Original Article

Is hemoglobin A1c level effective in predicting the prognosis of Fournier gangrene?

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Abstract

Objectives: To evaluate the effect of immune failure and/or diabetes mellitus (DM) association on the mortality and morbidity of the Fournier's Gangrene (FG), and interrelatedly, the usability of HbA1c level in the prediction of prognosis.

Materials and Methods: The data of 38 patients with the diagnosis of FG were investigated retrospectively. The patients were divided into two groups as patients with DM (Group 1, $n = 18$) and non-diabetics (Group 2, $n = 20$). The patients in group 1 were also divided into two subgroups as patients with HbA1c value ≥7 (Group 1a) and HbA1c value <7 (Group 1b).

Results: The mean age of all 38 male patients was 66.3 ± 6.4 years. The initial symptoms were scrotal rash and swelling ($n = 20$, 52.6%), high fever (>38°C) ($n = 22$, 57.8%), purulent discharge from genital or perineal areas ($n = 13$, 34.2%), skin bruises ($n = 11$, 28.9%) and general state disorder in five patients that were admitted from day care center (13.1%). DM, as the most often comorbid disease, was detected in 18 patients (47.3%). Six patients (15.7%) were deceased during the follow-up period.

Conclusion: In the present study, the researchers determined that diabetic patients with HbA1c level of 7 or higher had worse prognosis, and increased mortality.

Key Words: Diabetes mellitus, Fourniere's gangrene, hemoglobin A1c

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Received: 07.05.2015, **Accepted:** 05.08.2015

INTRODUCTION

Fournier gangrene (FG) is the sudden and rapidly progressive necrotizing fasciitis of the fascias in genital, perineal and perianal areas. Following its onset, it can progress upward in the facial plane, and spread to the abdomen wall.[1] The incidence of the disease is 1.6/100.000 in males, and its peak incidence occurs in the fifth and sixth decade.[2] The male/female ratio is approximately 10/1.[3]

Access this article online	
Quick Response Code:	Website: www.urologyannals.com
	DOI: 10.4103/0974-7796.184905

Effective pathogens taking part in FG etiology are generally skin, genitourinary, and gastrointestinal-derived polymicrobial anaerobic and aerobic microorganisms and they can be identified in 95% of the cases.[4] Pathogens that are often isolated from wound site cultures are *Escherichia coli*, *Streptococcus*, *Staphylococcus*, *Enterococcus*, and *Bacteroides* species.[5] Methicillin-resistant and *Candida* species can also be isolated from the patients who are hospitalized for a long

How to cite this article: Sen H, Bayrak O, Erturhan S, Borazan E, Koc MN. Is hemoglobin A1c level effective in predicting the prognosis of Fournier gangrene?. Urol Ann 2016;8:343-7.

period of time.[6] Bacterial infection leads to thrombosis in small subcutaneous veins, and thus creates a suitable condition for the growth of anaerobic microorganisms by lowering the amount of the oxygen in the tissue during the development process of the disease. The presence of the diabetic microangiopathy makes this situation worse. On the other hand, the enzymes such as collagenase, heparinase, hyaluronidase, streptokinase, and streptodornase, which are produced by either anaerobic or aerobic microorganisms, accelerate the tissue breakdown and cause rapid progress by disrupting the vascularity.[7]

In the present study, the demographic and clinical data, and the treatments of the patients who were admitted to the Urology Department in the last 5 years were investigated retrospectively. The study aimed to investigate the effect of immune failure and/or diabetes mellitus (DM) association on the mortality and morbidity of the disease, and inter-relatedly, the usability of hemoglobin A1c (HbA1c) level in the prediction of disease prognosis in this patient group.

MATERIALS AND METHODS

The data of 38 patients who were admitted to Gaziantep University Medical Faculty Urology Clinic between January 2008 and July 2013 with the diagnosis of FG were investigated retrospectively. The patients were divided into two groups as patients with DM (Group 1, $n = 18$) and nondiabetics (Group 2, $n = 20$). The patients in Group 1 were also divided into two subgroups as patients with HbA1c value ≥7 (Group 1a) and HbA1c value <7 (Group 1b).

The time period between the onset of the first symptoms and the time of admission was set at the first admission time. All patients underwent systemic and urological physical examination following their medical history during their initial evaluation. The patients who were monitored for vital findings (temperature, heart rate, respiratory rate, and arterial blood pressure) were hospitalized. Considering the possible etiology, consultation was requested from relevant departments including general surgery, endocrinology, cardiology, and gastroenterology. Routine laboratory tests (serum urea, creatinine, sodium, potassium, calcium, chloride, alanine transaminase, aspartate aminotransferase, whole blood count, sedimentation, and C-reactive protein level), arterial blood gas analyses, urine analysis, urine culture, blood cultures and when needed, radiological imaging were requested.

All patients were administered with empirical parenteral ceftriaxone (2 g/day), gentamicin (160 mg/day) or netilmicin (appropriate doses, according to level of creatinine) and ornidazole (1 g/day). Medical treatments of patients were readjusted in one of the following conditions: (1) Who had no recovery in their clinical or laboratory values within the first 48 h, (2) Who did not respond to empirical treatment, or (3) Growth of different types of microorganisms in cultures. Debridement under general anesthesia was performed for all patients, and multiple wound cultures from the collected tissues were sent for analysis. Urethral catheters or suprapubic catheter was used for urine drainage. During the postoperative early period, total parenteral nutrition and blood transfusion (when needed) were performed to provide calorie support.

Depending on the lesion extensity, wound debridement was performed once or twice per day. Debridement procedures were carried out within the intervention room in the urology service. Fentanyl (1–2 μg/kg) and/or midazolam (1 mg) intravenous (IV) was used as sedo-analgesics. Following the resection of necrotic tissues, wound sites were rinsed with povidone iodine and were closed with gauze containing 0.5% chlorhexidine acetate BP (Bactigras®). During the follow-up, the lesion was closed primarily (whenever possible), if the patient's wound site infection were recovered. In the case of wider lesions, split-thickness graft application was performed by the Department of Plastic and Reconstructive Surgery.

For each patient, Founier's Gangrene Severity Index (FGSI) that was defined by Laor *et al*.[5] and modified body surface area, nomogram were calculated to demonstrate the disease extent [Table 1]. In addition to the parameters within the index, the researchers also analyzed the HbA1c levels in DM patients. In addition, the effective pathogens in tissue cultures were recorded, and the growth $\geq 10^5$ colonies were considered significant.

Statistical analysis

SPSS windows version 11.5 (SPSS, Chicago, IL) was used for the analysis and *P* values lower than 0.05 were accepted as significant. Mann–Whitney U-test was used to compare the two independent groups, and the relationship between the categorical variables was tested by Chi-square analysis.

RESULTS

The mean age of all 38 male patients was 66.3 ± 6.4 years. The initial symptoms were scrotal rash and swelling ($n = 20$, 52.6%), high fever (>38°C) ($n = 22$, 57.8%), purulent discharge from genital or perineal areas ($n = 13$, 34.2%), skin bruises ($n = 11$, 28.9%), and general state disorder in 5 patients that were admitted from day care center (13.1%). DM, as the most often comorbid disease, was detected in 18 patients (47.3%). The other comorbid diseases were presented in Table 2. The underlying etiological factors were presented in Table 3. There was no etiological factor in

Table 1: FGSI

Physiologic variable	High abnormal values				Normal	Low abnormal values			
Point assignment	+4	+3	+2	+1	0	+1	+2	+3	+4
Temperature (°C)	>41	39-40.9	-	38.5-38.9	36-38.4	34-35.9	32-33.9	30-31.9	<29.9
Heart rate	>180	140-179	110-139	-	70-109	-	55-69	40-54	<39
Respiration rate	>50	35-49	-	25-34	12-24	10-11	6-9	-	<5
Serum sodium, mmol/L	>180	160-179	155-159	150-154	130-149	-	120-129	111-119	<110
Serum potasium, mmol/L	>7	6-6.9	-	5.5-5.9	3.5-5.4	3-3.4	2.5-2.9	-	<2.5
Serum creatinine, mg/100 mL, ×2 for acute renal failure	>3.5	2-3.4	1.5-1.9	-	0.6-1.4	-	<0.6	-	-
Hematocrit, %	>60	-	50-59.9	46-49.4	30-45.9	-	20-29.9	-	<20
White blood cell count, total/mm^3×1000	>40	-	20-39.9	15-19.9	3-14.9	-	1-2.9	-	<1
Serum bicarbonate	>52	41-51.9	-	32-40.9	22-31.9	-	18-21.9	15-17.9	<15

FGSI: Founier's gangrene severity index

10 patients (26.3%); however, these patients had bad self-care. The effective pathogens were presented in Table 4. Accordingly, *E. coli* was the most frequently isolated microorganism in both groups. When the clinical and laboratory values in Group I patients were compared to Group 2 patients, Group I had statistically significant mean age, shorter first admission time (as the disease progressed faster), longer hospitalization time, higher lesion width, and higher FGSI scores [Table 5]. Within Group I patients, patients in Group Ia had longer hospitalization times, broader lesion area, and higher FGSI scores compared to the patients in Group Ib [Table 6]. Six patients (15.7%) were deceased during the follow-up period. Most of these patients were in Group Ia ($n = 4$) while I patient was in Group Ib, and I was in Group 2. FGSI scores were significantly higher in the deceased patients (15.2 ± 3.3 vs. 5.2 ± 1.6, $P < 0.0001$).

DISCUSSION

The key to success in the treatment of FG is the early and aggressive debridement of the necrotized tissue.[8,9] The mortality rate may reach to 88% despite this aggressive treatment.[2] Immune suppression diseases such as DM with vascular damage, chronic alcohol consumption, HIV infection, cardiac disorders, systemic lupus erythematosus, renal failure, and trauma can be regarded as predisposing factors.[2] The mortality rate of FG is high, and the range is between 20% and 50% despite the recent developments.[10,11]

Criteria for determining mortality have been investigated and among these; the correlation between advanced age, primary anorectal infections, presence of DM, sepsis, delayed treatment, width and depth of involvement, low level of hematocrite, high leukocyte count, BUN, alkaline phosphotase and albumin levels, and prognosis has been studied.[2,10-13] On the other hand, there are some studies which indicate that the disease dissemination is the most important factor affecting the disease progression, as it reflects the status of the patient's immune system.[8,14]

In 1995, Loar *et al.*[5] developed FGSI in order to evaluate the severity of the disease. A total of nine parameters were defined in this index, and the degree of deviation from normal was graded from 0 and 4 [Table 1]. Again in the same study, the authors reported that the mortality risk was 75%, if the FGSI score is >9, and 78%, if the FGSI score is <9. In some of the following studies, FGSI has been shown to be used to predict the disease prognosis and mortality. In their 27 patient-series, Ulug *et al.* found that FGSI scores were 5.04 ± 2.49

Table 2: FG associated conditions

Co-morbite disease	Patients (*n*) (%)
DM	18 (47.3)
Chronic alcoholism	3 (7.8)
Liver chirrosis	2 (5.2)
Rectum carcinoma	1 (2.6)
Congestive heart failure	4 (10.5)
No	10 (26.3)

DM: Diabetes mellitus, FG: Fournier gangrene

Table 3: Bacterial organisms isolated from wound cultures of patients with FG

Organisms	Group 1 *n* (%)	Group 2 *n* (%)
Escherichia coli	16 (42.1)	12 (31.5)
Bacteriodes spp.	2 (5.2)	2 (5.2)
Pseudomonas aeruginosa	2 (5.2)	2 (5.2)
Staphylococus aeruginosa MRSA (+)	1 (2.6)	-
Enterobacter	1 (2.6)	-

FG: Fournier's gangrene, MRSA: Methicillin-resistant *Staphylococcus aureus*

Table 4: Etiological factors with FG

Etiological factors	Patients (*n*) (%)
Genitoperineal abscess	10 (26.3)
Urinary tract infection	12 (31.5)
Posthydrocelectomy	1 (2.6)
Postprostatectomy	1 (2.6)
Ureteral stricture	4 (10.5)
No	10 (26.3)

FG: Fournier's gangrene

Table 5: Clinical and laboratory findings in both groups

	Group 1 (*n*=18)	Group 2 (*n*=20)	*P*
Age (year)	60.1±5.1	64.2±7.1	0.001
First admission time (day)	1.4±0.6	3.1±0.9	0.001
Hospitalization (day)	22.5±6.8	19.0±4.8	0.006
Lesion length (cm^2)	197.5±98.9	99.1±13.7	0.007
FGSI	14.9±2.3	5.5±2.1	0.001
HbA1c	8.9±1.1	-	

FGSI: Founier's gangrene severity index, HbA1c: Hemoglobin A1c

Table 6: Clinical and laboratory findings in the subgroups of group 1

	Group 1a (*n*=6)	Group 1b (*n*=12)	*P*
Age (year)	70.0±2.0	68.9±1.4	0.80
First admission time (day)	1.6±0.8	2.4±0.6	0.76
Hospitalization (day)	28.4±5.3	21.2±3.8	0.002
Lesion length (cm²)	240±109.5	197.5±98.9	0.002
FGSI	16±2.1	14±1.8	0.033
HbA1c	11.8±1.4	6.6±0.4	0.001

FGSI: Founier's gangrene severity ındex; HbA1c: Hemoglobin A1c

and 13.6 ± 4.6 in surviving patients and deceased patients, respectively ($P < 0.0001$).[15] In the retrospective study by Yeniyol *et al*. on 25 patients, the authors found that FGSI levels were 3.0 ± 1.8 and 12 ± 2.4 in surviving patients and deceased patients, respectively.[16] On the other hand, in their 20 patient-series, Tuncel *et al*. defended that FGSI could not be used to predict the mortality and that predisposing factors and the length of the lesions were more important criteria.[17]

In our study, FGSI levels were found to be statistically significant as 14.9 ± 2.3 and 5.5 ± 2.1 in Group 1 and Group 2, respectively ($P = 0.001$). Similarly, FGSI scores were significantly higher in deceased patients compared to surviving patients (15.2 ± 3.3 vs. 5.2 ± 1.6, $P < 0.0001$).

DM, a metabolical disease, has been long recognized as a risk factor for FG, and is seen in 10–60% of DM patients.[18] Deterioration in chemotaxis, phagocytosis, and cellular digestion functions are seen in DM, which in turn increases the predisposition to infections.[19] Tuncel *et al*.[17] carried out a study on 20 FG patients and found that 66% of the deceased patients had DM, thus reporting that DM might be a major predisposing factor. HbA1c, which reflects the mean glycemic control of the past few months, is a very common laboratory test to predict the diabetes-associated complications in DM patients.[20,21]

In the present study, 4 patients in Group 1 required mechanical ventilator support, and these patients were deceased in the surgical Intensive Care Unit. At the same time, three of these 4 patients had HbA1c levels of 7 or higher. Hospitalization time was longer in DM patients (22.5 ± 6.8 days) compared to nondiabetic patients (19 ± 4.8 days) ($P = 0.03$).

Perineal infections are the most common cause of infections in FG. However, in their 1726 FG patient-series, Eke[10] reported that the infection foci was the skin in 24% of the patients, colorectal in 21% of the patients, and urogenital system in 19% of the patients, while the disease appeared idiopathically in 36% of the patients. On the other hand, the researchers of the present study did not determine any etiological factors in 26.3% of the cases, but detected urinary tract infection in 31.5% of the patients and genitoperineal abscess in 26.3% of the patients.

Aerobic and anaerobic patients can be isolated from FG patients. Most frequently isolated microorganisms include *E. coli* (80%), *Klebsiella pneumonia*, *Bacteroides*, *Pseudomonas*, *Staphylococci*, and *Enterobacter* species.[10,19,22] In the present study, the most frequently isolated microorganism was *E. coli*, and other isolated microorganisms were similar to the previous studies.

For FG, it is recommended to start with preoperative broad spectrum antibiotic treatment with double or triple combinations, and to continue the same treatment regime or change antibiotic type according to the result of the culture antibiogram.[10,19]

In the case of our patients, the triple empirical treatment involving ceftriaxone, ornidazole, and gentamicin was started IV after the initial evaluation, then the treatment regime was readjusted according to the result of the culture antibiogram. Frequent debridement is recommended to control the severe infection in FG patients.[23] For all patients, either urinary catheterization or cystostomy was performed, infected tissues were debrided and the debridement procedure was repeated in case of clinical requirement. The lesion area in both groups were 211 ± 101.4 cm² and 96.6 ± 13.2 cm² in Group 1 and Group 2, respectively ($P = 0.001$). The infected wound was treated with hydrogen peroxide and povidone iodine. The major limitations of our study are the small sample size, and retrospective nature. These results should be supported by prospective, randomize, and large patient series.

CONCLUSION

Despite the contradictory series regarding the correlation between DM, which is a risk factor in FG patients, and mortality, our findings showed that the presence of DM was both a predisposing factor for FG, and also worsened the progress of the existing clinical condition. In the present study, the researchers determined that the diabetic patients with HbA1c level of 7 or higher had a worse prognosis, and increased mortality. In addition to FGSI, which was described by Laor *et al*. for the first time, the researchers of the present study believe that HbA1c levels can also prove to be useful to predict the mortality and morbidity rates in diabetic patients.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

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