# Lipid profile and inflammatory biomarkers as a prognostic factor for outcome in DFUs: Is there any relationship?

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## Abstract

*Background & Aims*:  A diabetic foot ulcer (DFUs) is a major health problem, which concerns 15% patients with diabetes worldwide. Amputation is a feared complication of diabetes. Few studies have identified factors as predictors of clinical prognosis of patients with DFUs, especially of Iranian patients. In this study, we assessed the prognostic factors of Iranian patients with DFUs.

*Materials and Methods:* Prospective cohort hospital based study conducted in Patients with diabetic foot ulcer from June 2015 - June 2016. Diagnosis of diabetic foot ulcer was based on WAGNER – MEGGIT criteria and patients with grade 2 and more were evaluated. Patients were followed up for three months in order to determine the desired outcome (recovery or amputation). Data collection was done by checklist design and lipid profile (Triglyceride, Cholesterol, HDL-C, LDL-C) and inflammatory biomarker (ESR and CRP levels) were entered to the checklist. All statistical calculations and analyses were performed by using SPSS software (version 16). P value of less than 0.05 was considered significant.

*Results:* In total, the study included 72 patients with DFUs and 58.3% of the patients were man. Mean age of the patients was 59.19+/-11.94 years and mean duration of diabetes was 15.52+/- 8.62. The majority of patients (94.8%, 68 cases) had type 2 diabetes mellitus. 70.8% had ESR>= 50, 35.9% had CRP>= 3+, 95.6% had HbA1C >=7, 58.6% had LDL>100, 95.5% had HDL<50 and 67.2% had TG<200. Follow up time was 3 months from hospital discharge. The overall limb amputation rate in the current study was 21.3%.

*Conclusion:* Our results demonstrated that limb amputation rate is not correlated with sex, ESR, HbA1c, WBC, LDL, HDL. Significant univariate predictive factors for limb amputation was CRP level and Triglyceride level. (p= 0.91 and p= 0.064 respectively)

*Keywords*: Diabetes, Amputation, Risk factors, Epidemiology

## Introduction

Diabetes mellitus (DM) is a public health problem and various studies estimated that millions people have this disease, of whom around 50% are unaware of their condition and unfortunately often diagnosed only when complications have already set in (1). Among the

diseases associated with diabetes, diabetic foot ulcers (DFUs) is one of the most common long-term complications. The data regarding the prevalence of DFUs varies between 2.8% and 13.7% for patients with diabetes (2,3). Costs related to DFUs care are greater than $1 billion annually and rising. it is estimated that approximately 15-25% of diabetic patients developed DFUs in the course of their disease (3,4). Diabetic foot ulcers negatively impact quality of life (QOL), increase morbidity and mortality and also incur a substantial economic burden for society, patients and their families (5). Amputation is a serious consequence of diabetes. Lower limb amputation is performed 10-30 times more frequently among diabetic than among general population (6). Every 30s, somewhere in the world, a lower limb is lost as a complication of diabetes. More than 80% of non-traumatic lower limb amputations are occurred in diabetic patients (7,8). In addition to being a burden on the individual patients, the DFUs is also a major cost factor for the health system (9). Many risk factors for development of foot ulcers stand out: peripheral vascular disease, peripheral neuropathy, prior ulceration, longer duration of diabetes, and smoking, structural deformity of foots, poor glycemic control, bacterial and fungal infection on the foot and failure to self- examine the foots (8-10). The study of the epidemiology of DFUs has been beset by numerous problems related to diagnostic tests and population selection. Few studies have reported the prevalence of diabetic foot ulcers in Iran. The aims of this study was to detect the prevalence and risk factors and predictive factors (clinical, laboratory) and the associated diabetes complications among patients with DFUs.

**Material and methods**

Prospective cohort hospital based study conducted in Patients with diabetic foot ulcer from June 2015 - June 2016. The study was reviewed and approved by the Institutional Review Board/Research Ethics Committee of the Faculty of Medicine, Urmia university of medical sciences; Iran. Foot ulcers were graded according to the Wagner, s classification (Grade 0: high risk foot; Grade 1: superficial ulcer; Grade 2: deep ulcer penetrating to tendon, bone, or joints; Grade 3: deep ulcers with abscess or osteomyelitis; Grade 4: localized gangrene; Grade 5: extensive gangrene requiring a major amputation) and patients with grade 2 and more were evaluated. All Patients were reviewed weekly in the first month and followed up for three months in order to determine the desired outcome (recovery or amputation). Amputation was defined as the complete loss in the transverse anatomical plane of any part of the lower limb. Major amputation was defined as amputation above the ankle joint and a minor amputation as below the ankle joint. Medical documentations of all the 72 cases of DFU were systematically reviewed with respect to age, sex, duration and type of diabetes. Data collection was done by checklist design and HbA1c, lipid profile (Triglyceride, Cholesterol, HDL-C, LDL-C) and inflammatory biomarker (ESR and CRP levels) were entered to the checklist. All statistical calculations and analyses were performed by using SPSS software (version 16). P value of less than 0.05 was considered significant.

**Results**

Mean age of patients was $59.19 \pm 11.943$ years. Majority of patients were in their fifth and sixth decades. 68 (94.4%) patients had Type 2 diabetes, and 4 (5.6%) had Type 1. Mean duration of diabetes was $15.52 \pm 8.42$ years. Majority of patients (95.6%) had poor control of diabetes, as indicated by HbA1c level (>7%). The most common co morbidities were hypertension (23.6%), followed by IHD and stroke (47.2%). Risk factors included smoking (19.4%), alcohol use (9.4%), obesity (8.5%) and hyperlipidemia (51%). Totally 61 patients followed for 3 months from discharge, 13 (21.3%) cases had amputation. Results of predictive factors for limb loss illustrated in table 1.

**Discussion**

Per year, approximately 2-6% 0f all diabetics develop poorly healing and frequently chronic lesions on the feet which are associated with a high risk of minor or major amputation, especially if treated inadequately

(9). Nowadays, the diabetic foot problems remain a major medical, social and economic problem in most countries (10). The literature lists advanced age, male gender, long duration of diabetes, inadequate metabolic control, and the presence of diabetic complications (e.g., nephropathy, retinopathy) or risk factors (hypertension, hyperlipidemia) as additional causal factors for the development of a DFUs (11). In western countries diabetes remain the major cause of non-traumatic amputation and patients with diabetes have a 10-15 times greater risk of amputation than patients without diabetes (11,12). In our study, amputation rate was 21.3%. In a study in Asia, DFUs also leads to high rate of amputation. The overall amputation rate among diabetic foot patients reported was 28.8% in Iran (2,4,8,15), 25.4% in Japan (11) and 27.2% in Singapore (13). Several risk factors for amputation among patients with diabetes have been cited in the literature including age (2,4,5,7), sex (male) and stroke (4,7,8), co-morbidities such as IHD and hypertension (5,6,7), Peripheral Vascular Disease (PVD) (7,8,9), nephropathy (7,9,10), sensory neuropathy (6,8,9), duration of diabetes (4,7,9) and HbA1c level (4,7,9,11). Serum CRP level were also found to be independent risk factor for overall amputation in our analysis. The level of serum CRP had been found to rise in the patients with DFU, compared with patients without foot ulcers and normal control patients (11). Weigelt et al. (12) further revealed that CRP was associated with the severity of the ulceration and size of ulcer according to the University of Texas classification. Similar to our study, Volaco et al. (13) also found that the risk of amputation increased 5.4 times with CRP above 8 mg/dl in patients with diabetic foot lesions. In our study, 30% among patients with amputation had WBC count >12000 that not to be significant in their study (p= 0.348). In study conducted by Yesil et al. (14) also found patients who underwent amputation had increased WBC count at baseline. Eneroth et al. (15) showed that WBC counts >12000 was related to increased risk for amputation. This discordance with our results, may be related to little number of patients with amputation. Type 2 diabetes typically exhibits mixed dyslipidemia characterized by

elevation triglyceride and low levels of HDL-C. These lipid abnormalities and high serum cholesterol level have been proven to be risk factors of cardiovascular disease and have commonly been linked with worse outcomes (16,17). In our study the levels of LDL_C and HDL_C were inversely associated with amputation (p= 0.656, p=0.367 respectively). Triglyceride level were found to be independent risk factor for overall amputation in our analysis (p= 0.064). Other study (18-21) found both baseline serum triglyceride and cholesterol were related to lower extremity gangrene and/or amputation incidence. In reality, lower lipid levels were the manifestation of malnutrition in the patients with DFUs and rapid loss of protein and thus delay healing of wounds (22-24). It was shown that HbA1c was a significant risk factor for overall amputation in previous studies (25, 26) but was not an independent risk factor in our study (p= 0.445). Thus in our study HbA1c was not found to be a predictive factor for amputation. It is widely recognized that a multidisciplinary team is effective in the management of DFUs and results of multiple studies demonstrated that major amputation rates can be reduced by team work. (27,28) In summary, this study has shown that risk factors for the amputation in patients with a diagnosis of DFUs include elevated serum CRP level and lower lipid level. Following a diagnosis of DFUs more intensive surveillance and multidisciplinary team care, as well as early referral to specialty multidisciplinary care Centre may improve patients' outcome and reduce the amputations.

## Conflict of interest

There are no conflicts of interest.

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