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Phagocytic Activity of Patients with a Diabetic Foot in Wasit Province, Iraq

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ABSTRACT

Aims Diabetes mellitus has been known as a common disease that leads to many comorbid conditions. One of these common conditions is the diabetic foot which increases infections risk. This study was aimed to investigate phagocytic activity in patients with a diabetic foot.

Materials & Methods This study was carried out on 150 patients with a diabetic foot in al-Zahraa and al-Karama Teaching Hospitals, Iraq from January 2017 to January 2020. A total of 150 samples was collected for 3 groups (50 participants in each group). Blood samples were transferred into EDTA tubes, then 5ml of blood were pipetted in a plain tube. Thereafter, 0.5ml of working nitro blue tetrazolium solution was prepared by mixing an equal volume of 0.2% nitro blue tetrazolium solution with phosphate-buffered saline. Next, the plain tube was incubated at 37°C for 15 minutes in a water bath before being left for another 15 minutes at room temperature. A blood smear from the prepared mixture was then stained using Gemza stain. Finally, 100 neutrophils were randomly calculated, and the positive with formazan phenomena appear with blue-black granules were counted out of 100 cells. The statistical data analysis was performed with SPSS 22 using t-test.

Findings The phagocytic activity was significantly higher in healthy control individuals (14.10±3.96) compared to DM1 (10.54±3.60) and DM2 (11.88±3.54) ($p<0.05$). There was a significant difference between the control group with DM1 ($p=0.448$, $F=0.58$), and DM2 ($p=0.314$. $F=1.02$) in term of phagocytes activity.

Conclusion There is a clear reduction of phagocytic activity in patients with both types of diabetes mellitus with a diabetic foot comparing the healty group.

Keywords Diabetes Mellitus; Phagocytic; Diabetic Foot

CITATION LINKS

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Introduction

It has been demonstrated that disturbance in metabolism process of carbohydrate alongside with elevation of blood sugar level, accompanied with reduction in insulin secretion, as well as non-constant of peripheral resistance to the action of insulin. Altogether would be describe diabetes mellitus condition. Importantly, American Diabetes Association (ADA) has dispensed a list of criteria to be considered for diabetes mellitus diagnosis in 1997, these criteria were updated at 2003 and 2010 respectively. Notably, there was four abnormalities to be taken in account before giving the final diagnosis. Firstly, Hemoglobin A1C (A1C), secondly, fasting plasma glucose (FPG), thirdly, random elevated glucose with symptoms, and finally abnormal oral glucose tolerance test (OGTT). Consequently, people who are suffering impaired fasting glucose (IFG) that accompanied or not with impaired glucose tolerance (IGT), would ne indicated as having increased risk for diabetes [1-3].

Number of studies have revealed that the following symptoms of hyperglycemia would be considered for diabetes mellitus diagnosis, which are (thirst, polyuria, weight loss, blurry vision), accompanied with high value of a random blood glucose 200mg/dL (11.1mmol/L) or higher. Furthermore, association between glucose levels and the risk for developing retinopathy has been illustrated as other important diagnostic criteria. In the same line of thought, it has been revealed that prevalence of retinopathy would be associated with following observations, fasting plasma glucose values ≥126mg/dL (7.0mmol/L), two-hour post oral glucose challenge values of ≥200mg/dL (11.1mmol/L), and A1C values ≥6.5 percent [3]. In relative to an asymptomatic people, above mentioned criteria can be considered for diabetes diagnosis. In order to confirm the diagnosis, ode parameters should be repeated depending same tests. Approximately sixteen years ago, particularly at 2006 WHO has defined diabetes as a fasting glucose ≥126mg/dL (7.0mmol/L) or a two-hour post glucose challenge value ≥200mg/dL (11.1mmol/L). In addition, impaired glucose tolerance (IGT) has been defined as a fasting glucose <126 (7.0mmol/L), and a two-hour glucose ≥140mg/dL (7.8mmol/L) but <200mg/dL (11.05mmol/L) [4]. Moreover, impaired fasting glucose (IFG) is defined as a fasting glucose of 110 to 125mg/dL (6.1 to 6.9mmol/L). Consequently, in 2011, the WHO concluded that an A1C value of ≥6.5 percent (48 mmol/mol) can be used as a diagnostic test for diabetes [5].

Numerous studies have demonstrated that high morbidity percentage of diabetes mellitus patients resulted from foot problems. More specifically, 25% of diabetic patients are suffering a foot ulcer [6]. It has been shown that early recognition of foot diabetic is important. Thus, it is a preventable initiating event. Consequently, Foot amputations profoundly can be avoided when recognize at early stage. Based on that, routine examination of foot for patient with diabetic is essential to devoid foot ulceration risk. In the same line of thought, it has been reported that in order to diminish morbidity rate due to foot problems, systematic screening examinations is required [7, 8].

Aforementioned investigations have revealed that there is wide range of factors can be classified as a risk factor that association with foot ulcers and amputation. Despite, the importance of risk factors management to diminish foot ulceration morbidity, foot abnormality, capillary disease, and loss of protective sensation are all important factors that would lead to bad fate [6-9]. Interestingly, the impact of these factors has been confirmed by observations of previous experiment was included 1300 type 2 diabetic patients [10].

In order to enable accurate diagnosis of foot ulcer in patient with diabetic mellitus, numerous risk classification systems have been designed [11, 12]. International Working Group on the Diabetic Foot developed a system to categorized patients as follows:

Group zero: there is no evidence of neuropathy.

Group one: despite present of neuropathy, there is no sign of foot distortion and peripheral capillary abnormality.

Group two: shows neuropathy indications that accompanied with evidence of deformity or peripheral vascular disease.

Group three: there is a history of foot ulceration as well as lower extremity amputation.

Previous investigation has shown that foot ulcers are classified into two categories:

Acute ulcers, this type of ulcer has been defined as a secondary to dermal scratch from unwell fitting shoes, as well as chronic plantar ulcers that occurring over weight bearing areas.

Second type is chronic ulceration, characterized by combination of a decreased pain sensation (diabetic neuropathy), reduction in capillary density, and autonomic dysfunction, thus it is probably multifactorial [12].

In addition to symptoms mentioned above, there are number of signs that would alarming foot ulcer developing, include the following:

1-Wearing tight shoes leads to high pressure on adjacent toes, thus cause lesions between them.

2-Athlete's foot; this term refers to an area between toes, usually softened area. Notably, these lesions are often without pain and may go unnoticed until bacterial infection interrupts.

3-A painful swelling on the first joint of the big toe (Bunions), having an area of hardened skin (callused areas).

Furthermore, there are several signs would indicate present of diabetic foot infection, such as:

Superficial reddening of the skin (Erythema), Feeling of being warm (Warmth), these conditions would come in accompanied with tenderness.

In addition, few amounts of pus exit from the silt of ulcer may be seen. In condition of deep ulcer, the bone can bee also seen or detected using sterile probe, this condition has been known as osteomyelitis. In the same line of thought, large size of ulcer (larger than 2×2cm) would be another signs of osteomyelitis [13].

It has been illustrated that diabetic foot infections are usually polymicrobial. There are 5 to 7 different types of organisms might be involved in this infection. Thus, severity of diabetic foot wounds would be variable depending on the microbiology density involved [14-17].

Aerobic gram-positive cocci such as coagulase-negative staphylococci, *S. aureus* and *S. agalactiae*, have been known to cause superficial diabetic foot infections. On the other hand, deep ulcers usually categorized as chronic infection, and sometimes were treated previously. These infections due to present of above-mentioned organisms in addition to Pseudomonas aeruginosa, and Enterobacteriaceae, as well as anaerobes. Thus, it is known polymicrobial foot diabetic. Furthermore, ulcers areas that show abundant necrosis, local inflammation, and malodorous drainage, that accompanied with systemic toxicity signs, often presumed to have anaerobic organisms in addition to the mentioned organisms [18-22].

Clinical investigations have reported that traumatic injuries, crashes of skin, neuropathic, ischemic ulcers, or other defects in the skin of the foot or nail beds (paronychia) would be the main reasons behind development of diabetic foot infections. Thus, infection can be localized at the superficial layer of skin including the site of a preexisting lesion. In contrast, the infection might be in the deep layers of skin and spread elsewhere local trauma site. Notably, these types of infections can subsequently outspread to joints, bones as well as systemic circulation [18, 23]. Consistently, it has been shown that the cardinal manifestations of inflammation such warmth, erythema, swelling, and tenderness are usually concordance with a diabetic foot infections [15]. Even these signs are not enough to confirm the infection. As numerous investigations have revealed that certain infection might not accompanied with erythema and warmth. Furthermore, there is a diminish of sensation at the area of infection, thus diabetic patient might not complain of tenderness, even with the present of infection. This kind of infections categorized as dangerous one, as progress may reach to deep layer without any clinical attention [19].

It has been demonstrated that suggestive clinical manifestations are the primary base for diagnosis of diabetic foot infection. More specifically, presence of two or more signs of the following, swelling, warmth, tenderness, induration, erythema and purulent secretions) can be considered for the final diagnosis. Despite most wounds of diabetic patients with ulcers foot shows aggregation of bacteria, culture from infection area that show growth of microbial, without clinical signs is not realize to reach final diagnosis of infection [24, 25].

It has been illustrated that patients with a diabetic foot infections requires special management. Particularly, balanced and supportive nutrition, wound management with care, using the appropriate antimicrobial therapy, electrolyte balance, and glycemic control. In the same line of thought, wound management requires removing of necrotic tissue, eliminating of any foreign tissues, relief of pressure on the ulcer, and continuous wound cleansing [24, 25]. Moreover, it has been reported that severity of infection should be the indicator to select the most suitable Antimicrobial therapy [24]. Interestingly, it was well established that patients without infected ulceration should not take any antibiotic therapy [26, 27]. On the other hand, those patients must receive better local wound management, as well as try to diminish the pressure on the infection sit.

In most sever and moderate diabetic foot infection, surgical consultation is required. In fact, surgical elimination is important for cure of infections complicated by extensive bone or joint involvement, abscess, crepitus, gangrene and necrosis. As well as it is essential for source control in patients with severe sepsis [24, 28, 29]. It has been reported that patients who experienced surgical intervention during presentation time had low rate of above ankle amputation than patients who received intravenous antimicrobial therapy during three days before surgery.

It was well demonstrated that in addition to surgical debridement, capillarization or amputation may be necessary in some cases. Importantly, vascular evaluation is essential to determine the surgical requirement [23, 24].

Numerous studies have demonstrated that constant phagocytic activity is essential for normal body functions. Consequently, dysfunction of phagocytic process would result in a wide range of infections. Importantly, individuals who have been infected are more prone to fungal and bacterial infections, even they have viral infection resistance. Previous investigation has shown that abnormality of granulocyte development or its departure to the circulation would probably result in granulocytes function disorders. Furthermore, granule deficiency, glycogen storage disease type IB, and chronic granulomatous disease are the main reasons behind intrinsic phagocytic disorders [30]. It has been demonstrated that severe bacterial and fungal infections are majorly due to deficiencies of primary phagocytic [31]. Moreover, same investigation has concluded that individuals with chronic

granulomatous disease, shows abnormal response nontuberculous mycobacteria. Notably, in addition to organs and tissues with abscesses, skin and respiratory passages are the most infection sites [31].
This study was aimed to investigate phagocytic activity in patients with a diabetic foot.

Materials & Methods

A current experimental study was carried out on patients with a diabetic foot in Alzahraa and Alkarama Teaching Hospitals, Wasit, Iraq. Sample collecting was from January 2017 to January 2020. A total of 150 samples was collected. Blood samples were in three categories; 50 samples from patients with type one diabetes mellitus (DM1), 50 samples from patients with type two diabetes mellitus (DM2), and 50 samples from healthy individuals as a control. We excluded the patients with immune deficiency syndromes; immunological diseases; AIDS patients; other serious comorbid conditions like renal failure, etc.
Directorate Wasit of health under the supervision of ethically approved committee in college of medicine Wasit University approved this research. Demographic data such as age, gender were recorded before the checkup in Al-Zehra teaching hospital and Al-Krama teaching hospital. Blood samples were transferred into EDTA tubes, then 5ml of blood were pipetted in a plain tube. Thereafter, 0.5ml of working nitro blue tetrazolium solution (Thermo Fisher, USA) was prepared by mixing an equal volume of 0.2% nitro blue tetrazolium solution with phosphate-buffered saline (Medicago AB Uppsala, Sweden). Next, the plain tube was incubated at 37°C for 15 minutes in a water bath before being left for another 15 minutes at room temperature. A blood smear from the prepared mixture was then stained using Gemza stain [32]. Finally, 100 neutrophils were randomly calculated, and the positive with formazan phenomena appear with blue-black granules were counted out of 100 cells.
Relation between the phagocytic activities of the three groups was assessed using an independent sample t-test. A $p<0.05$ was considered significant. The statistical data analysis was performed with SPSS 22.

Findings

The mean±SD age of patients in the control, DM1, and DM2 groups were 29.78±8.13, 29.06±7.96, and 38.86±7.53, respectively. In the control, DM1, and DM2 groups 19 (38%), 20 (40%), 24 (48%) people were female, respectively.
The phagocytic activity was significantly higher in healthy control individuals compared to DM1 and DM2 ($p<0.05$; Table 1).

Table 1) Result of phagocytic activity for three groups

Group type	Mean±SD
Control	14.10±3.96
DM1	10.54±3.60
DM2	11.88±3.54

Also, there was a significant difference between DM1 and control ($p=0.448$, $F=0.58$), and DM2 and control ($p=0.314$. $F=1.02$) in term of phagocytes activity.

Discussion

Numerous studies have demonstrated that type 2 diabetes is a major public health problem that affecting approximately 10.4 % of Iraq population [33]. In the same line of thought, reports from United States have referred to 25% are remaining undiagnosed [34]. Furthermore, it has been demonstrated that the last three decades show doubling in the incidence of type tow diabetic mellitus [35]. Thus, diabetic mellitus type two profoundly increased around the world [36-38]. Despite studies have illustrated that type one diabetes affecting approximately less than 0.5% of whole population, its occurrence keep rising [39].
Our observations display that the phagocytic activity of neutrophiles significantly declined in samples from DM type one patients with a diabetic foot (mean 10.54%), and samples from DM type two patients with a diabetic foot (mean 11.88%) in comparison to control group (mean 14.10%), $p<0.05$. Importantly, results of current study are in agreement with outcomes of Albert and his group's study, which shoed clear reduction of phagocytic activity in patients with type two Diabetes Mellitus [40]. It has been revealed that interaction between plasma protein and glucose is main reason behind phagocytosis abnormalities [41]. Moreover, study by Sofia's team has shown that macrophage responses to cytokine stimuli would be profoundly induced due to high glucose exposure, which negatively reflected on phagocytic activity [42]. Another investigation has referred to a negative correlation between high level of blood glucose and phagocytic activity particularly in diabetic patients [43].
This study was mainly designed to determine whether there is any alteration of neutrophils function, particularly their phagocytic activity in patients with a diabetic foot which is important factor that can impact diabetic foot ulceration. It has been shown that number of factors would affect phagocytosis activity, for instance disruption of phagocytic receptors, and reduction in expression of adhesion molecules [44, 45].
we recommend immunohistochemistry studies to determine the main markers of inflammation that can give significant ideas about the phagocytic activity, especially in diabetes mellitus patients.

Conclusion

There is a reduction of phagocytic activity in patients with both types of diabetes mellitus with a diabetic foot comparing the healthy group.

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Ethical Permissions: This study was under the supervision of an ethically approved committee in the college of medicine of Wasit University.

Conflicts of Interests: -

Authors' Contribution: Adnan Mohammed H. (First Author), Introduction Writer/Methodologist/Main Researcher/Discussion Writer (34%); Qassim Mohammed H. (Second Author), Methodologist/Assistant Researcher (33%); Salman Omairi S. (Third Author), Assistant Researcher (33%).

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