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Research Article

The relationship between fibrinogen and the development of foot ulcer inflammation in patients with and without type 2 diabetes

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Abstract

Background: Diabetes-specific consequences include diabetic foot ulcer (DFU). In DFU a variety of bacterial communities have been found to be involved in the prognosis of infection. Fibrinogen is another easy and reliable indicator of inflammation. It has been observed that individuals with diabetic foot illness have higher levels of this protein.

Materials and Methods: In the current cross-sectional investigation, there were 100 samples total of diabetic type 2; 50 of the patients had type 2 diabetes with foot ulcers, while the other 50 did not. To identify the bacterial species, swab specimens were gathered and cultured.

Results: Based on the statistical analysis of this study, as age, and smoking there are a significant difference in most of the characteristics compared between the study populations. However, when comparing diabetic patients with foot ulcers to those without ulcers, the statistical analysis showed a statistically significant increase in fibrinogen levels. According to bacterial kind, gram-negative bacteria accounted for 78% of bacterial growth and gram-positive bacteria for 22%. The bacterial genera *Staphylococcus aureus* had the highest percentage of isolates from ulcers (34%), followed by *Klebsiella pneumonia* (28%), and *Proteus mirabilis* (26%).

Conclusion: There are many factors that increase the risk of developing diabetic foot ulcers and lead to a delay in wound healing and thus to amputation of limbs, which are obesity, smoking, and other diseases such as blood pressure and heart disease. In individuals with DFU, fibrinogen levels may be a useful as a marker for tracking the disease's advancement and determining how severe the condition is.

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Introduction

Diabetes mellitus is a chronic illness that continues to significantly enlarge. Its complications, including Diabetic foot infection (DFI) Type 2 diabetes mellitus (DM) which is a long-term metabolic disease whose global prevalence has been gradually rising. This trend is making it quickly turn into an epidemic in some parts of the world, where the number of affected individuals is predicted to double in the next ten years due to an increase in the aging population. This will add to the already heavy burden placed on healthcare provider particularly in less developed nations [1]. One of the consequences of diabetes is diabetic foot ulcers (DFU). In the severe state of DFU, this ailment can lead to a high rate of amputation, medical expenses, and even death. The incidence of pricey complications is caused by the severity of DFU. It can aid in preventive functions to understand the elements affecting it. Sufficient proof is required to address this issue [2]. Diabetes impairs wound healing because of reduced blood flow to both superficial and deep tissues. Additionally, sugarcoated microvasculatures, weakened host immune systems, and unseen lesions create an environment that is conducive to infection. From straightforward, superficial cellulitis to chronic osteomyelitis, infected DFUs can cause a range of dreadful consequences, including gangrene, systemic toxicity, and lower limb loss [3].

Over one-third of diabetics will at some point in their lives develop diabetic foot ulcers (DFUs), of which half will be infected and result in diabetic foot infections (DFIs). Amputation of the lower limb is necessary for 15% of patients with DFIs in order to stop the infection from spreading [4]. One major factor contributing to the chronicity of diabetic wounds is the diversity of bacterial communities present in the wounds. The microorganisms residing in the wound frequently exist in multiple layers, creating biofilms. These biofilms are made of self-produced hydrated extracellular polymeric material (EPS), also known as “slime,” which acts as a barrier against antimicrobial agents that hinder the healing of wounds [3]. According to microbiological studies, DFIs are polymicrobial. Aerobes such as *Staphylococcus aureus*, *Staphylococcus epidermidis*, coagulase-negative *Staphylococcus spp.*, *Enterococcus spp.*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Proteus mirabilis*, and *Klebsiella pneumoniae* are the most commonly identified isolates [5].

The primary coagulation factor for plasma proteins is fibrinogen. Because of this, there is a higher chance of bleeding when there is low plasma fibrinogen concentration because primary and secondary hemostasis are compromised. A classical positive acute-phase reactant protein, fibrinogen is an independent predictor of events related to coronary heart disease [6].

Increased thromboxane A2, decreased platelet nitric oxide generation, and increased platelet release of plasminogen activator inhibitor-1 (PAI-1), which inhibits thrombolysis, are all linked to diabetes mellitus (DM). It is produced in the liver and, after the coagulation pathway is activated, is changed into a fibrin monomer (by thrombin). This monomer then quickly aggregates to bind to nearby molecules, producing the core of the blood clot [7] . Fibrinogen is an efficient indicator of inflammation and has been found to be elevated in diabetic foot disease patients. Despite the fact that patients with DFU have been shown to have higher amounts of fibrinogen than people without ulcer [8] .

Materials and Methods:

This cross-sectional study included 100 participants: 50 patients with Type 2 diabetes who also have foot ulcers, and the other 50 patients with Type 2 diabetes without foot ulcer. The samples were provided by the Al-Imam Al-Hassan Center for Diabetes and Endocrinology. The swab method was used to

collect the specimens. The wound was initially cleaned with distilled water or saline to remove any surface contaminants. The ulcer was then scraped to gather exudate prior to sample. Before being applied in a zigzag pattern throughout the affected area, the swabs were lastly twisted to guarantee that the entire head of the swab made touch with the wound surface. In the end, the swabs were applied to the incision from the middle to the outside. In order to search for microorganisms, the swabs were delivered as soon as possible to a laboratory where they were cultured on in media such as MacConkey agar and Blood agar and preserved in a transport medium. Also, grown in an incubator on bacterial plates. While, a disposable syringe was used to extract three milliliters of venous blood from each participant, which was then put in a sodium citrate tube in order to assess each patient's fibrinogen level.

Ethical approval: The College of Science/University of Kerbala Ethics Committee approved this work before the collection of samples, all Patients who were registered in this study were informed and their verbal agreement was gained.

Statistical analysis: The Statistical Package for the Social Sciences software, version 23 (IBM, SPSS, Chicago, Illinois, USA), was used to generate the data analysis for the current study.

Results:

Table-1 displays the descriptive data of the study groups. The statistical analysis of the current study indicates that the majority of the studied parameters between the study populations diabetic patients with foot ulcers compared to diabetes groups without foot ulcers revealed significant differences (p<0.05) such as age and smoking.

Table (1): Study population demographics

Age group (year)						*P value* (P ≤ 0.05).
Study Group	**33-43**	**44-54**	**55-65**	**66-76**	**Total**	
Diabetic with foot ulcer	3 (6.0%)	8 (16.0%)	19 (38.0%)*	20 (40.0%)*	50 (50%)	.045
Diabetic without foot ulcer	5 (10.0%)	13 (26.0%)	16 (32.0%)*	16 (32.0%)*	50 (50%)	.0047
Total	8 (8%)	21(21%)	35 (35%)*	36 (36%)*	100 (100%)	.0001

Gender					
Study Group	**Male**	**Female**	**Total**	***P value* (P ≤ 0.05).**	**ODD (CI95%)**
Diabetic with foot ulcer	32 (64.0%)*	18 (36.0%)	50	0.005	2.087 (.936 – 4.653)
Diabetic without foot ulcer	23 (46.0%)	27 (54.0%)	50	.423NS	
Total	55 (55.0%)	45 (45.0%)	100 (100.0%)	.317NS	

Smoking					
Study Group	**Yes**	**No**	**Total**	***P value* (P ≤ 0.05).**	**ODD (CI95%)**
Diabetic with foot ulcer	32 (64.0%)*	18 (36.0%)	50	0.005	.501 (.207-1.214)
Diabetic without foot ulcer	39 (78.0%)*	11 (22.0%)	50	0.0001	
Total	71 (71%)*	29 (29%)	100(100%)	0.0001	

*Mean highly significant difference at the 0.05 level by chi-square test
NS: Non-significant

The concentration of fibrinogen in patients is shown in Table (2) based on other diseases. With the exception of the no illness group, the statistical analysis revealed a significant rise in fibrinogen levels in diabetes patients with foot ulcers compared to the diabetic patients without ulcers.

Table-2: Fibrinogen concentration in cases categorized by various diseases

Other Disease	**Con. of Fibrinogen (….) in patients Mean ± Std. Deviation**		***P value* (P ≤ 0.05).**
	Diabetic with foot ulcer	**Diabetic without foot ulcer**	
No disease	602.00±79.196	327.50± 104.500	0.147^{NS}
Hypertension	595.85±48.357	282.83± 60.558	**0.000***
Cardiovascular	609.67± 18.522	312.43± 20.057	**0.000***
Both disease	590.27± 30.837	311.97± 73.600	**0.000***
Total	596.08±41.351	305.66± 67.755	**0.000***
***P value*(P ≤ 0.05).**	0.815^{NS}	0.609^{NS}	

***mean highly significant difference under $p \leq 0.05$. NS: Non-significant

NS: Non-significant difference at the 0.05

The results of the bacterial culture are displayed in Figure (1). Of the samples cultured, 76% showed bacterial growth, whereas 24% showed no growth at all.

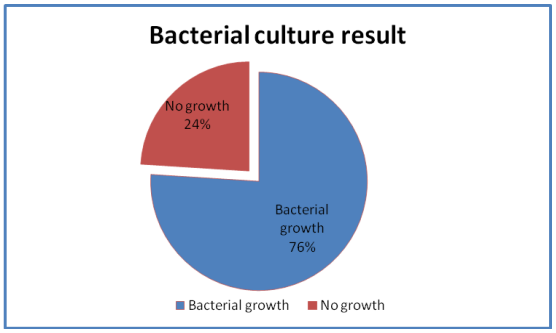


Figure 1: Bacterial culture percentage

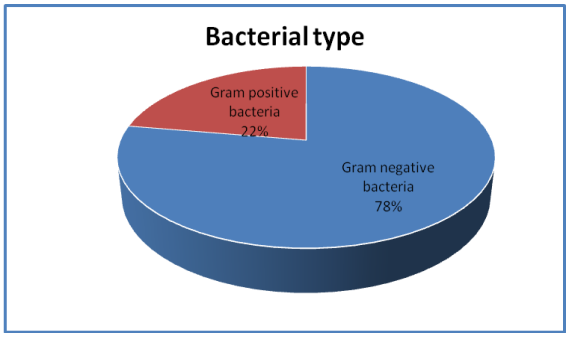
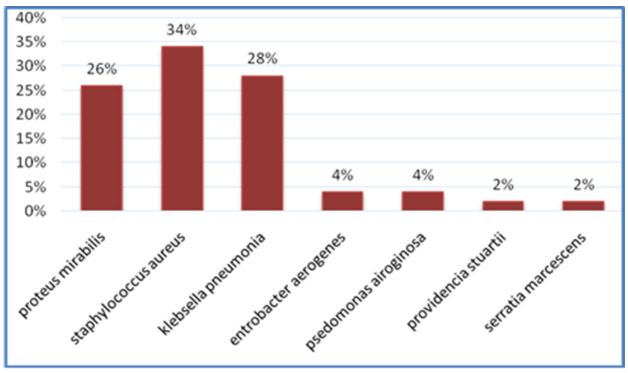


Figure 2: Bacterial kind percentage

Figure (2) showed that, with regard to bacterial kind, gram negative bacteria accounted for 78% of bacterial growth and gram positive bacteria for just 22%.

According to figure (3), *Staphylococcus aureus* had the highest percentage (34%) of isolates from ulcers, followed by *Klebsiella pneumonia* (28%), Proteus mirabilis (26%), and other bacterial genera.



Types of bacterial species isolated from ulcer (Figure 3)

According to smoking factor, the results in table (3) indicated a very significant difference in fibrinogen concentration in two patient groups; however, the influence of obesity factors was only statistically significant in the group of diabetic patients with foot ulcers as compared to the group of patients without foot ulcers.

Table-3: Fibrinogen Concentration in Patients Affected by Obesity and Smoking

Factors		Study population	N	Fibrinogen concentration		95% Confidence Interval for Mean		*P value* (P ≤ 0.05).
Smoking	Obesity			Mean	Std. Deviation	Lower Bound	Upper Bound	
yes	Yes	Diabetic with foot ulcer	15	611.67	44.974	586.76	636.57	0.000*
		Diabetic without foot ulcer	17	292.35	58.368	262.34	322.36	
	No	Diabetic with foot ulcer	17	590.41	31.992	573.96	606.86	0.000*
		Diabetic without foot ulcer	22	312.77	69.427	281.99	343.55	
No	Yes	Diabetic with foot ulcer	5	611.20	37.877	564.17	658.23	0.000*
		Diabetic without foot ulcer	6	326.00	98.618	222.51	429.49	
	No	Diabetic with foot ulcer	13	579.69	45.211	552.37	607.01	0.000*
		Diabetic without foot ulcer	5	295.20	57.954	223.24	367.16	

*Mean highly significant difference under $p \leq 0.05$

Discussion:

As the progress of age has some effects on many diabetic complications like foot ulcers [9]. The current study's findings exhibited a significant difference (P<0.05) between age and DFU development. A similar finding has been recorded in the studies of [10] and [11] who has discovered that the prevalence of DFU rises with age, because elderly patients are more likely to develop DFU. Furthermore, a study by performed [11] found that older diabetic patients had a higher incidence of DFU than younger diabetic patients did. However, a different study accomplished by [12] who found no connection between age and the development of DFU in people with type 2 diabetes. This variation may result from differences in the study subjects, sociocultural backgrounds as well as variables in the study group or study location.

In the current examination, there was no significant variation in gender between the tested groups (P>0.05). This finding is in the same line with the study conducted by [9], [13] reported that a significant difference between the genders of the patients was not found. On the other hand, several studies indicates that males may be associated with a higher risk of developing diabetic foot ulcers, contrary to the findings of [14] and [10] who stated that compared to females, males were more susceptible to diabetic foot infections. The incidence of DFU in males may be attributed to a number of factors, including gender-specific differences in lifestyle choices, poor personal hygiene, and certain types of footwear, and occupations that require the feet to withstand increased pressure from their labor increased trauma exposure. Other investigations have noticed similar patterns, and writers have proposed that males are more likely to work outside, which in the end raises the risk of foot damage and injury [15].

The most common way to use tobacco is to smoke it, usually in the form of cigarettes and burned tobacco. Even though cigarette smoking is on the decline in some countries most notably in Eastern Europe and central and Southeast Asia, which have the highest rates of smoking globally it is still a serious threat to public health worldwide. Global estimates from the World Health Organization (WHO) indicate that by 2050, there will be 1.5 billion smokers worldwide. It is well known that smoking cigarettes has a disastrous impact on one's health, increasing the risk of several diseases and ailments that influence every organ and system in the body. There is widespread knowledge that smokers with diabetes may have a quicker. Delaying the onset of diabetes and its complications requires treating smoking as the main modifiable risk factor, since prevalence rates of smoking among individuals with diabetes are similar to those in the general population. For diabetics, quitting smoking has clear benefits in terms of reducing or postponing their risk of cardiovascular disease and mortality [16].

In the current investigation, smoking was found to have a statistically significant (P<0.05) effect on the rate of DFU. These findings aligned with those reported by [17] who stated a strong link between DFU development and cigarette smoking. Conversely, the findings of the present investigation are not consistent with those published by [13] who mentioned that there is not connection between smoking cigarettes and the onset of DFU in those with type 2 diabetes. The discrepancies in sample sizes between this study and theirs may be the cause of this disagreement.

Elevated fibrinogen is linked to diabetes mellitus. It is produced in the liver and, after the coagulation pathway is activated, is changed into a fibrin monomer (by thrombin). This monomer then quickly aggregates to bind to nearby molecules, producing the core of the blood clot [18]. The concentration of Fibrinogen in patients according to other disease. The statistical analysis recorded a

significant increase in fibrinogen levels of diabetic patients with foot ulcer comparing to diabetic patients without ulcer according to other disease these results as similar to a study conducting by [7]. Patients with other diseases have a significant beneficial effect on plasma fibrinogen, so it is critical for determining the level of plasma fibrinogen in type 2 diabetic patients. Besides the usefulness of these indicators in the prediction of vascular lesions in people with newly diagnosed hypertension or diabetes, recent investigations have addressed the significance of therapeutic regulation of fibrinogen levels in high-risk patients for cardiovascular by [19]. In addition, the statistical analysis demonstrated that diabetic patients with foot ulcers had significantly higher fibrinogen levels in several studies accomplished by [8], [20] and [21]. When in attendance, study inconsistent with a study of [22] who reported there was non-significant difference in patient studies. The difference in the results apparent in this study is due to the small number of patients that the researcher examined during his research.

Current study result is consistent with a number of previous studies, such as those conducted by [23] and [24] who found all samples took from diabetic foot ulcers showed bacterial growth on different culture media and showed many types of bacteria; however, it is not consistent with a study conducted by [25]. In his analysis, 95% of the cultured samples showed signs of bacterial growth, whilst only 5% showed no development at all. Variations in the geographic location, the kind of treatment administered, and the severity of the infection could all be factors in the diversity of bacteria found in DFU patients. The variety in bacterial profiles observed in DFU patients may be caused by variations in the methods of sample collection, the setting, the kind of treatment administered, and the severity of the infection [11] and [26] demonstrated a relationship between the bacterial types of DFU infection and the ulcer's duration as well as prior antibiotic use. *S. aureus* continues to be the most prevalent bacterium despite differences in its distribution, according to multiple examinations carried out in various nations, including Australia (71.8%) and China (17.7%) [27], [25]. *S. aureus*, which secretes a variety of toxins and enzymes such as collagenase, lipases, proteases, hyaluronidases, and hemolysis, is commonly found on the skin and mucosal surfaces of diabetic patients. These compounds increase the bacterial growth and tissue invasion potential of the host tissues [28]. *Klebsiella pneumoniae* is a member of the Enterobacteriaceae family. It mostly affects those with weak resistances, which could have detrimental effects.

Osteomyelitis and "diabetic foot" infections can be serious complications for those with diabetes mellitus. *K. pneumoniae* produces a biofilm to evade the host's defenses once infection has taken hold [29]. Swarming colonies were apparent when *P. mirabilis* colonies were grown on blood agar. The bacterial isolates that were first isolated from clinical samples were grouped based on their microscopic features, culture morphology, and results of biochemical testing. *P. mirabilis* is a gram-negative bacillus that was identified culturally by looking at its colonial appearance under a microscope [30].

It has been demonstrated that smoking accelerates the healing process for diabetic foot ulcers and increases their risk. Several investigations shown that cyanides and carbon monoxide, two byproducts of cigarette smoke, halted the normal metabolism of healing. Furthermore, nicotine might affect blood vessel spasms or contractions, which could lead to tissue ischemia and inadequate ulcer healing [31]. The correlation between increased fibrinogen levels and cigarette smoking, these findings corroborate the researcher's findings, which indicate that fibrinogen levels were statistically significant in patients with type 2

diabetes mellitus[32] and [33].These results suggest that enhanced synthesis is a primary

factor in the hyperfibrinogenemia associated with smoking. Moreover, a mere two-week cessation of smoking leads to a notable decrease in the liver's fibrinogen synthesis rate, hence lowering plasma fibrinogen levels [34]. However, obesity characteristics only significantly affected the group of diabetics with ulcers when comparing them to the groups of diabetics without ulcers. Comparable to the finding that there were no meaningful connections between obesity and type 2 diabetes through [35]. Although obesity has a very high effect on fibrinogen concentration in diabetic patients, patients who are obese have greater levels of fibrinogen [36], [37]. According to this study by [38] and [39], obesity variables have a substantial impact on the group of diabetes patients with foot ulcers.

As a result, one should believe that the obesity challenge's outcomes should not change the current recommendations for therapy regarding the importance of weight loss for patients who belong to the overweight or obese patient category.

Conclusion:

The present study found that a number of factors, such as obesity, advanced age, smoking, and other diseases, increase the risk of developing diabetic foot ulcers, delayed wound healing, and ultimately amputation of limbs. High levels of fibrinogen marker are also significantly more common in people who have foot ulcers, suggesting that this marker may be a predictor of the severity of the disease.

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