The correlation of fasting blood glucose levels with the severity of diabetic foot ulcers and the outcome of treatment strategies.

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Abstract

Background: The prevalence of type 2 diabetes mellitus (T2DM) and related complications are rapidly rising worldwide. Diabetic Foot Ulcer (DFU) carries a high risk of proximal or distal amputation. This study explored the correlation of fasting blood glucose levels with the grades of DFUs and the outcome of treatment strategies offered.

Materials and methods: The data of all consecutive patients admitted to the surgical unit with DFUs was recorded for demographic information, grades of DFUs, fasting blood glucose, limb vascularity, treatment strategies offered and the outcome of treatment were recorded.

Results: Of a total of 252 patients, 144 (57.1%) had fasting blood glucose level of ≥ 220 mg (%) and 14 (5.6%) had values between 80-100 mg (%). Majority of patients (131; 51.9%) presented with grades 4 and 5 DFUs. A total of 123 amputations were performed, however, only 83 (32.9%) improved and 154 (61.1%) did not (p value 0.00).

Conclusion: In this study the majority of patients had poorly controlled T2DM with advanced stage of DFUs that necessitated amputations. An interdisciplinary approach with optimal control of fasting blood glucose and an early detection and aggressive treatment of tissue infection can reduce the frequency of lower limb amputations and T2DM-related morbidity.

Keywords: Diabetes mellitus, Diabetic foot ulcer, Diabetic neuropathy, Lower limb ischemia, Amputations.

Introduction

There is a dramatic rise in the prevalence of Type 2 Diabetes Mellitus (T2DM) and its associated complications across the globe. The projected worldwide burden of diabetic patients is estimated to escalate from 135 million in 1995 to 300 million in 2025 [1]. In addition, there is an exponential increase in the devastating long-term complications of T2DM including peripheral artery disease [2], strokes [3], cardiovascular disorders, biliary tract disease [4], hyperlipidemia [5], colorectal cancer [6] and sepsis [7]. A study has reported a prevalence of 8.1%-41.5% for T2DM related retinopathy, 21%-22% for albuminuria, 6.7%-46.3% for nephropathy and 21.9%-60% for neuropathy [8]. In parallel with the rest of the world, a report in 2013 has ranked Saudi Arabia in the seventh highest by showing 23.9% prevalence of adult DM in the world [9]. Alzahrani et al. have reported a 1-year cumulative incidence 1.8% for DFU and 0.6% for amputation [10]. Another study has reported an overall prevalence of 10.4% for DFU in Riyadh region of Saudi Arabia [11]. Unfortunately, an accurate data from nationwide registry about T2DM and DFU is not available in Saudi Arabia that hampers a true reflection of the burden and threat of T2DM in the country.

Owing to a high susceptibility to concomitant infection, hyperlipidemia, and peripheral vasculopathy in diabetic patients, long-standing T2DM invariably lead to neuropathy, lower limb ischemia and Diabetic Foot Ulcers (DFUs). The estimated lifetime risk of a diabetic patient to develop a DFU has been reported to range from reach 15% to 25% [12].
Furthermore, DFUs continue to be responsible for an ever increasing number of lower-limb amputations and increased risk of mortality [13]. Peripheral artery disease is found in about 50%-70% of DFUs and is a strong predictor of non-healing ulcers, limb amputation, and high morbidity and mortality [13]. The risk for mortality from a single DFU after 5 years has been reported to range between 43% and 55% [14]. The survival rate of patients with DFUs is reported to be much shorter than the patients diagnosed with malignancies of prostate, breast, colon or lung [15]. A plethora of cross-sectional clinical studies have shown that DFUs lead to a significantly low Health-Related Quality of Life (HRQoL) and depression [16-18]. Research-based evidence has clearly shown that healing of DFU leads to an improved HRQoL; whereas a non-healing ulcer is often associated with a further decrease in HRQoL [19,20].

Depending upon the severity of infection and ischemia, diverse management strategies are employed for DFUs including wound dressings and surgical debridement, antibiotics, control of T2DM, and amputations. In the USA, T2DM is a major cause of non-traumatic amputations (approximately 65,700 per year) with consequent morbidity and mortality [21]. Although appropriate control of T2DM can potentially reduce the prevalence of DFUs, there is scarcity of literature that has quantified the correlation between fasting blood glucose levels and the risk of the development of DFUs. This study aimed to determine the correlation of the severity of DFUs with fasting blood glucose levels of patients with DFUs. At the same time, the outcome of the range of treatment strategies offered to patients with various grades of DFUs is analysed in the studied cohort.

Methods and Materials

In this retrospective clinical study, during February to June 2017, the medical records of all consecutive patients aged more than 12 years admitted with diagnosis of DFUs through the surgical clinics and emergency room of Meeqat General Hospital Almadinah Almunawwarah during August 2012 to July 2016 were reviewed. The ethical approval was obtained at the start of this research. The patients with septic foot without diabetes mellitus were excluded from this study. The diagnosis of DFU was reached by a focused history, careful clinical examination, lab blood results, wound swabs when present, foot X-rays and a duplex scan of the lower limbs (Figure 1). The data about demographics, presenting features, fasting blood glucose, grades of foot ulcers according to the Meggitt-Wagner Ulcer Classification System [22], the treatment strategies offered, and the outcome of treatment were collected and further analysed.

The data was entered and analysed by Statistical Package for Social Sciences (SPSS) v. 20. The descriptive analysis was done by frequency distribution tables and the graphical presentation was done by cluster bar charts. The inferential statistics were done through Chi square of independence.

Results

An archival data of 252 patients from the selected four years was collected from medical records. Empirical results showed that 186 were men (73.8%) and 66 (26.2%) women, while the majority (32.7%) of patients was found to be in age group of 51-60 y (Table 1). As many as 180 (71.4%) were insulin dependent and only 72 (28.6%) patients were non-insulin dependent. Regarding the fasting blood glucose analysis, 144 (57.1%) patients had a value higher than 220 mg (%), and only 14 (5.6%) patients had normal fasting blood glucose levels.

The patients’ DFUs were ranked on the basis of traditional Meggitt-Wagner Ulcer Classification System as shown in Table 2. As many as 103 (40.8%) were found to have grade 4 ulcers, 49 (19.4%) grade 1 ulcers and 28 (11.1%) had grade 5 ulcers. The Chi square test of independence with value of 124.43 shows that there is significant difference among different grades of traditional Meggitt-Wagner ulcer classification system (p value<0.05).

Table 3 shows treatment strategies for DFUs; 104 (41.3%) patients with infected neuropathic ulcer were treated conservatively, 26 (10.3%) with complex diabetic foot with minimal salvage and then amputation, and 97 (38.5%) with complex diabetic foot were treated by amputations.

Table 4 presents the results of lower limb amputations and the results of final outcome in this study. Of a total 123 amputations, 56 (45.5%) were ray amputations, 36 (29.2%) had above knee amputation and 31 (25.2 %) below knee amputations. The age range of majority of patients with amputations ranged from 51-60 y while only 23 patients were found to be under 40 y of age. Major indications for amputation was sepsis and gangrene performed for 57 (46.3%) patients, while gangrene alone was the second major indication for amputation done on 41 (33.4) cases. Finally, the analysis of outcome of treatment offered to all 252 patients showed that 154 (61.1%) cases had no improvement and 83 (32.9%) patients reported improvement and only 15 (6%) patients’ condition worsened during the treatment.

Figure 2 graphically shows fasting blood glucose levels across different age groups as clustered bar chart. For convenience, age groups were grouped as 30-40, 41-50, 51-60, 61-70, 71-80 and more than 80 y. Severe effect of DM in terms of comorbidities was recorded in age group of 51 to 60 y.

Figure 1. An ischemic ulcer in a diabetic patient (A), osteomyelitis in the hallux, cellulitis with gangrene of 4th and 5th toe, and a healing wound after partial amputation.
The correlation of fasting blood glucose levels with the severity of diabetic foot ulcers and the outcome of treatment strategies

**Figure 2. Fasting blood glucose levels across different age groups in this study (N=252).**

**Discussion**

This study showed a high incidence of DFUs in men (186; 73.8%) than in women (66; 26.2%) with the maximum number of 80 (32.7%) patients in the age group of 51-60 y. Other studies have also reported a male preponderance in a similar age group [23,24]. Our study has reported that 144 (57.1%) patients had a fasting blood glucose value higher than 220 mg (%), and only 14 (5.6%) patients had normal fasting blood glucose levels. At the same time, as many as 131 (51.9%) patients presented with grades 4 and 5 DFUs as defined by the Meggitt-Wagner ulcer classification system. These findings clearly reflect that the majority of patients presented with poorly controlled T2DM and with a complicated foot ulcer either with osteomyelitis or with gangrene. In a prospective study on 4585 patients, Stratton et al. attempted to determine the correlation between hyperglycemia and the risk of microvascular and macrovascular complications of T2DM [25]. The investigators found a significant association between hyperglycemia and the risk of vascular complications in the lower limb. Another study by Kumar et al., conducted on 50 patients with Wegner grades 1 and 2 DFUs, showed that ulcer healing was faster in patients with low glycosylated hemoglobin levels; however there was no improvement of neuropathy or vasculopathy after 12 w of treatment [26]. Due to high rates of DFU recurrence, being as high as 50% after 3 years, a carefully scheduled follow up is mandatory [27].

The types of DFUs in our study showed a mixed pattern; neuropathic, ischemic and neuroischemic. The same pattern has been reported in other studies that reflects a combination of peripheral nerve damage, gradual narrowing of peripheral vessels with superimposed infection causing DFUs that ultimately result in osteomyelitis and/or gangrene [28,29]. Wound healing is a dynamic biological process that involves overlapping phases of hemostasis, inflammation, cellular proliferative and scaffolding with remodeling [30]. These entire biological cascades engage several cell types, extracellular components, growth factors and cytokines. In patients with T2DM, wound healing is significantly impaired due to persistent hyperglycemia, indolent chronic inflammation, microvascular dysfunction, and tissue hypoxia complicated by autonomic as well as sensory neuropathy and impaired neuropeptide signaling. An indicator of ongoing infection with cellulitis and potential sepsis is the leucocyte count. However, a normal leucocyte count can be misleading [31]. Diabetic peripheral neuropathy enhances the risk of DFUs due to the loss of cutaneous sensation as the patients become vulnerable to trivial trauma that goes unnoticed [32]. Diabetic neuropathy is also an established threat for the development of diabetic Charcot neuroarthropathy that can result in crippling foot deformities [33]. All such pathophysiological events can be arrested by achieving an optimal glycemic control that can significantly reduce the T2DM related morbidity and mortality [34].

In this study, 123 (41.3%) different kinds of amputations were performed and, interestingly, a maximum of 77 (62.6%) patients belonged to the age group of 51-60 y. We have found that the same age group, in our study, presented with adverse grades of DFUs and with poorly controlled T2DM. Statistics have shown that, out of the 80,000 amputations performed in the USA per annum, approximately half of these belong to below-knee or more proximal amputations [35]. The estimated 1-year mortality rate after a below-knee amputation ranges between 20.8% and 35.5% [36], with a reported contralateral limb loss rate of 53.3% within 5 years [37]. Research has deduced that proximal amputations result in decreased ambulatory status due to inefficient biomechanics, hence when possible, partial foot amputation is recommended that will reduce morbidity and will help restore biomechanics esp. in old frail patients [38,39]. The results of our study articulate well with this understanding as, of a total of 123 amputations, a highest number of 56 (45.5%) ray amputations were performed in our cohort, followed by 36 (29.2%) above knee and 31 (25.2%) below knee amputations. Partial first ray resection was performed for ulcers underneath the first metatarsal head that were complicated by cellulitis or osteomyelitis; whereas amputation of the hallux and removal of the first metatarsal head was considered in cases of proximal spread of infection or hallux ulcerations. The recovery of the limb after amputation is predominantly influenced by the extent of arterial disease but, unfortunately, revisions of minor amputation sites or even proximal amputations are frequent and the non-healing of minor amputations has been shown to be approximately 30%-45% [40].

As many as 154 (61.1%) patients in our cohort did not show any signs of improvement despite optimizing T2DM, wound dressings and pressure off-load, antibiotics, surgical debridement and/or amputations. In contrast, 83 (32.9%) patients improved and 15 (6%) deteriorated despite multidisciplinary care. Old age, patient general health status, advanced degree of ulcers at the time of presentation, poorly controlled T2DM and severe comorbidities (neuropathy, nephropathy, sepsis, poor nutritional and immune status, and ischemia) might have potentially contributed to this low response. Our hospital is not equipped with modern state-of-the-art dressing such vacuum assisted closure dressing [41], topical growth factor therapy [42], negative pressure wound therapy [43], or hyperbaric oxygen that could have improved the outcome to some extent. This emphasizes the need for a structured work-placed based educational program [44] as well as accredited surgical training platforms [45] that can supplement the specialist surgeons’ learning needs in
concordance with their learning styles [46]. This necessitates a multi-disciplinary integrated surgical approach that adheres to the core principles of interprofessional education and practice [47]. Implementing modern techniques in stem cell technology and tissue engineering for replacing or regenerating human tissues by regenerative medicine [48]. Lastly, enhancing surgeons’ skills and knowledge can reduce the incidence rates of surgical complications [49] with improved patient safety and quality of life [50].

**Table 1.** Frequency distribution of patients with diabetic foot infections in this study (N=252).

<table>
<thead>
<tr>
<th>Area</th>
<th>Components</th>
<th>Frequency</th>
<th>Chi square</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>Male</td>
<td>186 (73.8%)</td>
<td>8.72</td>
<td>0.00'</td>
</tr>
<tr>
<td>Age</td>
<td>30-40 y</td>
<td>20 (7.9%)</td>
<td>86.33</td>
<td>0.00'</td>
</tr>
<tr>
<td>Insulin</td>
<td>Dependent</td>
<td>180 (71.4%)</td>
<td>10.56</td>
<td>0.00'</td>
</tr>
<tr>
<td>Fasting blood glucose (mg (%))</td>
<td>80-100</td>
<td>14 (5.6%)</td>
<td>222.76</td>
<td>0.00'</td>
</tr>
<tr>
<td>Treatment offered</td>
<td>Dressings and pressure off-loading</td>
<td>93 (44.4%)</td>
<td>46.5</td>
<td>0.00'</td>
</tr>
</tbody>
</table>

Note: ’represent variable is significant at 5% level of significance.

**Table 2.** Frequency distribution of traditional Meggitt-Wagner Ulcer Classification System (N=252).

<table>
<thead>
<tr>
<th>Category</th>
<th>Components</th>
<th>Frequency</th>
<th>Chi square</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1</td>
<td>Superficial</td>
<td>49 (19.4%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 2</td>
<td>Deep ulcer</td>
<td>35 (13.8%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Table 3.** Treatment strategies for diabetic foot ulcers in this study (N=252).

<table>
<thead>
<tr>
<th>Type of diabetic foot</th>
<th>Range of treatment strategies</th>
<th>Frequency</th>
<th>Chi square</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neuropathic ulcer</td>
<td>Conservative</td>
<td>62 (24.6%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infected neuropathic ulcer</td>
<td>Conservative</td>
<td>104 (41.3%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complex diabetic foot</td>
<td>Minimal salvage</td>
<td>41 (16.3%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complex diabetic foot</td>
<td>Amputation</td>
<td>97 (38.5%)</td>
<td>39.43</td>
<td>0.00'</td>
</tr>
<tr>
<td>Complex diabetic foot</td>
<td>Minimal salvage and then amputation</td>
<td>26 (10.3%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischemic diabetic foot</td>
<td>Angioplasty, surgical bypass and graft</td>
<td>47 (18.6%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note: ’represent variable is significant at 5% level of significance.

**Table 4.** Lower limb amputations performed for diabetic foot in this study (N=252).

<table>
<thead>
<tr>
<th>Feature</th>
<th>Frequency</th>
<th>Chi square</th>
<th>P value</th>
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</thead>
<tbody>
<tr>
<td>Amputation analysis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amputation</td>
<td>Above knee</td>
<td>36 (29.2%)</td>
<td>8.54</td>
</tr>
<tr>
<td></td>
<td>Below knee</td>
<td>31 (25.2%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ray amputation</td>
<td>56 (45.5%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>30-40 y</td>
<td>23 (18.7%)</td>
<td>154.6</td>
</tr>
<tr>
<td>Age at amputation</td>
<td>41-50 y</td>
<td>19 (15.4%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>51-60 y</td>
<td>77 (62.6%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>61-70 y</td>
<td>3 (2.4%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>71-80 y</td>
<td>1 (0.8%)</td>
<td></td>
</tr>
</tbody>
</table>

Indications of amputation

<table>
<thead>
<tr>
<th></th>
<th>Frequency</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sepsis and gangrene</td>
<td>57 (46.3%)</td>
<td>12.49</td>
</tr>
</tbody>
</table>

Outcome

<table>
<thead>
<tr>
<th></th>
<th>Frequency</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No improvement</td>
<td>154 (61.1%)</td>
<td></td>
</tr>
<tr>
<td>Deteriorated and got worse</td>
<td>15 (6%)</td>
<td></td>
</tr>
</tbody>
</table>

**Table 2.** Frequency distribution of traditional Meggitt-Wagner Ulcer Classification System (N=252).

<table>
<thead>
<tr>
<th>Category</th>
<th>Components</th>
<th>Frequency</th>
<th>Chi square</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 3</td>
<td>Deep ulcer osteomyelitis</td>
<td>37 (14.6%)</td>
<td>124.43</td>
<td>0.00'</td>
</tr>
<tr>
<td>Grade 4</td>
<td>Deep ulcer gangrene</td>
<td>103 (40.8%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 5</td>
<td>Gangrene of the whole foot</td>
<td>28 (11.1%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note: ’represent variable is significant at 5% level of significance.
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Note: Total number of amputations is 123. Note: *represent variable is significant at 5% level of significance.

Conclusion

DFUs pose a major threat to well-being of the diabetic patients and contribute to significant morbidity. Fasting blood glucose levels are correlated with the severity of DFUs. A high rate of failure in improvement reflects an advanced stage of T2DM and DFUs, complicated by T2DM related comorbidities that become refractory to medical and surgical therapies. This study emphasizes the need to carefully identify the patients at greatest risk of developing foot ulcers by meticulous clinical examination of the feet, education about diabetes control and foot hygiene and rigorous follow-up.

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Authors’ Contributions

SYG substantially contributed to the conception or design of the work, the acquisition, analysis, interpretation of data, and drafting the work and revising it critically for important intellectual content. HH, NAM, KYF, BAA, and HAA contributed by data collection, revising the drafts of manuscripts. All authors approved the final version to be published and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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