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ARTICLE

Impact of patients' gender on microvascular lower extremity reconstruction

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ABSTRACT

The physiological differences between genders have significant implications for health and disease. With regard to microsurgery, results remain elusive as to whether male or female gender is an independent risk factor for free flap reconstruction. This study evaluated the impact of gender on outcomes of lower-extremity free-flap reconstructions. Within 7 years, 358 patients received 393 microvascular lower limb free flap reconstructions. The cases were divided into two groups according to patients' gender: male vs. female. Retrospective data analysis evaluated patients' demographics, perioperative details, surgical complications and flap outcomes over a 3-month follow-up period. Major and minor surgical complications, including total and partial flap loss, showed no significant differences between the investigated groups ($p>.05$). In addition, there was no significant difference with regard to the rate of surgical revision surgery, or the incidence of arterial and venous thrombosis ($p>.05$). Comparison of different flap types (fasciocutaneous ALT vs. gracilis muscle flaps) and type of anastomosis (end-to-end vs. end-to-side) also revealed no difference in outcomes in respect to gender. In conclusion, gender cannot be regarded as an independent risk factor for free flap reconstructions in patients with lower-extremity defects.

Abbreviations: ASA: American Society of Anesthesiologists; ALT: anterolateral thigh; BMI: body mass index; DM: diabetes mellitus; ELAF: extended lateral arm flap; HLS: hospital length of stay; LDM: latissimus dorsi muscle; min: minutes; n: number; PAD: peripheral arterial disease; SD: standard deviation

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Introduction

Health care has progressed toward personalized medicine and individualized risk factor assessment [1]. This also holds true for microsurgery, where our study group previously assessed several patient-related risk factors with regard to free flap outcome [2–5]. The impact of an important demographic variable, namely gender, has however not been fully appreciated to date.

By nature, gender defines distinct physiological characteristics. Males and females differ significantly on several different levels, including anatomy, cell physiology and endocrine hormone activity. Previous studies have established a relationship between estrogen and testosterone levels and, among others, inflammation, immunology, wound healing and cancer [6–13].

Gender-related differences have also been explored across surgical disciplines with regard to postoperative outcomes and perioperative morbidity [14]. Results differ depending on the surgical procedure performed, or the complications investigated, as to whether male or female gender is a risk factor [15–18]. In line with this, study groups have looked into gender as an independent risk factor in free flap reconstruction, however, results remain elusive. Overall, current literature shows conflicting results and is based on limited patient populations, or pooled data across a broad range of defect locations [19–22]. While a recent study found a link between gender and the severity of free flap complications in head and neck reconstructions [19], there are no current data on a possible gender-related risk associated with free flap outcome in lower limb reconstructions.

To shed further light onto this controversially debated topic, the presented study analyzed a large number of lower extremity reconstructions performed at a single surgical site. Patients were stratified into two groups according to their gender, in order to evaluate gender-related risks for flap outcome.

Materials and methods

Investigated sample

The study population investigated included patients receiving microvascular free flap reconstruction for lower extremity defects. All free flaps were performed at a single surgical site over a period of seven years. Defects requiring reconstruction were caused by trauma, infection or malignancy. Thus, a total of 358 patients receiving 393 free flaps for lower extremity reconstruction were included in the study. No exclusion criteria were defined. The cases were divided into two groups regarding the gender of the patients: male vs. female.

Data analysis

Patients' medical records and hospital files were screened retrospectively. Data analysis included demographics, patient characteristics, perioperative details, postoperative complications, and free flap outcome. Patients' preoperative physiological status was assessed according to the American Society of Anesthesiologists (ASA) Classification of Physical Status [14]. Surgical complications were divided into major and minor complications. Major complications were defined as total flap loss, partial flap loss of more than 10%, as well as revision surgery due to vascular compromise

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(arterial or venous thrombosis) or hematoma. Minor complications were defined as partial flap loss of less than 10%, wound dehiscence, skin graft failure and wound infection. Patients were followed up for three months. A separate analysis was performed for anterolateral thigh (ALT) and gracilis muscle flaps, the most commonly used flap types for defect reconstruction in the study population. Complications were also evaluated with regard to the type of anastomosis utilized (end-to-end vs. end-to-side).

Statistical analysis

Continuous variables are shown as mean and standard deviation (SD). Student's *t*-test was used to determine the significant difference between the various datasets for data with normal distribution. Categorical variables were assessed using the Chi-squared test. *p* Values $\leq$.05 were considered as statistically significant to guide clinically relevant conclusions.

Results

Patient demographics

The 'male' group included 243 patients (mean age: 51.6 (SD: 17.2) years, range 18–88 years) who received 266 free flaps for lower limb reconstruction (Table 1). The 'female' group included 115 patients (mean age: 55.0 (SD: 19.7) years, range: 18–92 years) who received 127 free flaps for lower limb reconstruction. Prevalence of comorbidities such as hypertension, peripheral arterial disease (PAD), diabetes mellitus (DM), obesity (BMI $\geq$30 kg/m^2) and smoking status revealed no significant difference between both groups ($p>$.05). Preoperative ASA scores were comparable between both groups ($p>$.05).

Perioperative details, defect and flap characteristics

The free ALT ($n=161$) and gracilis muscle flap ($n=152$) were used most commonly for defect reconstruction, followed by latissimus dorsi (LDM) muscle flap ($n=32$), groin flap ($n=15$), parascapular flap ($n=14$), vascularized bone flap ($n=12$; fibula, femur, iliac crest) and extended lateral arm flap (ELAF) ($n=7$) (Table 2). Significant differences between both groups with regard to flap type were found for ALT- (male: 45.1% vs. female: 32.3%), groin- (male: 2.3% vs. female: 7.1%) and parascapular flap reconstructions (male: 1.1% vs. female: 8.7%) ($p<$.05). Overall, the type of flap utilized did not differ significantly between the groups in respect to free fascio-cutaneous and free muscle flaps ($p>$.05). Approximately, two-thirds of all lower extremity defects requiring free flap reconstruction resulted from trauma (male: 72.9% vs. female: 77.2%; $p=$.369). The mean time between trauma and surgery was 23.1 (SD 18.4; range 2–66) days. Recipient vessels utilized revealed no significant difference between the 'male' and the 'female' group ($p>$.05). Analysis of flaps dimensions (cm^2),

Table 1. Patient demographics according to patients' gender.

	Male	Female	*p* Value
Number of patients (*n*)	243	115	
Mean age (years)	51.6	55.0	.113
Range of age (years)	18–88	18–92	
SD (years)	17.2	19.7	
Comorbidities (*n*)			
Hypertension	55 (22.6%)	35 (30.4%)	.112
PAD	20 (8.2%)	9 (7.8%)	.896
Diabetes mellitus	31 (12.8%)	18 (15.7%)	.457
Mean BMI (SD)	23.8 (7.33)	24.4 (8.21)	.505
Range BMI	16.1–41.7	15.6–42.2	
Mean ASA (SD)	2.32 (0.79)	2.29 (0.76)	.731
Smoking status (*n*)			
Non smoker	195 (80.2%)	92 (79.1%)	.956
Smoker	48 (19.8%)	23 (20.9%)	

SD: standard deviation; PAD: peripheral arterial disease; BMI: body mass index; ASA: American Society of Anesthesiologists Classification of Physical Status.

Table 2. Flap characteristics and perioperative details according to patients' gender.

	Male	Female	*p* Value
Flap type (*n*)			
ALT	120 (45.1%)	41 (32.3%)	.016
Groin	6 (2.3%)	9 (7.1%)	.019
Parascapular	3 (1.1%)	11 (8.7%)	.000
ELAF	5 (1.9%)	2 (1.6%)	.831
Gracilis	102 (38.3%)	50 (39.3%)	.845
LDM	22 (8.3%)	10 (7.9%)	.893
Vascularized bone[a]	8 (3.0%)	4 (3.1%)	.939
Etiology for free flap			
Trauma	194 (72.9%)	98 (77.2%)	.369
Infection	69 (25.9%)	23 (18.1%)	.086
Malignancies	3 (1.2%)	6 (4.7%)	.026
Recipient vessel			
Anterior tibial artery	110 (41.4%)	64 (50.4%)	.092
Posterior tibial artery	132 (49.6%)	55 (43.3%)	.241
Dorsalis pedis artery	24 (9.0%)	8 (6.3%)	.356
Flap dimension			
Size (cm^2)	192.8	173.3	.184
Range (cm^2)	20–1535	48–700	
SD (cm^2)	177.7	110.4	
Mean operative time (min)	327.4	332.3	.689
Range (min)	60–840	65–693	
SD (min)	110.5	114.9	
Mean ischemic time (min)	56.6	53.3	.253
Range (min)	15–200	25–190	
SD (min)	29.5	25.3	
Hospitalization (days)			
HLS before reconstruction (days)	19.6 (SD 20.3)	19.1 (SD 22.5)	.839
HLS after reconstruction (days)	19.4 (SD 17.9)	19.9 (SD 14.5)	.778
Total flaps (*n*)	266	127	

ALT: anterolateral thigh; ELAF: extended lateral arm flap; LDM: latissimus dorsi; SD: standard deviation; HLS: hospital length of stay.
[a]Fibula, femur, iliac crest.

Table 3. Detailed characteristics of patients requiring reconstruction due to trauma.

Characteristics	Male	Female	*p* Value
Number of patients (*n*)	194	98	
Defect location			
Thigh	11 (5.7%)	7 (7.1%)	.396
Shank	104 (53.6%)	59 (60.2%)	
Foot	79 (40.7%)	32 (32.7%)	
Bone involvement			
Yes	137 (70.6%)	72 (73.5%)	.610
No	57 (29.4%)	26 (26.5%)	
Defect dimension			
Size (cm^2)	131.8	116.7	.231
Range (cm^2)	20–870	25–540	
SD (cm^2)	111.8	95.8	
Flap dimension			
Size (cm^2)	178.5	167.1	.406
Range (cm^2)	40–750	48–700	
SD (cm^2)	105.8	112.9	
Mean operative time (min)	322.5	328.1	.677
Range (min)	60–660	115–693	
SD (min)	105.3	109.7	
Mean ischemic time (min)	57.2	51.9	.120
Range (min)	15–200	25–190	
SD (min)	30.2	25.9	
Type of anastomosis (*n*)			
End-to-end	132 (68.0%)	75 (76.5%)	.132
End-to-side	62 (32.0%)	23 (23.5%)	

SD: standard deviation.

mean operative time (min) as well as mean ischemia time (min) did not show any significant difference between both groups ($p>.05$). Time to ambulation after defect reconstruction was comparable between both genders. Further information on characteristics of patients within the largest etiology group, requiring reconstruction after trauma, are summarized in Table 3.

Postoperative complications

Taken together, major and minor surgical complications showed no significant differences between both groups during the 3-month follow-up period ($p>.05$) (Tables 4–6). Total and partial flap loss >10%, as well as rates of surgical revision surgery were comparable between the groups ($p>.05$). Analysis of reasons for revision surgery revealed no significant difference between both groups ($p>.05$); both groups had similar total percentages of arterial and venous thrombosis as well as bleeding complications ($p>.05$) (Table 4).

Detailed analysis of ALT- and gracilis muscle flaps revealed no differences regarding the rate of major and minor surgical complications as well as total and partial flap loss >10% ($p>.05$) between the 'male' and 'female' group. There was also no significantly different incidence or reason (arterial/venous thrombosis, bleeding) for revision surgery ($p>.05$) (Table 5).

The type of anastomosis (end-to-end vs. end-to-side) was distributed evenly between the 'male' and 'female' group of patients. There were no significant differences in major or minor surgical complications between the groups ($p>.05$) (Table 6).

Table 4. Postoperative complications according to patients' gender.

	Male	Female	*p* Value
Major	76 (28.6%)	36 (28.3%)	.963
Total flap loss	18 (6.8%)	11 (8.7%)	.502
Partial flap loss >10%	9 (3.4%)	6 (4.7%)	.516
Revision surgery	49 (18.4%)	20 (15.7%)	.515
Arterial thrombosis	9 (3.4%)	4 (3.1%)	.906
Venous thrombosis	23 (8.6%)	10 (7.9%)	.796
Hematoma	17 (3.8%)	6 (4.7%)	.510
Minor[a]	28 (10.5%)	15 (11.8%)	.703
Total flaps (*n*)	266	127	

[a]Wound dehiscence, skin graft failure, wound infection and partial flap loss <10%.

Table 5. Postoperative complications according to patients' gender divided between ALT- and gracilis-muscle flaps.

	Male	Female	*p* Value
ALT flaps (*n*)	120	41	
Major	47 (39.2%)	13 (31.7%)	.394
Total flap loss	11 (9.2%)	4 (9.8%)	.911
Partial flap loss >10%	5 (4.2%)	3 (7.3%)	.423
Revision surgery	31 (25.8%)	6 (14.6%)	.141
Arterial thrombosis	5 (4.2%)	2 (4.9%)	.847
Venous thrombosis	16 (13.3%)	5 (12.2%)	.852
Hematoma	10 (8.3%)	2 (4.9%)	.467
Minor[a]	14 (11.7%)	8 (19.5%)	.207
Gracilis flaps (*n*)	102	50	
Major	20 (19.6%)	14 (28.0%)	.243
Total flap loss	5 (4.9%)	5 (10.0%)	.236
Partial flap loss >10%	2 (2.0%)	2 (4.0%)	.461
Revision surgery	13 (12.7%)	7 (14.0%)	.830
Arterial thrombosis	3 (2.9%)	1 (2.0%)	.733
Venous thrombosis	5 (4.9%)	3 (6.0%)	.776
Hematoma	5 (4.9%)	3 (6.0%)	.776
Minor[a]	10 (9.8%)	5 (10.0%)	.970

[a]Wound dehiscence, skin graft failure, wound infection and partial flap loss <10%.

Discussion

Personalized medicine and individualized clinical decision-making aims at tailoring therapeutic approaches to individual patients, by determining their individual risk profile. Studies are evaluating patient related risk factors in various fields of medicine, especially in cancer treatment [23]. But also in microsurgery, patient-specific reconstructive approaches are of increasing importance. Our study group previously demonstrated that smoking, diabetes, old age and preoperative ASA scores, commonly regarded as perioperative risk factors [24–27], have no significant impact on overall free flap outcome [2–5]. However, to date, the influence of gender, an important demographical variable, on free flap outcome remains debatable. In the presented study, aim was to further elucidate whether patients' gender is a potential risk factor with regard to complications and outcomes of free flap based lower extremity reconstructions.

The data presented within this manuscript show no significant differences between the two groups of patients regarding the rate of major complications, including total flap loss and partial flap loss >10%, or surgical revision surgeries. Comparable literature on gender-related outcome of lower extremity free flap reconstruction is scarce and limited by small patient populations. While Wong et al. based their analysis on a total of 778 free flaps, only 36 of these were lower extremity reconstructions [28]. In accordance with our results, their study showed no association of flap failure with gender. Sanati-Mehrizy et al. included a subgroup of 127 extremity free flaps in their study and also reported no gender-related risk [20]. Conversely, in head and neck reconstructions, female gender is considered an independent risk factor for free tissue transfer, however, based on a limited number of only 94 flaps [19]. Gender has been evaluated as a risk factor in lower extremity reconstructions using perforator-based propeller flaps and free-style flaps [21,22], showing no significant differences between male and female patients and thus complying with our results. Recently, Yang et al. published risk factors for ALT flap failure in 128 lower-limb reconstructions and found no significant differences related to patients' sex [29]. Accordingly, when analyzing all ALT- and gracilis muscle flaps separately, we observed no

Table 6. Postoperative complications according to patients' gender and type of anastomosis.

Characteristics	Male	Female	*p* Value
Number of patients (*n*)	243	115	
Type of anastomosis (*n*)			
End-to-end	161 (66.3%)	84 (73.7%)	.197
End-to-side	82 (33.7%)	31 (26.3%)	
Complications			
End-to-end anastomosis (*n*)			
Major	52 (32.3%)	29 (34.5%)	.725
Total flap loss	12 (7.5%)	9 (10.7%)	.387
Partial flap loss >10%	4 (2.5%)	5 (5.9)	.171
Revision surgery	33 (20.5%)	16 (19.0%)	.788
Arterial thrombosis	8 (5.0%)	3 (3.6%)	.616
Venous thrombosis	13 (8.1%)	8 (9.5%)	.701
Hematoma	12 (7.5%)	5 (5.9%)	.661
Minor[a]	18 (11.2%)	12 (14.3%)	.482
End-to-side anastomosis (*n*)			
Major	24 (29.3%)	7 (22.6%)	.477
Total flap loss	6 (7.3%)	2 (6.5%)	.873
Partial flap loss >10%	5 (6.1%)	1 (3.2%)	.544
Revision surgery	16 (19.5%)	4 (12.9%)	.411
Arterial thrombosis	1 (1.2%)	1 (3.2%)	.470
Venous thrombosis	10 (12.2%)	2 (6.5%)	.377
Hematoma	5 (6.1%)	1 (3.2%)	.544
Minor[a]	10 (12.2%)	3 (9.7%)	.708

[a]Wound dehiscence, skin graft failure, wound infection and partial flap loss <10%.

differences regarding the rate of major and minor surgical complications as well as of total and partial flap loss between male and female patients.

Numerous studies have established a correlation between gender and the incidence of deep venous thrombosis or pulmonary embolism, with a predominance in male patients [10,11]. Henderson et al. analyzed late anastomotic thrombosis after free tissue transfer in a large patient population [30]. The incidence of late thrombosis was 0.7%, with 82.6% of affected patients being females [30]. Interestingly, in the setting of lower limb revascularization, women show inferior short-term, but similar long-term outcomes compared with men [31]. On the contrary, while we did not differentiate between early and late onset of complications, our data show that percentages of arterial and venous thrombosis were comparable between both groups. Further analysis with regard to the type of anastomosis (end-to-end vs. end-to-side), once again showed no significant difference in major or minor complications between both groups.

A substantial body of work demonstrates that the differential expression of sex hormones in males and females has a gender-related impact on healing of acute and chronic wounds [32–34]. In this regard, estrogens have been described as being enhancers within wound healing processes [35,36]. In addition, with regard to surgical site infections, studies have shown a generally higher rate in men, while this may vary across different procedures [17,37,38]. Opposing aforementioned findings, in the patient population investigated in this manuscript, there were no gender-related differences in minor complications, including wound healing disturbances and wound infections. Female gender has been associated with longer lengths of hospital stay in various medical disciplines [39–43]. Contrary, Schoeneberg et al. found significantly shorter ICU stay and total hospital stay for female patients after severe trauma injury [44]. Here, both patient populations showed comparable time to ambulation, without significant differences between both groups.

In the literature, a higher prevalence of asymptomatic PAD and a higher proportion of critical limb ischemia is reported in females as compared to males [45,46]. The patient population investigated in this study, however, showed a comparable distribution of PAD in both groups. Additionally, large studies have reported gender related differences with regard to obesity, with a predominance in females, and type 2 diabetes, with a higher prevalence in males [47,48]. Here, for the patients receiving lower extremity reconstructions in the presented study, the distribution of comorbidities such as DM, hypertension and obesity, as well as preoperative ASA scores, were comparable between both groups.

The high sample size of 358 patients that received 393 free flap lower extremity reconstructions is a major strength of this study. To the best of our knowledge, no other study investigated the impact of patients' gender on lower limb microsurgical reconstruction in a population as large. Additionally, the homogeneity of both groups with regard to comorbidities, smoking status, ASA scores, recipient vessels, etiology of defects, flap dimensions, mean operative times as well as mean ischemia times adds further strength to the study. Further, there was no selection bias as all lower extremity free flap reconstructions over a time period of seven years at a single surgical site were included. Unfortunately, this study lacks data on the severity of the trauma causing the soft tissue defects. Detailed knowledge of the respective Gustilo classification would add further strength to the study. The retrospective nature of this study might be considered a limiting factor. In the future, large multi-center studies or pooled data from national flap registries could add further information with regard to risk factors in microvascular free flap surgery.

Conclusions

This study analyzed a large series of microsurgical lower extremity free flap reconstructions investigating the potential impact of gender on flap outcomes and complications. According to the presented data, gender has no impact on the rate of major and minor surgical complications, including total and partial flap loss. Additionally, no gender-related differences with regard to the rate of revision surgery were observed. In conclusion, gender does not pose an independent risk factor for free flap reconstruction in this specific patient population.

Disclosure statement

The authors have no commercial associations or financial disclosures that might pose or create a conflict of interest with the methods applied or the results presented in this article.

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