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# Predisposal factors leading to early re-amputation among diabetic patients who underwent minor amputation

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**Ethics Committee Approval**
The study was approved by Dokuz Eylül University Non-Interventional Research Ethics Committee (Reference number: 2022/37-03, date: November 23, 2022).
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

**Conflict of Interest**
No conflict of interest was declared by the authors.

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## Abstract

**Background/Aim:** Prolonged wound complications and the possibility of reoperations are significant outcomes following minor amputations. As time progresses after the initial surgery, re-amputations become more prevalent. Contrary to prevailing beliefs, the incidence of early amputations remains consistent. Additionally, it is widely acknowledged that the first 6 months following the initial surgery pose the highest risk period for reoperation. This retrospective clinical study aims to investigate the risk factors contributing to ipsilateral re-amputation procedures within 6 months of the initial minor amputation.

**Methods:** A retrospective cohort study was conducted involving amputee patients from 2008 to 2020. Patients with traumatic events, musculoskeletal tumors, prior major amputations, and those who underwent soft tissue procedures such as debridement, incision, drainage, or secondary closure were excluded. Patients who had undergone preoperative lower limb arterial Doppler ultrasound and whose initial preoperative laboratory records were accessible were included. The total cohort comprised 168 patients, comprising 57 women and 109 men. The mean follow-up duration was 1.5 years (range: 1.1–3.2 years). Patients who underwent ipsilateral re-amputation were categorized into two groups based on the timing of the subsequent surgery. The first group comprised 110 (65.5%) patients who underwent ipsilateral re-amputation 6 months after the initial amputation, while the second group encompassed 58 (34.5%) patients who underwent ipsilateral re-amputation within 6 months of the initial amputation.

**Results:** Among the 168 patients, 58 (34.5%) experienced ipsilateral re-amputation within 6 months of their initial minor amputations, while 64.5% underwent re-amputation surgery after the initial 6 months. The absence of peripheral arterial disease was not linked to early re-amputations ($P$=0.001). Although the mean C-reactive protein values (80.30 mg/dL and 84.26 mg/dL for groups 1 and 2, respectively) did not display significance between the groups ($P$=0.40), the group undergoing amputation within 6 months demonstrated significance with elevated serum white blood cell mean levels (10.44 mcL and 11.96 mcL for groups 1 and 2, respectively; [$P$=0.004]). Moreover, lower hemoglobin levels (11.41 g/dL and 10.77 g/dL for groups 1 and 2, respectively) were associated with re-amputation within the initial 6 months following the initial surgery ($P$=0.024).

**Conclusion:** The study underscores that the incidence of re-amputation after minor amputations in diabetic patients is comparably high, as has been reported in recent literature. While the selection of the initial amputation level remains pivotal, and not all patient-specific factors were examined in this study, the research brings attention to specific laboratory values and the vascular status of the diabetic limb as crucial considerations for surgeons prior to the initial surgery.

**Keywords:** minor amputation, re-amputation, diabetic foot

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## Introduction

Recently, there has been a surge in the incidence of lower extremity diabetic amputations. Among these amputations, those that arise due to diabetes predominantly involve minor procedures, encompassing the removal of toes or portions of the foot up to the ankle [1-4].

Indeed, the choice of a minor amputation harms the quality of life and can lead to prolonged wound complications. What's even more concerning is that minor amputation often paves the way for subsequent re-amputations [5]. In a retrospective analysis of forefoot amputations involving 81 patients, the average period between the primary and subsequent amputation was 10.9 months. This group conducted 23 out of 29 major amputations within two months following the forefoot amputation [6]. Beaulieu et al. [7] documented 94 instances of re-amputation out of 100 readmissions in a cohort of 152 transmetatarsal amputations. A decade-long observational study by Izumi et al. [8] revealed that the greatest risk for a patient to undergo further amputation of the same limb occurs 6 months after the initial minor amputation. Their data indicates a re-amputation rate of 60% over 5 years.

Numerous descriptive studies have reported risk factors, including infection, peripheral arterial disease, chronic renal disease, and Hemoglobin A1c (HbA1c) levels associated with re-amputation. Alongside these variables, modifications in human serum parameters influence the necessity and timing of re-amputation [2,9-11]. This study focused on investigating the risk factors that lead to ipsilateral re-amputation procedures within 6 months after the initial amputation. We hypothesize that patients affected by malnutrition, peripheral arterial issues, and renal disease are predisposed to undergoing early re-amputation procedures.

## Materials and methods

A retrospective study was conducted on patients with amputations between 2008 and 2020. Approval from the local ethics committee was obtained under the reference number 2022/37-03. The amputations were carried out following a multidisciplinary approach to determine the appropriate level of amputation. Patients with amputations resulting from traumatic events, musculoskeletal tumors, previous major amputations, or those who had undergone soft tissue surgeries such as debridement, incision, drainage, or secondary closure were excluded from the study.

The study involved the assessment of records from 249 patients who had undergone at least one minor ipsilateral re-amputation. The analysis was carried out by excluding sixty-eight patients who did not have lower limb arterial Doppler ultrasonography performed within a month before the initial surgery. The peripheral arterial disease (PAD) diagnosis was exclusively confirmed for patients who had undergone Doppler ultrasonography. Patients exhibiting monophasic Doppler signals at the ankle level were included in the PAD category. From the remaining pool of 181 patients, thirteen individuals lacking serum hemogram, creatinine, and C-reactive protein (CRP) values within 2 days prior to the initial surgery were subsequently excluded. HbA1c values were recorded monthly following the initial surgery [5,12-14]. The American Society of Anesthesiologists (ASA) physical status classification was employed to categorize participants based on their physical condition prior to the anesthesia for the initial amputation. The ASA values of the 163 patients were segregated into groups according to their preoperative scores.

The total patient count is 168, comprising 57 women and 109 men. The average follow-up duration was 1.5 years (1.1 to 3.2 years). Patients who underwent ipsilateral re-amputation were categorized based on the timing of their subsequent surgeries. The initial group encompasses 110 (65.5%) patients who experienced ipsilateral re-amputation 6 months after the primary amputation. Meanwhile, the second group comprises 58 (34%) patients who underwent ipsilateral re-amputation within 6 months of their initial amputation. An investigation was conducted on these two groups, focusing on serum hemoglobin, white blood cell (WBC) count, albumin levels, CRP levels, creatinine levels, HbA1c levels, ASA scores, smoking habits, and PAD. Due to incomplete documentation on peripheral neuropathy presence and infection progression, these parameters were excluded from the analysis.

**Statistical analysis**

The study findings underwent statistical analysis utilizing IBM SPSS Statistics, version 22 (IBM SPSS, Armonk, NY). The normal distribution of parameters was evaluated through the Shapiro-Wilk test, a widely employed technique for assessing data normality. Statistical evaluations encompassed Wilcoxon rank sum tests for continuous variables, Pearson's chi-squared tests and Fisher's exact tests for categorical variables. These analyses considered diverse attributes such as hemoglobin levels, presence of PAD, gender distribution, WBC count, HbA1c levels, CRP levels, serum albumin levels, creatinine levels, and ASA scores.

The study further undertook an analysis aimed at identifying factors linked to the occurrence of PAD. To assess the relationships between these characteristics and the presence of PAD, odds ratios (ORs), confidence intervals (CIs), and *P*-values were calculated. The significance threshold was established at $P<0.05$.

## Results

The initial group comprised 110 patients with a mean age of 58 (53.62), while the second group consisted of 58 patients with an initial mean age of 56 (52.59). The age parameter exhibited no significant difference between the two groups ($P=0.30$). The distribution of male and female participants' percentages is detailed in Table 1, revealing no statistical disparity between genders ($P=0.70$). The percentages of smokers and non-smokers are presented in Table 1 as well, indicating no statistically significant distinction between the two groups ($P=0.60$).

In the initial group, 30 patients underwent PAD determination in accordance with our study protocol. Within the second group, comprising patients who underwent amputation within 6 months, 23 cases were identified with PAD. The absence of PAD did not correlate with early re-amputations. A statistically significant disparity between the two groups was observed ($P=0.001$).

Age was uniformly distributed both between the groups and among genders. The mean hemoglobin value was 10.77 (1.73) in the second group and 11.41 (1.78) in the first group. The group subjected to re-amputation within 6 months exhibited notably lower serum hemoglobin levels than group one, with a statistically significant difference ($P$=0.024).

The initial mean WBC values were 10.44 (4.01) for group 1 and 11.96 (3.81) for group 2. The early amputation group (Group 2) displayed significantly higher values than the first group, with a $P$-value of 0.004. As an indicator of malnutrition, the mean serum albumin levels were 3.18 (0.66) for group 1 and 3.17 (0.70) for group 2. However, statistical analyses regarding serum albumin values did not reveal any significant difference between the two groups ($P$=0.50).

CRP levels (80.30 [72.93] for group 1 and 84.26 [67.53] for group 2) and HbA1c values (8.51 [2.07] for group 1 and 8.59 [1.50] for group 2) were higher in the second group. Nonetheless, the two groups did not have a statistically significant difference in CRP levels ($P$=0.40) and HbA1c values ($P$=0.40).

The mean serum creatinine levels were 1.38 (0.98) for group 1 and 1.77 (1.75) for group 2. These higher levels were observed in the early amputation group (Group 2), although no significant values were obtained (Table 1). Percentages of participants within each ASA category were presented in Table 1, showing no significant difference between the groups ($P$=0.70).

Table 1: Demographic findings, comorbidities and serum parameter values of both groups

| Variable | Re-amputation after 6 months n=110 Mean (SD) n (%) | Re-amputation within 6 months n=58 Mean (SD) n (%) | *P*-value |
|---|---|---|---|
| **Age** | 58.31 (8.18) | 56.88 (6.31) | 0.30 |
| **Gender** | | | 0.70 |
| Male | 72 (65%) | 36 (62%) | |
| Female | 38 (35%) | 22 (38%) | |
| **Smoking** | | | 0.60 |
| Smokers | 24 (22%) | 15 (26%) | |
| Non-smokers | 86 (78%) | 43 (74%) | |
| **Peripheral Arterial Disease (PAD)** | | | 0.001 |
| PAD (+) | 30 (%27) | 35 (%60) | |
| PAD (-) | 80 (%73) | 23(%40) | |
| **Hemoglobin (g/dL)** | 11.41 (1.78) | 10.77 (1.73) | 0.024 |
| **White Blood Cells (mcL)** | 10.44 (4.01) | 11.96 (3.81) | 0.004 |
| **HbA1c (mmol/mol)** | 8.51 (2.07) | 8.59 (1.50) | 0.40 |
| **CRP (mg/dL)** | 80.30 (72.93) | 84.26 (67.53) | 0.40 |
| **Albumin (g/dL)** | 3.18 (0.66) | 3.17 (0.70) | 0.50 |
| **Creatinine (mg/dL)** | 1.38 (0.98) | 1.77 (1.75) | 0.40 |
| **ASA (n=163)** | | | 0.70 |
| 1 | 9 (8.6%) | 2 (3.4%) | |
| 2 | 57 (54%) | 35 (60%) | |
| 3 | 23 (22%) | 12 (21%) | |
| 4 | 16 (15%) | 9 (16%) | |

## Discussion

In this retrospective analysis, our objective was to determine the rate of ipsilateral re-amputation and identify the factors contributing to early re-amputation. Our findings indicate that the percentage of ipsilateral re-amputation 6 months after the initial amputation is 34.5%. Interestingly, the absence of PAD is not correlated with early re-amputations. While CRP values did not exhibit significant differences between the groups, we speculate that there might exist a propensity for early re-amputation in the patient group with higher WBC levels.

In their study focusing on diabetic patients, specifically examining six-month readmissions and re-amputations, Ratliff et al. reported an ipsilateral re-amputation rate of 24%. They observed a higher incidence of more proximal-level amputations following minor amputations [15]. In a population-based cohort study, the prevalence of ipsilateral re-amputation after a minor amputation was documented at 10.7% [16]. Murdoch et al. [17] found that within 1 year after the initial amputation, 60% of all individuals underwent subsequent amputations, 21% required a third amputation, and 7% needed a fourth. Comparatively, our observed rate of ipsilateral re-amputation over 6 months is higher. This could be linked to evolving trends, particularly in determining amputation levels.

Inadequate selection of the initial amputation level can lead to suboptimal debridement and subsequent re-amputations. Moreover, a proclivity to preserve extremity length by favoring more distal amputations might contribute to the escalation in the re-amputation rate. Skoutas et al. [9] suggest a considerable likelihood of re-amputation in diabetic foot conditions, especially within the first 6 months following the index amputation, primarily due to poorly informed choices regarding the amputation level, ostensibly aimed at retaining extremity length.

The presence of PAD was assessed through physical examinations (including peripheral pulse palpation or ankle-brachial index measurements) or diagnostic tools such as angiography or Doppler ultrasonography. Re-amputation rates can escalate to as much as 60% over 5 years when associated with PAD [2,18]. A recent study investigating the risk of major amputation after an initial minor amputation found that individuals with both PAD and diabetes faced a higher risk of subsequent major and minor amputations compared to patients with only one of these conditions. Notably, around half of the cases of limb loss occurred approximately 1 year following the initial minor amputation. The rate of subsequent minor amputations stood at 16% for cases with both PAD and diabetes, as opposed to 15.2% for those with only PAD and 12.2% for patients with diabetes [19]. However, this study did not provide information regarding the laterality of the amputations (ipsilateral or contralateral).

In our study, over 6 months following the initial minor amputation in diabetic patients, we did not find any statistically significant difference related to PAD. Moreover, any combination of comorbidities with PAD did not show significance in cases of re-amputation within 6 months. Nevertheless, we speculate that patients without PAD may have undergone ipsilateral minor amputations less frequently than those diagnosed with PAD within 1 year of the index surgery. Our vascular disease determinations relied solely on Doppler ultrasonography; including records involving angiography, ankle-brachial index measurements, or the degree of vascular occlusion could have yielded more substantial analyses.

Various combined parameters, encompassing initial serum levels of CRP, hemoglobin, WBC, HbA1c, and renal disease, have been explored in existing literature [20]. A recent study identified HbA1c, CRP, WBC, and creatinine levels as upper reference bounds for predicting re-amputation. Additionally, lower levels of albumin were linked to increased amputation rates. The study emphasized the significance of HbA1c levels as highly sensitive indicators for anticipating the likelihood of re-amputation [21].

In our study, only lower serum hemoglobin levels and higher WBC values demonstrated significance. These differences did not yield statistically significant outcomes despite observing higher serum HbA1c and creatinine levels and lower albumin levels in the re-amputation group within the 6-month timeframe. Notably, a mere 1 mg/dl difference in hemoglobin levels was observed between the two groups, yet both values fell below those of healthy individuals.

**Limitations**

The retrospective nature of data collection is this study's primary limitation. Notably, the specific levels of amputations performed were not detailed; all instances were categorized as minor amputations. This classification doesn't account for the variability from toe to heel amputations, which could have introduced differences in the analyses. While the timing of subsequent surgeries was factored into the group categorization, patient-specific comorbidities and prior peripheral vascular conditions were regrettably not considered. Noteworthy unmeasured variables include sensitivity analysis and the progression of infections, both of which could exert significant influence. Despite these limitations, the study holds value in its focused inclusion of exclusively ipsilaterally reamputated minor amputations.

**Conclusion**

The study reveals that re-amputation following minor amputations in diabetic patients is strikingly consistent with the rates reported in recent literature. While acknowledging that the selection of the initial amputation level is pivotal and certain patient-specific factors were not addressed in this study, this research underscores the need for surgeons to pay particular attention to laboratory parameters and the vascular condition of the diabetic limb prior to the initial surgical intervention. To advance our understanding, future cohort studies should strive for greater homogeneity within the groups and should encompass an algorithm for guiding decisions regarding amputation levels.

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