

# Is high level of hemoglobin A1C an indicator for extended period of antibiotherapy in diabetic foot ulcers?

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## ABSTRACT

**OBJECTIVE:** Diabetic foot ulcers are the most common cause of hospitalization among the diabetic complications. Hemoglobin A1C (HbA1C) has a critical role in medical follow-up of diabetic patients. In fact, the role of HbA1C and related clinical parameters has been investigated in literature there are only a few studies investigating the relationship between HbA1C and the prolonged antibiotherapy. We aim to reveal the reciprocal relationship between this two parameters.

**METHODS:** The clinical data of 139 patients who admitted with diabetic foot ulcers are analyzed retrospectively. Besides the demographic information, the levels of HbA1C wound localizations, the degree of the wounds regarding the Wagner classification, culture antibiogram, and the duration of the antibiotic agents. The data have been analyzed with IBM SPSS Statistics (IBM Statistical Package for the Social Sciences) for Windows 22.0.

**RESULTS:** The clinical data of the 139 diabetic foot patients are retrospectively assessed. The mean age was 56.50 ( $\pm 4.12$ ). There were 81 male (58.27%) and 58 (41.73%) female patients. The distal type diabetic foot ulcers were found to be the most frequent type ( $n=83$ , 59.71% [ $\pm 3.12$ ]). The mean HbA1C level was 9.60 ( $\pm 1.10$ ). The "7–15%" subgroups of HbA1C level patients showed statistically significant prolongation of the antibiotherapy time ( $p < 0.01$ ).

**CONCLUSION:** The results showed that the higher levels of HbA1C have a significant effect on treatment duration and formation of deeper and larger wounds with advanced stages of Wagner classification. This result may reveal the importance of the exact starting time of the treatment besides the proper glycemic control. Larger scaled studies may clarify the credited parameters related to diabetic foot ulcers for a reinterpretation of the issue.

*Keywords:* Antibacterial agents; diabetic foot; hemoglobin A1c.

**Cite this article as:** Dogan M, Onar LC, Aydin B, Gumustas SA. Is high level of hemoglobin A1C an indicator for extended period of antibiotherapy in diabetic foot ulcers? *North Clin Istanbul* 2019;6(1):21–27.

Diabetes has been shown to be one of the leading causes of death worldwide [1]. In addition, surviving patients face a wide range of complications, from renal failure to major amputations, from vision loss to acute coronary events. Although the weight of this disease appears to be a major problem when the patients

are evaluated individually, the actual size of the problem becomes manifest when the huge number of diabetic patients (>200 million) worldwide is taken into consideration [1]. One of the most important complications related to diabetes is lower extremity ulcers. In literature, the frequency of diabetic foot ulcers is reported to be be-



Received: July 18, 2016 Accepted: February 01, 2018 Online: February 12, 2019

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tween 15% and 25% [1]. In addition, hemoglobin A1C (HbA1C) has been recognized by the increasing popularity over the past decade as an indispensable parameter for mid-term monitoring of glycemic control over a period of 2–3 months [2]. Although diabetic foot ulcers are especially associated with impaired immunity and peripheral polyneuropathy, microangiopathy, and emergence of reactive oxygen species resulting from glycosylation of proteins play an important role in the disruption of skin integrity [2, 3]. While the development of foot ulcers in about 1/5 of diabetic patients is facilitated by these biochemical reactions, the role of high HbA1C values in the duration of treatment of these ulcers is not frequently discussed.

In this study, we aimed to determine the HbA1C values, the classification of wounds according to Wagner classification [4] and their relationships with known risk factors, mainly the duration of antibiotherapy.

## MATERIALS AND METHODS

After the approval of Noninvasive Clinical Researches Ethics Committee of Namık Kemal University dated February 23, 2017 and numbered 2017/14/01/14 was obtained, data from 139 patients including those referred to our clinic from almost every location in our geographic region where our hospital is situated and those consulted our clinic with the indication of diabetic foot were investigated retrospectively. The pre-requisite for this group of patients aged between 29 and 86 years, who applied between June 2014 and September 2016, was follow-up of HbA1C level, which is an important criterion of diabetes control and, its follow-up treatment, especially independent of type of diabetes. In addition to demographic and clinical information, HbA1C values, the location of wounds, their ratings according to the Wagner classification [4], wound culture studies and duration of treatment were evaluated. In this study, diabetic foot accompanied by foot ulcer, peripheral neuropathy, and arterial disease of different severity in controlled or uncontrolled diabetes is defined as diabetic foot, and the infection caused by colonized microorganisms on the setting of diabetic ulcer is turned as diabetic foot infection. Patients in the study group were classified according to the target HbA1C levels of <7% as recommended by American Diabetes Association and American Heart Association for the treatment of diabetes [7-19]. Doppler ultrasonography, magnetic resonance imaging (MRI) and in case of

need conventional angiography modalities were used for patients with peripheral arterial disease, in that order. While for patients with suspect osteomyelitis, soft tissue MRI, and scintigraphy were used. The statistical analysis was performed using the SPSS software for Windows 22.0. To test both the mathematical differences of the factors to be examined for independent groups and also the variability of the factors among subgroups Student's t-test and Mann-Whitney U-test were used. Chi-square test was used to compare descriptive statistical methods and qualitative data. The results were evaluated within a confidence interval of 95% and a significance level of  $p < 0.05$ .

## RESULTS

Between June 2014 and September 2016, the files of 139 patients who presented to our clinics of infectious diseases, plastic surgery, cardiovascular surgery, and orthopedics were retrospectively reviewed (Table 1). A total of 10.362 out of 129.532 patients hospitalized in this period were diabetic patients and 429 of these patients had diabetic foot wounds. The 139 of these patients were included in the study. The mean age of the patients was  $56.50 (\pm 4.12)$ , while 58.27% ( $n=81$ ) of the patients were male and 41.73% ( $n=58$ ) of them were female.

Considering all patients, 59.71% ( $n=83$ ) of the open wounds were found to be distally located (finger). The mean HbA1C level was  $9.60 (\pm 1.10)$ . The mean treatment duration in patients with Wagner stage 3-4-5 was  $36 \pm 4.0$  days ( $p=0.01$ ). In the group with advanced stage Wagner classification (3-4-5) with a longer duration of treatment, the rates of major amputation and death were found to be statistically higher ( $p=0.01$ ). The relationship between HbA1C level and duration of treatment and wound size is summarized in Table 3. Duration of treatment was significantly shorter in patients with HbA1C levels <7% ( $p < 0.01$ ). As seen in the table 2 designed according to the progressive increase in HbA1C levels, any statistically significant difference was not detected in the comparison of HbA1C subgroups with HbA1C values over 7% which is accepted as the target value ( $p > 0.05$ ).

Peripheral arterial system imaging of the patients in the study group showed that 6 (4.31%) of 7 patients with HbA1C values <7% had increased intimal thickness and non-critical stenosis of the main femoral artery (anastomotic false aneurysm) and superficial femoral artery (SFA) in arterial Doppler ultrasonography. In 21 (15.1%)

**TABLE 1.** Demographic and basal clinical parameters (n=139)

|                               |                    |                              |                  |                   |                  |      |     |     |     |     |
|-------------------------------|--------------------|------------------------------|------------------|-------------------|------------------|------|-----|-----|-----|-----|
| Age                           | 56.50<br>(±4.12)   |                              |                  |                   |                  |      |     |     |     |     |
| Gender                        |                    |                              |                  |                   |                  |      |     |     |     |     |
| Male, %                       | 58.287<br>(n=81)   |                              |                  |                   |                  |      |     |     |     |     |
| Female, %                     | 41.73<br>(n=58)    |                              |                  |                   |                  |      |     |     |     |     |
| Diabetes                      |                    |                              |                  |                   |                  |      |     |     |     |     |
| Type I, %                     | 23.02<br>(n=32)    |                              |                  |                   |                  |      |     |     |     |     |
| Type II, %                    | 76.97<br>(n=107)   |                              |                  |                   |                  |      |     |     |     |     |
| Fasting blood sugar, %        | <110               | 110-200                      | >200-300         | >300-400          | >400             |      |     |     |     |     |
|                               | n=6<br>(4.31)      | n=49<br>(35.25)              | n=69<br>(49.64)  | n=10<br>(7.19)    | n=5<br>(3.59)    |      |     |     |     |     |
| *HbA1C, %                     | <7%                | 7-9%                         | 9-12%            | 12-15%            | >15              |      |     |     |     |     |
|                               | n=7<br>(5.03)      | n=51<br>(36.69)              | n=64<br>(46.04)  | n=15<br>(10.79)   | n=2<br>(1.43)    |      |     |     |     |     |
| Wagner Score, % [4]           | 1                  | 2                            | 3                | 4                 | 5                |      |     |     |     |     |
|                               | n=8<br>(5.75)      | n=34<br>(24.46)              | n=65<br>(46.76)  | n=15<br>(10.79)   | n=17<br>(12.23)  |      |     |     |     |     |
| **Location of the wound       | 1                  | 2                            | 3                | 4                 | 5                | 6    | 7   | 8   | 9   | 10  |
|                               | n=29               | n=35                         | n=19             | n=12              | n=6              | n=11 | n=9 | n=6 | n=9 | n=3 |
| Surgical treatment applied, % | Dressing+ VAC      | Debridement                  | Debridement+ VAC | Minor amputation  | Major amputation |      |     |     |     |     |
|                               | n=12<br>(8.63)     | n=56<br>(40.28)              | n=37<br>(26.61)  | n=26<br>(18.70)   | n=8<br>(5.75)    |      |     |     |     |     |
| ***Prognosis, %               | Complete treatment | Only reduction of wound size | Persisting ulcer | Loss of extremity | Death            |      |     |     |     |     |
|                               | n=107<br>(76.97)   | n=11<br>(7.91)               | n=11<br>(7.91)   | n=8<br>(5.75)     | n=7<br>(5.35)    |      |     |     |     |     |

\*HbA1C values are classified by ACC and ADC guidelines based on 7% defined as target value; \*\*The definition of wound localizations is shown in figure 1;

\*\*\*Since patients with extremity loss and fatal outcome contain the same patients, this group comprised 144 subjects; HbA1C: Hemoglobin A1C.

of 64 patients with HbA1C values of 9–12 (15.1%), SFA occlusion was detected in MR angiography and conventional angiography. In 6 of 15 (4.2%) patients with HbA1C values between 12 and 15% ulcerated plaques and occlusions distal to Hunter's canal were detected.

MRSA (n=51; 36.69%) was the most common microorganism in initial cultures followed by *Escherichia coli* (n=18; 20.22±2.12%) and *Pseudomonas spp.* (n=17; 19.10±3.02%). There was no statistically significant relationship between basal HbA1C levels and microorgan-

**TABLE 2.** The relevance between HbA1C levels and clinical complication rates

| HbA1C                     | <7%        | 7–9%         | 9–12%        | 12–15%       | >15        |
|---------------------------|------------|--------------|--------------|--------------|------------|
| Complication              | n=7 (5.03) | n=51 (36.69) | n=64 (46.04) | n=15 (10.79) | n=2 (1.43) |
| Nephropathy               | -          | n=9 (6.47)   | n=32 (23.02) | n=4 (2.87)   | n=1 (0.71) |
| Retinopathy               | n=4 (2.87) | n=18 (12.94) | n=54 (38.84) | n=5 (3.59)   | n=1 (0.71) |
| Peripheral artery disease | n=1 (0.71) | n=5 (3.59)   | n=21 (15.10) | n=6 (4.31)   | -          |
| Osteomyelitis             | n=1 (0.71) | n=5 (3.59)   | n=16 (11.51) | n=7 (5.03)   | n=2 (1.43) |

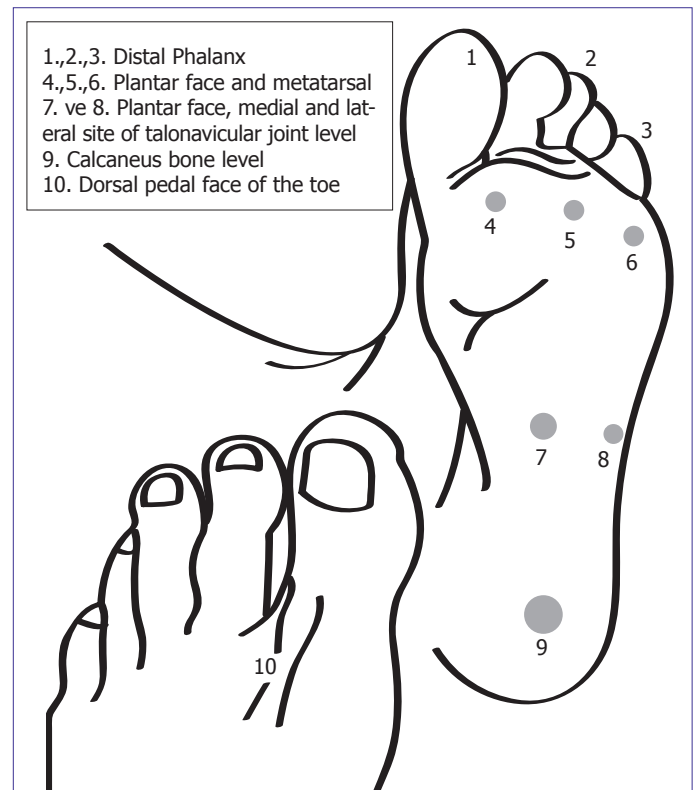
**TABLE 3.** The relationship between serum levels of HbA1C, duration of treatment, and the wound size

| HbA1C levels                      | <7%                 | 7–9%                | 9–12%                | 12–15%               | >15                  |
|-----------------------------------|---------------------|---------------------|----------------------|----------------------|----------------------|
|                                   | n=7 (5.03)          | n=51 (36.69)        | n=64 (46.04)         | n=15 (10.79)         | n=2 (1.43)           |
| Mean duration of treatment (days) | 31 ( $\pm 1.15$ )   | 39 ( $\pm 8.24$ )   | 33 ( $\pm 5.80$ )    | 36 ( $\pm 8.20$ )    | 22 ( $\pm 0.12$ )    |
| Wound size (cm <sup>2</sup> )     | 3.52 ( $\pm 1.15$ ) | 9.30 ( $\pm 2.20$ ) | 13.45 ( $\pm 4.20$ ) | 15.80 ( $\pm 2.20$ ) | 18.12 ( $\pm 0.62$ ) |

isms grown in cultures ( $p > 0.05$ ). When the relationship between resistant microorganisms and patients with high HbA1C levels was examined, a statistically significant relationship was found between the two variables ( $p < 0.01$ ;  $r = 0.9$ ). The mean HbA1C ( $12.40 \pm 1.21$ ) value of individuals with resistant microorganisms was significantly higher than the mean HbA1C value of the whole sample. The most preferred agent among empirically started antibiotherapy was combination of ampicillin/sulbactam ( $n = 30$ ;  $30.33\% \pm 1.89$ ). Vancomycin was the most commonly used drug ( $n = 25$ ;  $28.08 \pm 1.18\%$ ). The mean duration of treatment was 32.2 days. When the patients were divided into 5 groups (<7%; 7–9%; 9–12%; 12–15%; >15%) in terms of HbA1C levels, it was observed that the wound size increased in relation to HbA1C level. In addition, the relationship between HbA1C values and the duration of antibiotherapy which is the main interest of the study is summarized in Table 2 and 3.

Retinopathy was found in 4 of the patients with HbA1C levels <7%. One patient from this group had peripheral artery disease and osteomyelitis. Peripheral angioplasty was performed on this patient, and the complete cure was achieved on the 34<sup>th</sup> day after debridement. The mean duration of treatment in the second group (HbA1C 7–9%) was 39 days ( $\pm 8.24$ ), while it was 33 days ( $\pm 4.60$ ) in the third and 36 days ( $\pm 5.20$ ) in the fourth groups. One of two patients in the group with HbA1C levels >15% died of sepsis after the knee amputation, and the other one died on the 22<sup>nd</sup> day due

to acute renal failure. When the same parameters were evaluated based on Wagner staging and periods of antibiotherapy, a statistically significant relationship was found between these two parameters ( $p < 0.01$ ). Accord-

**FIGURE 1.** The schematization and classification of ulcer localizations

ingly the incidence of osteomyelitis was higher in the two groups with HbA1C levels of 12% and above ( $p < 0.01$ ).

## DISCUSSION

In our study, we found that the duration of treatment was significantly prolonged in the patient group whose HbA1C value was  $>7\%$ . Diabetes is a multisystemic disease characterized by impaired carbohydrate, lipid, protein metabolism, and immune system. While the incidence is around 9.3% in the world, the rate in our study area is around 9.9% [1]. In addition, although the incidence of diabetic foot ulcers among all people with diabetes is reported as 6.1% [1, 2]. Its rate was approximately 5% among the patients who applied to our center. Although diabetic foot is basically an endocrine pathology, it requires a multidisciplinary and systematic approach. Impaired peripheral microvascular blood circulation also affects tissue perfusion, which may result in amputation, resulting in delayed recovery and increased susceptibility to infection due to the emergence of resistant microorganisms. Neuropathy associated with diabetes causes deterioration in pain and heat sensation. Accordingly repeated minor traumas and injuries induce ulcers more rapidly than expected in areas where tissue perfusion is worsened [5, 6]. Ischemia, neuropathy, and local infections lead to osteomyelitis and gangrene resulting in amputation. In fact, patients with impaired immunity may be lost immediately after the time of diagnosis due to sepsis.

Previous studies have shown that a 1% decrease in HbA1c results in a 21% reduction in all diabetic complications [7, 8]. However, this correlation is affected by many external factors and its relation to the duration of antibiotherapy is not clearly defined. For this reason, it is important to examine the relationship between HbA1C levels and duration of antibiotherapy which is an important indicator of diabetes regulation [5–7, 18, 19].

When the results of the study were examined, it was seen that the duration of treatment was prolonged statistically significantly in the patient group who had HbA1C value above 7%, the level of HbA1C which was recommended to deal with other complications of diabetes, mainly cardiovascular disease risk [1]. When patients were grouped according to HbA1C levels, patients with higher HbA1C levels (excluding  $>15\%$  group) had a longer treatment duration (Table 3). This result can be interpreted that the HbA1C target value should be kept

$<7\%$  in the treatment of diabetic foot wound infections.

Other complications of diabetes in groups with HbA1C  $>7\%$  increase the morbidity and may lead to shorter duration of antibiotic treatment than expected due to poor clinical outcome (amputation and death). Patients with HbA1C level of over 15% have a shorter duration of antibiotherapy (Table 3). This is a common condition in which HbA1C is associated with high mortality and other complications. As a matter of fact, in our study group, diabetes of the patients with poor diabetes regulation and chronic renal failure and osteomyelitis could not be kept under control, the health state of these patients rapidly worsened due to sepsis or multiorgan failure, finally these patients died, and their antibiotherapy terminated within a short time.

One of the most important determinants of prognosis in patients with impaired immunity and serious infections of opportunistic microorganisms is the selection of appropriate antibiotics. Therefore, another condition related to the duration of treatment is the efficacy of the empirically-initiated antibiotic against the pathogen. Although the current guidelines suggest that antibiotic therapy has emerged as a result of studies on large cohorts [8–11], clinicians may initially take their guideline for antibiotic treatment into consideration, and prioritize their personal opinions in the termination of therapy.

When the wound size was examined, a significant correlation was found between HbA1C levels and wound sizes (Table 3). This correlation was evaluated as a finding suggesting that the clinical course of the disease was also affected by glycemic control. In addition, in some patients with poor glycemic control, but with appropriate antibiotic treatment, wound healing may occur in a shorter time. The Wagner classification of patients before empirical antibiotherapy should be considered as one of the conditions that may affect prognosis.

Although the number of patients is not sufficient to make clear judgments on the subject, the results obtained from this study have shown that despite the HbA1C values exceeding the impaired critical level, proper wound care can be dealt with even with large diabetic foot wounds with appropriate and timely antibiotherapy. However, with the increase in ulcer depth and ulcer stage, the amputation rate increased and increase in the rate of amputation has been also seen in ulcers progressing to bone level. In cases of infection and ischemia, clinical course may deteriorate due to nephropathy, retinopathy,

and osteomyelitis regardless of the duration of antibiotic treatment.

In addition, the previous history of ischemic stroke, the presence of major amputation in the contralateral limb, and history of smoking were found to be associated with poor outcome. These results are consistent with previous studies on the subject [14]. Another important result, we obtained from our study, is that the patients with advanced stage Wagner classification can have a good HbA1C level and vacuum assisted wound closure treatment after debridement and/or minor amputation can result in a good clinical outcome.

The role of antibiotherapy in the treatment of diabetic foot infections is very important. Although the combination of ampicillin/sulbactam was the most commonly selected combination of antibiotics in our study, it was found that the microorganism produced by MRSA did not contradict with the guidelines. Pathogens in individuals with HbA1C levels above the target level of 7 were often very drug resistant.

Another important result is the early application of surgical treatment with the empirical antibiotic treatment for possible causative microorganisms, and the application of vacuum-assisted wound closure methods as a complementary treatment exert a favorable impact on the clinical outcomes. There are a number of studies in the literature examining the importance of empirical antibiotic therapy in the treatment of diabetes-related infections [10-13]. As is known, the first issue to be considered in the empirical antibiotic treatment is the fact that the antibiotic, which is the most common agent against the microorganisms, should be given in the way that it can reach a high concentration in the tissue.

In addition to empiric antibiotherapy started at admission, tissue perfusion, soft tissue, and bone imaging should be performed if possible, and at the end of these examinations in case of need the treatment should be tailored based on angioplasty and/or debridement, and antibiotic should be changed depending on the bacteria grown in wound culture.

The main limitations of our study were that it was designed retrospectively and the number of patients was limited to the patients admitted to our clinic. Specifically, the association of HbA1C levels with the duration of antibiotic use may produce inspiring ideas for large-scale prospective studies concerning antibiotic use and hospitalization periods.

## Conclusion

Diabetic foot infection is an important health problem which causes economic and social losses due to severe complications, amputation, and even mortality. Considering the health expenditures transferred to the diagnosis and treatment of diabetes in the major countries of the world, it can be seen that these expenditures exceed the budgets of countries with lower income. It is not only the treatment costs but also the loss of the workforce and productivity of the patients due to the loss of the limb face us as a separate socioeconomic problem. Therefore, keeping the HbA1C level <7% in the development of diabetic foot wounds is important for the prevention of diabetic foot and other major complications. For this purpose, the risk factors of the patient should be examined thoroughly, and the individuals at risk should be identified and trained. When clinicians identify individuals at risk, it is possible to reduce amputation rates with correct and timely treatment. Treatment of diabetic foot infections with a multidisciplinary approach can be accomplished, and morbidity can be reduced [12].

The prolongation of antibiotic therapy has been associated with poor prognosis in many studies in literature [1]. One of the main aims of this study was to determine the factors affecting the duration of antibiotic treatment; therefore, the poor prognosis and duration of treatment were also considered. As a result, one of the most important issues in the prevention of complications is to keep HbA1C levels <7%. Another important result obtained from our study is that timely and most effective approach to diabetic foot wound infections can reduce morbidity, shorten treatment time and prevent other complications of diabetes.

**Conflict of Interest:** No conflict of interest was declared by the authors.

**Financial Disclosure:** The authors declared that this study has received no financial support.

**Authorship Contributions:** Concept – M.D.; Design – M.D.; Supervision – S.A.G.; Materials – B.A.; Data collection &/or processing – L.C.O.; Analysis and/or interpretation – L.C.O.; Writing – M.D.; Critical review – M.D.

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