



The correlation of HbA1c levels on the healing process of postoperative fractures in diabetes mellitus patients

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ABSTRACT

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Fracture is defined by the loss of bone or cartilage continuity, either total or partial. Diabetes mellitus (DM) is a group of metabolic diseases characterized by hyperglycaemia resulting from defects in insulin secretion, insulin action, or both. HbA1c could be used as a diagnostic tool and determines the glycaemic control of DM patients. This study aimed to investigate the correlation between serum HbA1c levels and the healing process of postoperative fractures in DM patients. This was an observational study with a retrospective cohort design. The study population was DM patients who were admitted to the Department of Emergency, Dr. Wahidin Sudirohusodo General Hospital, Makassar due to long bone fracture within the period of September 2019-February 2020. The bone fractures healing was evaluated based on the radiographic union scale in tibial fractures (RUST) scores. The results are analysed using the Chi-square test. A total of 70 DM patients who underwent fracture reduction surgery were involved in this study. Out of 35 patients with controlled DM (HbA1c <7%), we obtained 24 (68.6%) patients and 11 (31.4%) patients with good and delayed union, respectively. The other 35 patients had uncontrolled DM (HbA1c >7%), and there were 13 (37.1%) patients and 22 (62.9%) patients with good and delayed union, respectively. The Chi-square test showed a significant relationship ($p=0.008$). It can be concluded that the increase in HbA1c levels was related to the obstacles in bone fractures healing. Moreover, an infection contributes to the healing status of bone fractures.

ABSTRAK

Fraktur didefinisikan sebagai putusnya sambungan tulang atau tulang rawan baik seluruhnya atau sebagian. Diabetes melitus adalah kelompok gangguan metabolik yang ditandai dengan hiperglikemia akibat gangguan sekresi insulin, aktivitas insulin atau keduanya. HbA1c dapat digunakan sebagai alat diagnosis untuk melihat kadar gula darah pasien DM terkontrol. Penelitian ini bertujuan untuk mengkaji hubungan antara kadar HbA1c dengan proses penyembuhan fraktur pasien DM setelah operasi. Penelitian ini adalah penelitian observasi dengan rancangan *retrospective cohort*. Populasi penelitian adalah pasien DM yang masuk Departemen Emergensi, RSUP Dr. Wahidin Sudirohusodo, Makassar karena mengalami fraktur tulang untuk waktu yang lama selama September 2019-Februari 2020. Kesembuhan fraktur tulang dinilai berdasarkan skor *radiographic union scale in tibial fractures* (RUST). Hasil yang diperoleh dianalisis dengan uji Chi-square. Sebanyak 70 pasien DM yang menjalani bedah perbaikan fraktur terlibat dalam penelitian. Dari 35 pasien DM dengan kadar gula darah terkontrol (HbA1c <7%), 24 (68,6%) pasien dan 11 (31,4%) pasien mengalami berturut-turut proses penyembuhan fraktur dengan baik dan tertunda. Dari 35 pasien DM lain dengan kadar gula darah tidak terkontrol (HbA1c >7%), 13 (37,1%) pasien dan 22 (62,9%) pasien mengalami berturut-turut proses penyembuhan fraktur dengan baik dan tertunda. Uji Chi-square menunjukkan hubungan nyata ($p=0,008$). Dapat disimpulkan bahwa kenaikan kadar HbA1c dapat dihubungkan dengan keterlambatan penyembuhan fraktur tulang. Selain itu, infeksi berperan proses penyembuhan fraktur tulang.

Keywords:
diabetes mellitus;
fracture;
HbA1c;
long bones;
RUST score;

INTRODUCTION

Fracture is the loss of bone continuity, joint cartilage, and epiphyseal cartilage, both total and partial. Fracture diagnosis is based on history, physical examination, and investigation. Patients usually experience localized pain, which increases when moved, swelling, impaired limb function, deformity, movement disorders, crepitus, or other symptoms. On physical examination, we should give more attention to signs of shock, anaemia or bleeding, damage to other organs such as the brain, spinal cord, or organs in the thoracic, pelvic and abdominal cavities, and predisposing factors such as pathological fractures. A local examination includes inspection (look), palpation (feel), movement (move), neurological examination, and radiological examination.¹ Although the treatment of tibial fractures by intramedullary nailing shows a good outcome, there remains a lack of consensus among orthopedic surgeons in the assessment of body union.¹

Older people with diabetes mellitus (DM) have a 2- to 8-fold risk of bone fractures compared to people of the same age without DM due to lack of bone mineral density. HbA1c is now suggested as a standard for testing and monitoring DM, particularly in type 2 DM. HbA1c levels within 6.5 and 6.9% are the optimal range of glycaemic control for fractures. Since DM is associated with several comorbidities, recommendations for individuals with DM include a healthy lifestyle (diet and exercise) and maintaining an HbA1c level below 7.0%.^{2,3}

Glycaemic control assessed by HbA1c is associated with higher mortality. In addition to the effects of hyperglycaemia in interfering with fracture healing and bone remodeling, poor glycaemic control might also leave the body vulnerable to infection and increase the incidence of complications after a fracture. In DM

patients, achieving stable glycaemic control and intensive care to prevent postoperative complications might decrease mortality after experiencing a fracture. This study aimed to determine the relationship between serum HbA1c levels and the healing process of postoperative fractures in patients with DM.⁴

The radiographic union scale in tibial fractures (RUST) score is a novel fracture assessment tool that was developed to help standardize the radiographic assessment of tibial fracture sites *in vivo* models. It was reported that the RUST score is a reliable assessment tool of fracture healing with good agreement among five observers (intraclass correlation of 0.86).⁵ The RUST score has been used in various clinical studies since its introduction and further validated for use in small animal models. Further confirmation of the reliability or the RUST score may substantiate the use of the score for both clinical assessment and research tools.⁶

MATERIALS AND METHODS

Subjects

An observational study with a retrospective cohort design was used to evaluate the correlation of HbA1c levels and the healing process of postoperative fractures in DM patients. The population were all people with DM who were admitted to the Department of Emergency of Dr. Wahidin Sudirohusodo General Hospital, Makassar with long bone fractures from September 2019 until February 2020. A total of 70 patients with type 2 DM who experienced fractures of the long bones and met the inclusion and exclusion criteria were involved in this study. The inclusion criteria were patients over the age of 18 years who had undergone internal fixation surgery, radiologically re-evaluated 3 months after surgery for bone fracture,

patients who had measured serum HbA1c levels before undergoing surgery, and patients who had complete medical record data on identity, diagnosis, laboratory results, and radiological evaluation. The exclusion criteria were pregnant/lactating women, patients who have terminal stage comorbidities, and patients who were using corticosteroids, immunosuppressants, and antibiotics.

Procedure

HbA1c levels indicated long-term glucose control that reflects the condition in 8-12 weeks before was examined using an immunoassay (ELISA). Controlled and uncontrolled DM patients are defined by HbA1c levels of <7% and >7%, respectively. The fracture healing state was distinguished into 2 categories according to the RUST. A normal and delayed healing state are defined by an RUST score of ≥ 10 , and < 10, respectively.

Statistical analysis

This study used Microsoft Excel 2013 software to conduct data collection.

The data were manually managed by computer using the Statistical Package for the Social Sciences (SPSS) Version 21 software. The study results were presented in a tabular and narrative form, showing the relationship between HbA1c and postoperative fracture healing state. It was analysed by correlation and proportional tests accordingly. Then, an evaluation and conclusion were drawn by the formulation of the existing problem.

RESULTS

Characteristics of patients

This study involved 70 patients with type 2 DM who underwent fracture reduction surgery consisting 37 (52.9 %) male and 33 (47.1%) female. The average age of the patients was 57.8 ± 9.2 years. As a common feature found in patients with DM, the average HbA1c level in this study was increased, accounting for $7.5 \pm 1.9\%$. Tibial bone was the most common fracture site in 31 (44.2%) patients (TABLE 1).

TABLE 1. Characteristics of research subjects (n=70)

Characteristics	Results
Sex n (%)	
• Female	33 (47.1)
• Male	37 (52.9)
Age (mean \pm SD) years	57.7 ± 9.2
Location of fracture n (%)	
• Humerus	12 (17.1)
• Femur	27 (38.6)
• Tibia	31 (44.3)
HbA1c (mean \pm SD %)	7.4 ± 1.9
RUST score (mean \pm SD)	9.4 ± 2.1
Fracture status n (%)	
• Union	37 (52.9)
• Delayed-union	33 (47.1)

HbA1c: haemoglobin A1c or glycated hemoglobin; SD: standard deviation; RUST: radiographic union scale in the tibia

Healing of bone fractures against HbA1c in diabetic patients

TABLE 2. Relationship between HbA1c levels and healing status of bone fractures in DM patients

Variable	Recovery status		p*	φ
	Union	Delayed-union		
HbA1c (%)				
• <7	24 (68.5)	11 (31.4)	0.008	0.31
• ≥7	13 (37.1)	22 (62.8)		

*Chi-square test; φ Phi Cramer’s V; HbA1c: haemoglobin A1c or glycated hemoglobin

Healing of bone fractures with age in diabetic patients

TABLE 3. The relationship status of bone fracture recovery to age in DM patients

Variable	Recovery status [n (5)]		p*
	Union	Delayed-union	
Age (year)			
• <65	29 (60.4)	19 (39.6)	0.06
• ≥65	8 (36.3)	14 (63.7)	

* Chi-square test

Healing of bone fracture and infection in diabetic patients

TABLE 4. The relationship of the bone fracture healing status to wound infections in DM patients

Variable	Recovery status [n(%)]		p*	φ
	Union	Delayed-union		
Infection				
• Not	4 (21.0)	15 (79.0)	0.001	0.389
• Yes	33 (64.7)	18 (35.3)		

* Chi-square test; φ Phi Cramer’s V

Healing of bone fractures on the type and location of the fracture in DM patients

TABLE 5. Relationship of bone fracture healing status to the type and location of the fracture in DM patients

Variable	Recovery status [n(%)]		p*
	Union	Delayed-union	
Fracture type			
• Closed	18 (50.0)	18 (50.0)	0.62
• Open	19 (55.8)	15 (44.2)	
Location of fracture			
• Humerus	7 (58.3)	5 (41.6)	0.79
• Femur	15 (55.6)	12 (44.4)	
• Tibia	15 (48.3)	16 (51.7)	

* Chi-square test

Healing of bone fractures against anti-diabetic therapy

TABLE 6. Characteristics of recovery status based on the use of oral antidiabetic therapy and insulin alone or in combination with study subjects

Variable	Recovery status [n(%)]	
	Union	Delayed-union
Single/combination antidiabetic		
Metformin	23 (50.0)	23 (50.0)
Sulfonylureas	6 (54.5)	5 (45.5)
Tiazolidindion	7 (58.3)	5 (41.7)
GLP-1 agonist	7 (70.0)	3 (30.0)
DPP4 inhibitors	4 (50.0)	4 (50.0)
Insulin	16 (53.3)	14 (46.7)

DPP4: dipeptidyl peptidase 4; GLP-1: glucagon-like peptide-1

DISCUSSION

We divided the subjects into two categories in this study according to the RUST scores. The RUST scores were evaluated 3 months after surgery. The patients with an RUST score of <10 were identified as patients who experienced delayed fracture or delayed union healing. Meanwhile, the patients with RUST scores ≥ 10 did not experience delayed fracture or delayed union healing. A total of 11 (31.4 %) well-controlled DM patients experienced obstacles in healing bone fractures. Concurrently, 13 (37.1 %) patients with uncontrolled DM showed normal bone healing.

Our results revealed that the increased of HbA1c levels are related to inhibition of healing bone fractures as assessed by RUST scores (TABLE 2). Furthermore, an analysis of some comorbidities found that infection contributes to the healing status of bone fractures. Zura *et al.*⁷ found that some comorbidities were related to the possibility of disturbances in the healing process of bones, including DM, which might be found at all ages.

There are at least two mechanisms by which high HbA1c levels can affect the healing of bone fractures. First, higher HbA1c levels are considered

capable of supporting osteoblast apoptosis and inducing procollagen type I N-terminal propeptide (P1NP) through ROS production.⁷ Second, HbA1c levels are known to be related to insulin resistance. It was successfully proven by Al-Hakeim and Abdulzahra,⁸ who conducted a retrospective cohort study to determine the relationship of glycemic control, measured by the HbA1c parameter to insulin resistance. In this study, we discovered that HbA1c is correlated with insulin resistance in patients with DM.⁷ Insulin resistance in DM is associated with some adverse effects on bone health. Skeletal defects found to be associated with DM included the characteristic of poor bone healing processes.^{9,10}

There were 22 (31.4 %) patients with DM who were categorized as elderly patients. Although the elderly are known to be associated with inhibition of fracture healing, we did not find an association of age and fracture recovery status in this study (TABLE 3). This result differs from the study of Clark *et al.*¹¹ who found that skeletal systems show physiological changes that occur with increasing age. Decreased healing potential in the skeletal system was also found in the elderly, and this might lead to an increase in the incidence of inhibition of fracture healing to

failure of fracture healing.⁹ One cohort retrospective study involving 47,437 to 56,492 fracture patients found that the failure rate of healing of fractures in the elderly is lower compared to younger patients, although the results of this study have some data limitations.¹¹

A total of 19 (27.1 %) patients with DM had infections in postsurgical wounds. Fifteen (78.9 %) patients with DM and infections in postoperative wounds experienced obstacles in healing bone fractures (TABLE 4). There was a relationship between wound infection and the healing status of the bone. The same result was also found in a meta-analysis study in patients who underwent total joint arthroplasty. They discovered that the high levels of HbA1c and conditions of hyperglycemia perioperatively correlated to the risk of larger periprosthetic joint infection after arthroplasty procedure. Thus, it recommended the screening of perioperative HbA1c and blood glucose as an effective procedure to prevent infection.^{6,12}

There were 34 (48.5%) patients with DM and open fractures; 15 (44.1%) patients experienced delayed healing bone fractures. Simultaneously, there were 18 (50.0 %) patients with DM and closed fractures who experienced delays in bone fracture healing. There was no association between the type of fracture and the healing status of bone fractures in patients with DM (TABLE 5). The most common fracture site in this study was the tibia, which was found in 31 (44.2%) patients. There was no association between fracture location and bone fracture recovery status in patients with DM. A meta-analysis that evaluated the risk of fractures in patients with DM found a tendency of increased risk of fractures at all sites in patients with DM. Nevertheless, some studies showed heterogeneity of data that has an impact on research results.¹³

In this study, we found 40 (57.1

%) patients who were using either single antidiabetic oral therapy or in combination with other oral antidiabetic agents. Single insulin therapy was used in 4 (5.7%) patients and in combination with oral antidiabetic therapy in 26 (37.1%) patients (TABLE 6). Insulin should be used to improve control of the disease and in cases of low adherence to oral therapy. Oral antidiabetics appear to have an influence on the healing process of bone fractures and increase the likelihood of failure in fracture healing.¹⁴ Insulin can bind to the receptors of osteoblasts and stimulate anabolism, increasing bone formation through increased levels of IGF-1 and GLUT-4.^{15,16}

CONCLUSION

In conclusion, HbA1c has a significantly relationship with the healing status of bone fractures. The increase of the HbA1c levels and the presence of underlying infections are significantly related to obstacles in the healing process of bone fractures in patients with DM. However, there is no significant relationship between age, type, and location of bone fractures and the healing status of bone fractures in patients with DM. Most patients with DM who use antidiabetic oral therapy, singly, or in combination with antidiabetic oral therapy, tend to show resistance in the healing of bone fractures in patients with DM.

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