risk estimates will be tested (test of homogeneity) using a chi-square test. A violation of this test implies that the studies being grouped differ from one another. In the presence of significant heterogeneity of the effect measure among studies being compared, we will perform a random effect analysis that is based on the method described by Der Simonian and Laird (1986). The random effect analysis accounts for the interstudy variation because the test of homogeneity has low power.

**Evidence of publication bias:**

Risk of bias for individual studies will be made according to The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions.

## 3. Results

**Table (2):** Patients' demographic characteristics in all studies (IHD= ischemic heart disease, HTN= hypertension, ESRD= end stage renal disease).

| No. | Study | Total / No. Pts | Gender | | Mean Age (yrs) | Comorbidities |
|---|---|---|---|---|---|---|
| | | | Males | Females | | |
| 1 | Cohen et al. 1999 | 33 | 15 | 18 | 55 | Uremia (N=5) |
| 2 | Attinger et al. 2002 | 19 | 14 | 5 | 56 | HTN (N=15)<br>IHD (N=10)<br>Uremia (N= 5) |
| 3 | Moucharrafieh et al. 2003 | 10 | 9 | 1 | 62.3 | No comorbities |
| 4 | Yetkin et al. 2003 | 12 | 7 | 5 | 50 | Not reported |
| 5 | Verehelle et al. 2004 | 19 | 15 | 4 | 59 | IHD (N=4)<br>Hypertension (N= 6) |
| 6 | Ozkan et al. 2005 | 13 | 12 | 1 | 55.4 | IHD (N=4)<br>Uremia (N=1) |
| 7 | Demirie et al. 2006 | 18 | 15 | 3 | 63.7 | Not reported |
| 8 | Hong et al. 2006 | 71 | 50 | 21 | 51.4 | Not reported |
| 9 | Kim et al. 2007 | 16 | 12 | 4 | 62.8 | Not reported |
| 10 | Mahmoud et al. 2008 | 50 | 29 | 21 | 51 | No comorbidities |
| 11 | Randon et al. 2009 | 76 | 60 | 16 | 65.5 | Cardiac problems (N= 38)<br>Uremia (N= 31) |
| 12 | Ramanujam et al. 2010 | 83 | 64 | 19 | 52 | Not reported |
| 13 | Roukis et al. 2010 | 16 | 12 | 4 | 64 | IHD (N= 6 of which 3 have congestive heart failure) |
| 14 | Alexandru et al. 2012 | 24 | 19 | 5 | 69.1% | IHD (N=21) |
| 15 | Altindas et al. 2013 | 17 | 9 | 8 | 61.5 | Not reported |
| 16 | Rose et al. 2014 | 66 | 45 | 21 | 59.8 | Not reported |
| 17 | Shirol et al. 2014 | 8 | 6 | 2 | 53.3 | Not reported |
| 18 | Lin et al. 2015 | 11 | 9 | 2 | 48.8 | HTN (N=3) |
| 19 | Sato et al. 2015 | 4 | 3 | 1 | 44.7 | ESRD on hemodialysis (N= 3) |
| 20 | Carvaggi et al. 2016 | 23 | 20 | 3 | 62 | IHD (N=8)<br>Uremia (N=3) |
| 21 | Rodriguez et al. 2017 | 5 | 3 | 2 | 48 | Not reported |
| | | 594 | 428 | 166 | | |

A total of 21 selected papers gave details on 600 reconstructive procedures for soft tissue coverage in a combined total of 594 patients. All patients were diabetic where described; mean average is used along with 95% confidence intervals. Study sizes ranged from 4 to 83 cases. The largest study accounts for 13.9% of all patients ***(Ramanujam et al 2010),*** a total of 83 cases. twenty of the included studies are prospective studies. Table (3) shows the studies included in this review and the reconstructive modalities used in each study.

**Patient characteristics**

From the 21 studies there were 594 patients with a mean age of 57.3 yrs (range from 44.7- 69.1 yrs). 72% of all patients were males. Follow up ranged from 10 m to 32m, whilst the average hospital stay varied with the different reconstructive modalities used, being a round 5.5wks with free tissue transfer, 1.6wks with local flaps and 1 wks with skin grafts. Average hospital stay was not reported in studies utilizing regional flaps for coverage. There was little data on type of diabetes (I or II) and insulin use. patients across all studies were chosen on the basis of having chronic non healing foot or ankle ulcers. Nine

studies **(1, 4-7, 11, 15, 19, 20)** specifically mentioned failure of conservative management and wounds which showed no signs of healing following thorough debridement and standard of care. Table (4) shows patients' characteristics in the aforementioned studies commenting on total number of participant patients, patients' gender, mean age and associated comorbidities.

**Table (3):** Preoperative Assessment (ABPI = ankle brachial pressure index, TCPO2 = transcutaneous oxygen tension, HBA1C = hemoglobin A1C or glycated hemoglobin)

| No. | Study | Microbiology swabs for C & S | Angiography | U/S duplex | Foot X-ray | CT angio | PET bone scan | ABPI | TCPO2 | HBA1c level |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Cohen et al. 1999 | | ✓ | | | | | ✓ | | |
| 2 | Attinger et al. 2002 | ✓ | ✓ | | | | | | ✓ | |
| 3 | Moucharrafieh et al. 2003 | ✓ | ✓ | | ✓ | | ✓ | | | |
| 4 | Yetkin et al. 2003 | Not report | | | | | | | | |
| 5 | Verehelle et al. 2004 | ✓ | ✓ | | | | | | | |
| 6 | Ozkan 2005 | | ✓ | ✓ | ✓ | | ✓ | | | |
| 7 | Demirie 2006 | | ✓ | ✓ | | | | ✓ | | |
| 8 | Hong 2006 | ✓ | ✓ | | | | ✓ | | ✓ | ✓ |
| 9 | Kim 2007 | ✓ | | ✓ | ✓ | ✓ | ✓ | | | |
| 10 | Mahmoud et al. 2008 | ✓ | | | | | ✓ | | | |
| 11 | Randon 2009 | | ✓ | | | | | | | |
| 12 | Remanujam et al. 2010 | ✓ | | ✓ | | | ✓ | | | ✓ |
| 13 | Roukis et al. 2010 | | | | | | ✓ | | | |
| 14 | Alexandru et al. 2012 | ✓ | ✓ | ✓ | | | | | | |
| 15 | Altindas et al. 2013 | ✓ | | | | | | | | |
| 16 | Rose et al. 2014 | Not report | | | | | | | | |
| 17 | Shirol et al. 2014 | | | | ✓ | ✓ | | | | |
| 18 | Lin et al. 2015 | | ✓ | | | | ✓ | | | |
| 19 | Sato et al. 2015 | ✓ | | ✓ | | | | | ✓ | |
| 20 | Carvaggi et al. 2016 | ✓ | ✓ | | | | | | ✓ | |
| 21 | Rodriguez et al. 2017 | Not report | | | | | | | | |

**Table (4):** Locations of defects.

| No. | Study | Planter | Heel | TMA stump | Dorsum | Ankle | Dorsum + ankle | Foot lateral | Foot medial | Planter + heel | Achiles |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Cohen et al. 1999 | **26** | **8** | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 2 | Attinger et al. 2002 | **9** | **10** | 0 | 0 | **2** | 0 | 0 | 0 | 0 | 0 |
| 3 | Moucharrafieh et al. 2003 | Not report | | | | | | | | | |
| 4 | Yetkin et al. 2003 | **8** | **4** | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 5 | Verehelle et al. 2004 | 0 | **13** | **4** | **2** | 0 | 0 | 0 | 0 | 0 | 0 |
| 6 | Ozkan et al. 2005 | Not report | | | | | | | | | |
| 7 | Demirie et al. 2006 | | **9** | | **2** | **4** | 0 | **3** | | | |
| 8 | Hong et al. 2006 | Not report | | | | | | | | | |
| 9 | Kim et al. 2007 | **2** | **4** | | **3** | **1** | 0 | **6** | 0 | 0 | 0 |
| 10 | Mahmoud et al. 2008 | **11** | **8** | **9** | **16** | **6** | 0 | 0 | 0 | 0 | 0 |
| 11 | Randon et al. 2009 | 0 | 0 | **34** | **12** | **9** | | | 0 | **23** | 0 |
| 12 | Remanujam et al. 2010 | **33** | 0 | 0 | **13** | **1** | **0** | **19** | **17** | 0 | 0 |
| 13 | Roukis et al. 2010 | **3** | | 0 | **1** | 0 | 0 | **2** | **10** | 0 | 0 |
| 14 | Alexandru et al. 2012 | **3** | **6** | **2** | 0 | **12** | 0 | **2** | 0 | 0 | 0 |
| 15 | Altindas et al. 2013 | **4** | **13** | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 16 | Rose et al. 2014 | **49** | | 0 | 0 | 0 | **17** | 0 | 0 | 0 | 0 |
| 17 | Shirol et al. 2014 | | **6** | 0 | | 0 | 0 | **2** | 0 | 0 | 0 |
| 18 | Sato et al. 2015 | **4** | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 19 | Lin et al. 2015 | | **4** | 0 | | 0 | 0 | 0 | 0 | 0 | **7** |
| 20 | Carvaggi et al. 2016 | **21** | **2** | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 21 | Rodriguez et al. 2017 | 0 | 0 | 0 | **5** | 0 | 0 | 0 | 0 | 0 | 0 |

**Inclusion and exclusion criteria:**

As mentioned before. All patients had chronic non healing foot or ankle ulcers. Only 6 studies reported specific inclusion or exclusion criteria, ***Hong et al 2006***; reported good glycemic control and control of infection (Bacterial count < $10^5$ /ml in wound swabs) as criteria of inclusion. ***Verehelle et al 2004*** included previously ambulant revascularizable cases with peripheral arterial disease and complex foot wounds with minimal general health problems. ***Carvaggi et al 2016*** included cases with grade 2 or 3 (Texas classification) uninfected neuropathic plantar

ulcers and excluded ulcers showing signs of infection. Ankle brachial pressure index > 0.8 was a prerequisite for inclusion in the study of ***Roukis et al 2010***. ***Rose et al 2014*** excluded all wounds due to Antecedent trauma or fasciotomy. ***Mahmoud et al 2008***. Included only cases with foot ulcers ≥ $2cm^2$ size and ankle brachial pressure index ≥ 0.4 and excluded all cases associated with medical comorbidities (e.g., heart failure, uremia, liver disease or recent myocardial infarction) and cases with exposed bones, osteomyelitis or underlying wound infection with B-hemolytic streptococci in recent wound cultures.

**Wound characteristics**

None of the included studies except (Carvaggi et al.) used validated wound scoring system for the perioperative assessment of wounds making a true comparison of the included studies difficult. Eighteen of the included studies gave information on the location of wounds treated (**1, 2, 4-7, 9-21).** Description of wound location was given for 501 patients. 34.5% of the wounds treated were on the plantar aspect, 17.5% were heel defects, 9.7% were on trans metatarsal amputation stump, 8.3% were dorsal foot wounds, 6.8% were located over the lateral aspect, 6% were ankle defects, 5.7% were involving dorsal midfoot and ankle, 5.5% were medial foot wounds, 4.5% of the defects involved plantar midfoot and heel and 1.5% of the ulcers were located on achiles tendon. Table (6) shows specific locations of the defects in the studies included.

**Table (5):** Specific types of free flaps in included studies (DIEP= deep inferior epigastric perforator flap, tensor FL= Tensor fascia lata, LD- Latissimus dorsi, Radial FA= Radial Forearm, ALT= Anterolateral thigh).

| Study | ALT | Rectus | Radial FA | LD | Serratus | Tensor FL | Gracilis | Lat. arm | Scapular | Parascapular | DIEP | Temporal FC |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Moucharafieh et al. 2003** | 0 | **7** | **1** | **1** | 0 | 0 | 0 | 0 | **1** | 0 | 0 | 0 |
| **Verehelle et al. 2004** | 0 | 0 | **9** | **3** | **4** | **1** | 0 | 0 | 0 | 0 | 0 | **1** |
| **Ozkan et al. 2005** | **5** | 0 | **3** | 0 | 0 | **1** | **1** | **1** | 0 | **1** | **1** | 0 |
| **Hong et al. 2006** | **71** | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| **Kim et al. 2007** | **16** | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| **Randon et al. 2009** | **4** | **59** | 0 | **10** | **2** | 0 | 0 | **3** | 0 | 0 | 0 | 0 |

**Table (6):** Regional flaps utilized in the included studies.

| Study | Med. Plantar a. | Peroneal a. perforator | Post. Tibial a. perforator | Lat. Supramalleolar. | Reverse sural | Ant. Tibial a. perforator |
|---|---|---|---|---|---|---|
| **Cohen et al. 1999** | **34** | 0 | 0 | 0 | 0 | 0 |
| **Demirie et al. 2006** | **4** | 0 | 0 | **9** | **5** | 0 |
| **Alexandruv et al. 2012** | 0 | **15** | **9** | 0 | 0 | **1** |
| **Sato et al. 2015** | **4** | 0 | 0 | 0 | 0 | 0 |

Presence of osteomyelitis of the underlying bones (prior to debridement and reconstruction) was reported in 51% of the patients underwent free tissue transfer for coverage, 5% of patients with regional flap coverage and 59% of the patients with ulcers covered by intrinsic muscle flaps. No associated osteomyelitis was reported in any of the cases managed by local random flaps or split thickness skin grafts. Conversely, two of the studies utilizing local fasciocutaneous flaps or skin grafts reported the presence of any sign of infection or osteomyelitis as exclusion criteria for the cases. (15, 21)

Regarding defect size, only 16 of the included studies reported the average size of the defects to be reconstructed (1-4, 7-9, 13-21). The pooled mean size of defects covered by free flaps was 87.4 cm whilst the mean size of defects covered by regional flaps equal 56.8 cm. ulcers covered by intrinsic muscle flaps measured 5 cm on average, whilst those covered by local flaps were of 7 cm average size. Finally, with skin graft coverage, the average size was 53.7 cm.

**Reconstructive techniques**

All studies used single reconstructive modality for coverage of all wounds in the included patients. All studies described the specific types and numbers of reconstructive procedures performed. Free tissue transfer was used in 6 studies (3, 5, 6, 8, 9, 11) for coverage of 206 wound accounting for 34.3% of all procedures, whilst regional flaps were the chosen modality in 4 studies (**1, 4, 7, 18**) including 81 ulcers accounting for 13.5%. local fasciocutaneous flaps were used in 4 studies (4, 13, 18, 20) for closure of 62 wounds representing 10.3% of all cases, whilst intrinsic muscle flaps were used in 4 studies (2, 15, 17, 21) accounting for 8.5% of all reconstructive procedures. 3 studies (10, 12, 16) documented the use of Split thickness skin grafts for coverage of 199 ulcers representing 33.2% of the total number of

procedures carried out. Free ALT flap was the commonest among all free flaps done (48% of all free tissue transfer), whilst medial plantar artery was the most common regional flap utilized (34%). Abductor digiti minimi muscle flap represented the majority of all intrinsic muscle flaps (72%) and square random fasciocutaneous flap was the most commonly used local random flap representing 37%.

More detailed description of the types and numbers of all reconstructive techniques involved is shown in tables (7, 8 & 9)

**Mortality rate**

In-hospital mortality was reported in 4 studies (1,2,5,6). In all of these studies, free tissue transfer was the reconstructive modality utilized. 30-day mortality was 2.9%. No post operative mortality was reported in the remaining studies where other surgical modalities were used.

**Table (7):** Local fasciocutaneous and intrinsic muscle flaps involved.

| Study | Abd. Digiti minimi | Abd. Hallucis | Flexor digitorum brevis | Extensor digitorum brevis | Flexor digiti minimi | Square random FC | V-Y advancement | Biloped | Bipedicled |
|---|---|---|---|---|---|---|---|---|---|
| Attinger et al. 2002 | **12** | **5** | **2** | **1** | **1** | 0 | 0 | 0 | 0 |
| Yetkin et al. 2003 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | **12** | 0 |
| Roukis et al. 2010 | 0 | 0 | 0 | 0 | 0 | 0 | **16** | 0 | 0 |
| Altindas et al. 2013 | **17** | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Shirol et al. 2014 | **8** | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Lin et al. 2015 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | **11** |
| Carvaggi et al. 2016 | 0 | 0 | 0 | 0 | 0 | **23** | 0 | 0 | 0 |
| Rodriguez et al. 2017 | 0 | **5** | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

**Table (8):** Early post operative complications.

| Total no of procedures | Major complications | | Minor Complications | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Significant/ total flap necrosis / graft loss | Amputations TMA, BKA or AKA | Infection | Hematoma | Dehiscence | Anastomosis failure (art/venous) with successful revision | Marginal/ partial flap necrosis or graft loss | Others |
| Free tissue transfer (N= 207) | N = 4(1.93%) | N = 11 (5.3%) | N = 4 (1.93%) | N = 3 (1.44%) | N = 3 (1.44%) | N = 3 (1.44%) | N = 8 (3.86%) | Skin graft loss (N = 7) 3.3%<br>Donor site infection (N = 1) 0.44% |
| Regional flaps (N= 81) | N = 2 (2.4%) | N = 6 (6.23%) | N = 2 (2.4%) | 0 | 0 | 0 | N = 11 (13.5%) | Osteomyeltis (N = 2) 2.4% |
| Intrinsic m. flaps (N= 51) | 0 | N = 2 (3.9%) | 0 | 0 | N = 4 (7.8%) | 0 | N = 1 (1.9%) | Skin graft loss (N = 4) (7.8%)<br>Sural n. neuroroathy (N = 1) (1.9%) |
| Local random flap (N= 62) | 0 | N = 2 (3.2%) | N = 1 (1.6) | 0 | N = 10 (16.1%) | 0 | 0 | Transfer ulceration (N = 1) (1.6%) |
| Split thickness skin grafts (N= 199) | N = 48 (24.1%) | N = 4 (2%) | N = 6 (3%) | 0 | 0 | 0 | N = 7 (3.5%) | Donor site infection (N = 2) (1%) |

**Complication rate**

The minor complications rate such as wound infection, minor/marginal flap necrosis/ graft loss, haematoma, arterial/venous anastomosis failure (requiring surgical revision and dehisence pooled across the studies was 13.5%. More detailed description revealed the variation in the minor complications according to the reconstructive modality used, being highest with local intrinsic muscle flaps and local random flaps (19.6% and 19.3% respectively) and lowest with spilt thickness skin graft (STSG) (7.5%) whilst the rate is 18.5% with regional flaps and 14% with free tissue transfer. Dehiscence was the most common minor complication encountered with the local random and intrinsic muscle flaps (16% and 8% of all operated cases respectively developed wound dehiscence in the post operative period) while minor/marginal flap necrosis represented the majority of minor complications following reconstruction by regional flaps or free tissue transfer (13.5% and 4% respectively of all patients included).

The major complications rate e.g. Complete/major flap necrosis/graft loss and amputations (transmetatarsal amputation, below knee and above knee amputation) was 13.1% (9.2-16.7, CI 95%). A deeper review shows that skin grafting was associated with the highest incidence rate of major complications (26%), specifically complete/major graft loss (24% of all operated cases) requiring additional reconstructive procedure, while the lowest incidence of major complications was associated with

local random and intrinsic muscle flaps (3.2% and 3.9% respectively). Finally, Incidence rate of major complications following regional flaps and free tissue transfer was 8.6% and 7.2% respectively (Table 10).

**Success rate:**

Success was defined as complete flap survival or skin graft take without development of any major complication indicating additional reconstructive procedure or major limb amputation. The combined average success rate for free flaps was 91.9% (ranging from 78.5 - 97.1, confidence interval 95%). Infection was the predominant cause for early flap loss. Of the successful flaps primary patency was achieved in 89%. The remaining flaps were successfully revised to achieve secondary patency. Reasons for a return to theatre included haematoma, arterial and venous anasto- mosis revision and partial flap necrosis requiring debridement.

The pooled average success rate for regional flaps was 90% (ranging from 82.3 – 100, confidence interval 95%) of which 80.8% achieved primary success, while the remaining flaps required revisional surgeries most commonly due to superficial/marginal flap necrosis indicating debridement with or without skin grafting. The mean average success rate for intrinsic muscle flaps was 95% (ranging from 88 – 100, confidence interval 95%) of which 91.8% were primarily successful and the remaining required minor surgical revision for dehiscence. For Local random flaps, the combined average success rate was 96.7% (ranging from 87.5 – 100, confidence interval 95%) of which 91.6% achieving primary success and the remaining achieved success after revisional surgeries for dehiscence. Finally, 73.8% of the split thickness skin grafts done were successful with none of them requiring surgical revision. There was no indication as to the number of returns to theatre each of the successfully revised cases required, nor was there any data available on the time perspective for the flaps and grafts which did fail.

**Table (9):** Success rate, post operative mortality.

| Reconstructive | Success rate | Post operative mortality rate |
|---|---|---|
| Free tissue transfer (207) | 92% | 2.9 % |
| Regional flaps (81) | 90% | 0% |
| Intrinsic m flaps (51) | 95% | 0% |
| Local random flaps (62) | 96.7% | 0% |
| Split thickness skin graft (199) | 73.84% | 0% |

## 4. Discussion

This systematic review has demonstrated that excellent rates of wound healing and limb preservation are achievable in highly specialized units using reconstructive surgical procedures in selected patients with diabetes and neuropathic or neuroischemic foot and ankle wounds. Although several systematic review studies were performed to analyze clinical studies carried out to detect the outcomes and effectiveness of the different surgical reconstructive techniques, none of these studies compared between more than one modality of reconstruction in diabetic foot ulcers.

This review aimed to estimate the prospective outcomes following surgical reconstruction of the diabetic foot wounds. This includes the success and failure rates, rate of post operative complications and post operative mortality rate. The pooled success rates of free flaps, regional flaps, intrinsic muscle flaps and local random flaps were 92%, 90%, 95% and 96.7% respectively. The difference between these values was statistically insignificant. However, the pooled success rate of skin graft coverage in diabetic foot was 74% indicating a statistically significant difference between skin grafting and other modalities of reconstruction.

These values of mean average success estimated in this study are comparable to the published systematic review studies performed on diabetic foot reconstruction and limb salvage. ***O'Connor et al. (2010)*** performed the largest systematic review of all clinical studies utilizing free flaps for coverage of lower limb defects in diabetic patients including 528 patients from 18 studies. Of the flaps that failed, infection was the predominant cause. Given the rate of preoperative osteomyelitis in the studies of 47%, the risk of residual deep seated infection is likely to have contributed to this source of flap failure. All efforts at eradication of osteomyelitis should be viewed as a priority, either via the use of surgery or antibiotics.

***Ramanujam et al. (2018)*** reviewed all published articles about soft tissue reconstruction of diabetic foot and ankle wounds using local muscle flaps, a total of 13 selected studies used for data extraction from a total of 113 patients in which 92 local intrinsic muscle flaps were performed for lower limb reconstruction in diabetic patients, of which 87% muscle flaps demonstrated success where success was defined as achievement of complete wound closure without the development of any major or minor complication.

Although the literature in this area is sparse, ***McCartan and Dinh*** performed a meta-analysis of the few available publications on STSG placement for diabetic wounds. They computed a graft take rate of >90% in 78% of patients by 8 weeks and therefore recommended it as a viable option in wound care.

Although local random flaps have been used in reconstructive surgery for centuries, the first case series demonstrating their use in diabetic foot wounds was published by ***Colen et al. in 1988***. In 2018, ***Ramanujam and Zgonis*** published a systematic review of the available publications to assess the outcomes of the use of local random flaps for soft tissue closure in diabetic foot wounds including 25 studies used for data extraction about 512 patients in which 199 of these underwent 204 local random flap procedures. Successful wound closure at last follow-up was demonstrated in 75.5%.

When it comes to the postoperative lower limb amputation rate, regional flaps were associated with the highest rate (6.2%) followed by free flaps (5.3%) and intrinsic muscle flaps (3.9%). whilst local random flaps and split thicknesss skin grafts were associated with a significantly lower rate of post operative amputations, being 3.2% and 2% respectively. The participants from all included studies show variability regarding the presence of peripheral arterial disease or osteamyelitis and their severity and hence, lack of matching of the study population in these elements limits the ability to draw certain conclusions.

As for the minor complications rate, A detailed description demonstrates the variation in the rate according to the reconstructive modality used, with the highest rate associated with local intrinsic muscle flaps and local random flaps (19.6% and 19.3% respectively) and lowest with STSG (7.5%) whilst the rate is 18.5% with regional flaps and 14% with free tissue transfer. The difference in the rate of minor complications between skin grafting and the other modalities is statistically significant (p. value < 0.05)

Dehiscence was the most common minor complication encountered with the local random and intrinsic muscle flaps (16% and 8% of all operated cases respectively) while minor/marginal flap necrosis represented the majority of minor complications following reconstruction by regional flaps or free tissue transfer (13.5% and 4% respectively of all patients included). The majority of these complications did not require further surgical intervention and were managed conservatively with aggressive local wound care, oral antibiotic therapy, and off-loading. In addition, some patients underwent concomitant surgical procedures such as bone resection and/or deformity correction, which may have affected outcomes, specifically affecting the flap success and complication rates.

Studies in our systematic review agreed that in the use of any pedicled muscle flap, an essential requirement was a healthy vascular bed at the recipient site. Medical optimization of the patient with diabetes is essential for the patient's successful recovery. In addition, appropriate staged, surgical debridement to remove any infected or nonviable soft tissue and bone, culture-guided antibiotic therapy, and thorough vascular assessment to ensure perfusion at the donor and recipient sites are vital components in restoring any soft tissue and/or osseous wounds of the foot and ankle in patients with diabetes. Careful consideration of any underlying deformity, biomechanical alterations and precise surgical dissection, with or without the use of external fixation as an adjunct for surgical offloading, are some of the key elements for providing long-term successful outcomes.

Interestingly only 2 of the 21 studies included the criterion that patients must have no major systemic illness ***(Verehelle et al., 2004; Mahmoud et al., 2008).*** Renal disease is an identified risk factor in free flap failure ***(Colen et al., 1988)***. Renal failure was mentioned specifically in 6 of the 21 studies. One study demonstrated that renal failure was a strong predictor of limb loss ***(Randon et al., 2009).*** In the cohort of patients under examination, however, these comorbidities are widely prevalent and so total exclusion would leave you with a very small treatable population.

Although our systematic review provides collective information and outcomes on the surgical reconstruction of foot and ankle wounds in patients with diabetes, it may be limited due to inherent selection bias of the patient populations in the included studies by the authors. Additional limitations include the variability in the patient and wound characteristics, associated medical comorbidities and confounding factors such as adjunctive medical treatments and surgical techniques, which greatly limit an objective analysis and make it difficult to formulate any predictive models for successful surgical reconstruction of the diabetic foot wounds. Furthermore, studies before 1999 were excluded due to lack of extractable data as they omitted important patient and/or procedure related information, including failure to reveal complications and follow-up times that might have had an impact on the reported data.

**Conclusion**

Reconstruction of the diabetic foot ulcers should be based on the patient's overall medical status and local wound condition.

Free tissue transfer achieves successful wound healing in selected patients with diabetes and difficult

to heal wounds (that would otherwise have been treated by amputation) in highly specialized units with microsurgical expertise. Regional flaps (especially perforator based fasciocutaneous flaps from the leg) provide an effective and versatile alternative for reconstruction of moderate sized defects of the foot and ankle especially in old patients with multiple comorbidities who are not candidate for free tissue transfer.

In order to ascertain which patients are likely to benefit from this form of limb saving surgery it is vital to use established scoring systems, when reporting data to allow meaningful analysis.

Pre-operative optimization of the patient's medical condition and vascular supply and eradication of infection is vital to successful diabetic foot ulcer reconstruction.

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