

Delayed Fracture Healing in Diabetics with Distal Radius Fractures

Opožděné hojení zlomenin u diabetiků se zlomeninou distálního radia

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ABSTRACT

PURPOSE OF THE STUDY

Diabetics may have an increased fracture risk, depending on disease duration, quality of metabolic adjustment and extent of comorbidities, and on an increased tendency to fall. The aim of this retrospective one-centre study consisted in detecting differences in fracture healing between patients with and without diabetes mellitus. Data of patients with the most common fracture among older patients were analyzed.

MATERIAL AND METHODS

Classification of distal radius fractures was established according to the AO classification. Initial assessment and follow-up were made by conventional X-rays with radiological default settings. To evaluate fracture healing, formation of callus and sclerotic border, assessment of the fracture gap, and evidence of consolidation signs were used.

RESULTS

The authors demonstrated that fracture morphology does not influence fracture healing regarding time span, neither concerning consolidation signs nor in fracture gap behaviour. However, tendency for bone remodeling is around 70% lower in investigated diabetics than in non-diabetics, while probability for a successful fracture consolidation is 60% lower.

CONCLUSIONS

To corroborate the authors' hypothesis of delayed fracture healing in patients with diabetes mellitus, prospective studies incorporating influencing factors like duration of metabolic disease, quality of diabetes control, medical diabetes treatment, comorbidities and secondary diseases, like chronic nephropathy and osteoporosis, have to be carried out.

Key words: diabetes, delayed fracture healing, distal radius fractures, callus formation, blood glucose level, osteoblasts.

INTRODUCTION

Diabetes is one of the frequent metabolic diseases in the industrialized countries. Up to 2030, 366 million people will be suffering from diabetes. This corresponds to a doubling of the prevalence in 30 years (34). Also among adolescents, an increasing prevalence of type 2 diabetes has been demonstrated, which is due to poor nutrition, juvenile obesity, and the decreasing physical activity of the youth aged under 18 years (8). Therefore, diabetes is becoming one of the big players in health policy.

The chronic-progredient disease can cause macro- and microvascular changes as well as nerve damage and wound healing disorders with serious consequences, which entail very cost-intensive treatment regimes. Besides the frequent “classic” secondary diseases, diabetic osteopathy is the most underrated side effect of long-time diabetes mellitus. Depending on the time that has passed since the onset of diabetes, the quality of regulation of the metabolism and the extent of secondary diseases, like e.g. peripheral sensomotoric polyneuropathy and diabetic retinopathy, diabetics may dispose of an increased tendency to fall, and therefore of an increased incidence of fractures. Despite these external risk factors, the number of long bone fractures is strongly elevated in type 1 as well as in type 2 diabetics. This increase is caused by diabetic osteopathy (2, 25, 33).

While the bone mineral density is reduced by hypercalciuria and a defective bone formation among other things in type 1 diabetics, the situation is much more complex in type 2 diabetics. Despite a normal or elevated bone mineral density compared to the age-related healthy population, the type 2 diabetics dispose of an insufficient bone quality (1, 15) and the risk of fractures is considerably increased in this group of patients (17). More recent data have revealed a decreasing bone density in type 2 diabetics depending on the extent of the insulin resistance and on an existing hyperinsulinemia (28).

As type 2 diabetes often correlates with long-lasting obesity, it is believed that the increased bodyweight causes a mechanical stimulation of the bone, which might explain the elevated bone mineral density (7). It is assumed that the reduced bone quality is due to an imbalance between the organic and inorganic matrix surrounding the osteogenetic cell pool (10).

In the future, it is indispensable to gain a better understanding of the pathophysiology in diabetic bone disease. Due to the disorders in blood circulation and wound healing, fracture healing is further complicated. The bad convalescence leads to a reduced quality of life and eventually to an important loss of independence of the patients. The goal of the present retrospective study consisted in answering the question, if the differences concerning the fracture consolidation can be found between diabetic and non-diabetic patients in the distal radius fracture, the most common traumatic fracture type in older patients.

MATERIAL AND METHODS

In this study, patients that have been treated with a unilateral or bilateral distal radius fracture that were treated with a volar locking plate osteosynthesis (Aptus Radius 2.5/Medartis GmbH) at the Dept. of Traumatology of the Klinikum rechts der Isar of the Technische Universität München between January 2007 and February 2010 have been included. The patient data were recorded retrospectively. A vote of the ethics committee was not required.

On the other hands, patients with a prolonged postoperative immobilisation of the wrist (≥ 4 weeks) or with a postoperative wound healing disorder have been excluded from this study. Other exclusion criteria were the use of steroids, of phenprocumoron, and of immunosuppressive medication, the existence of a malignant underlying disease, the proof of a hepatic impairment (serological), identified bony non-unions, and insufficient compliance of the patient.

The radiological assessment was performed after the initial trauma, intraoperatively via fluoroscopy, on the day after surgery and at the 6-week post-treatment normal follow-up in this clinical set-up. Postoperatively, the forearm was immobilized over 4 weeks with a dorsal 1/3 splint, day and night. After the second week, the splint was removed for the passive-assistive physiotherapy training of the wrist three times a week.

During the registration of the patient data from the patient's records, the patient's age, the relevant comorbidities, the current medication as well as the body mass index (BMI) which was calculated from the weight and the height (Table 1), were documented. All patients have been informed and only enrolled in the study after having signed an informed consent form.

Fracture classification. The classification of the distal radius fractures was carried out by using the x-rays which had been performed preoperatively according to the AO classification based on the radiographs taken in 2 planes in accordance with the radiological default settings (Table 2). This classification was reviewed once again by two independent traumatologists at the retrospective evaluation of the radiographies.

Table 1

	Diabetics	Control group
Number of patients (%)	17 (9%)	175 (91%)
Sex		
female	13	129
male	4	46
Mean age $\pm$ SD (range)	73.1 $\pm$ 12.8 (50.7–89.2)	56.7 $\pm$ 18.6 (15.4–95)
BMI [kg/m ²]	24.5 $\pm$ 3.8 (17.7–30)	24.5 $\pm$ 3.9 (17.6–47.5)
GFR	73.9 $\pm$ 22.1 (26.4–104.1)	82.5 $\pm$ 21.6 (20.5–104.1)
Chronic renal insufficiency		
stage I	5	59
stage II	8	95
stage III	3	18
stage IV	1	3

Table 2

Type of fracture (AO classification) N (% of the respective group)	Diabetics	Control group
A2	0 (0%)	24 (13.7%)
A3	7 (41.2%)	64 (36.6%)
B1	1 (5.9%)	8 (4.6%)
B2	0 (0%)	8 (4.6%)
B3	1 (5.9%)	4 (2.3%)
C1	5 (29.4%)	17 (9.7%)
C2	2 (11.8%)	28 (16.0%)
C3	1 (5.9%)	22 (12.6%)

Fracture healing. For the assessment of fracture healing, three criteria were used. The conventional postoperative images (1-2 days postoperative) were compared by two surgeons and one radiologist with the control radiographies which were taken with an identical radiographic technique after 6 weeks (+/- 1 week).

- *Criterion 1:* Formation of callus or of a sclerotic border
- *Criterion 2:* Evaluation of the fracture gap (stage 1: fracture gap unchanged from the control, stage 2: fracture gap no longer detectable)
- *Criterion 3:* Proof of signs of consolidation (stage 1: no signs of consolidation, stage 2: proof of beginning consolidation, stage 3: consolidation)

RESULTS

1. Fracture morphology. The defined signs of fracture healing (see above) were not influenced by the fracture morphology over the first 6 weeks after open reduction and internal fixation, neither concerning the signs of consolidation, nor concerning the evaluation of the behavior of the fracture gap.

2. Callus formation. Out of the 192 patients, which received a follow-up examination, 149 patients exhibited a radiologically verifiable callus formation after 6 weeks. However, 43 patients demonstrated no callus formation at all. Among the diabetic patients ($n = 17$), 10 patients exhibited callus formation, while no callus formation was visible in 7 patients.

In comparison to non-diabetic patients, a Fisher's exact test showed no significance ($p = 0.067$) which suggests a delayed callus formation in diabetics.

3. Fracture gap. Stage 1 (unchanged to the control): 9 patients (52.9% of the diabetics) against 51 non-diabetic patients (29.1%). Stage 2 (fracture gap no longer detectable): 1 patient (5.9% of the diabetics) against 6 non-diabetic patients (3.4%).

In terms of a beginning bone remodeling at the fracture site, the bone remodeling tendency of diabetics was around 70% lower than that of non-diabetics (odds ratio: 0.310; 95% CI: 0.11-0.89; $p = 0.029$). After age standardization, no usable significance was found. No correlation was found between the closing of the fracture gap and the time between admission and operation. The mean time span was 1.7 days.

4. Fracture consolidation. At the follow-up examination after 6 weeks, 7 patients (41.2%) out of the group of diabetics exhibited no signs of consolidation in the group of diabetics, while in the control group, 39 patients (22.3%) demonstrated no such signs. On the other hand, 9 patients (52.9%) among the diabetics and 130 patients (74.3%) from the control group, demonstrated clear signs of consolidation. However, only one patient (5.9%) out of the diabetics group and 6 patients (3.4%) out of the control group exhibited a complete consolidation ($p = 0.118$).

According to these results, the probability of a successful fracture consolidation of diabetics is 60% lower than that of non-diabetics (odds ratio: 0.410; 95% CI: 0.15-1.15; $p = 0.089$). If the age of the patients has been adjusted, the prognosis for a successful fracture consolidation tends to be lower in diabetics, but these numbers indicate only a tendency. However, no dependence was found between the consolidation and the time elapsed from the accident to the surgery.

In the aforementioned period, 192 patients with distal radius fractures were included in the study. Their mean

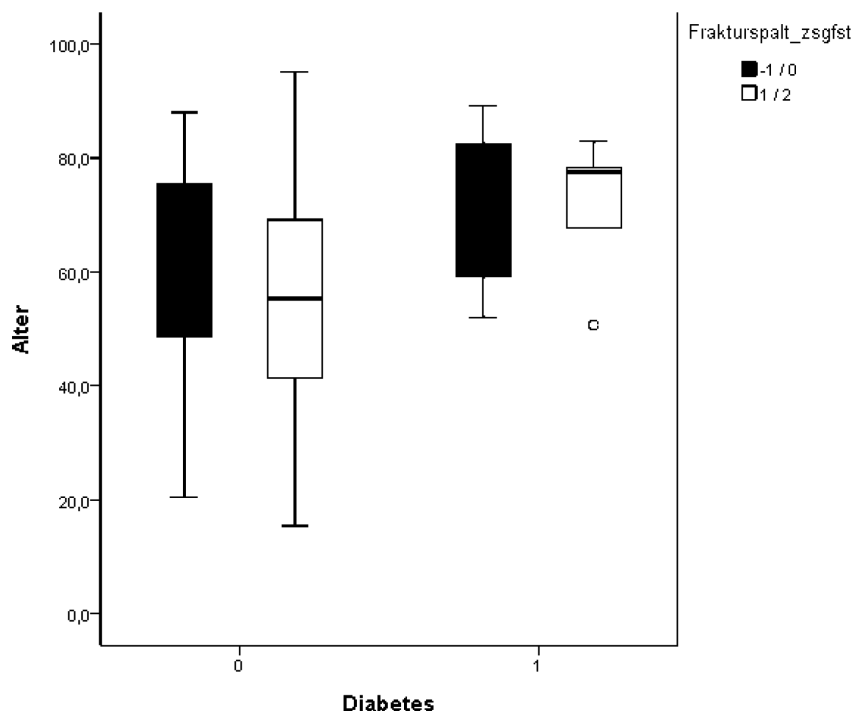


Fig. 1. Fracture gap 4 weeks postoperative. Black: Fracture gap unchanged in comparison to the post-operative control. White: Fracture gap no longer detectable. Odds ratio: 0.310; CI: 95% (0.11-0.89); $p = 0.029$

age was 73.1 years (50.7-89.2). Out of the 192 patients who participated at the follow-up examination, 149 patients in total exhibited a radiologically detectable callus formation after 6 weeks, while in the remaining 43 patients, no callus formation was visible. In the group of the diabetic patients ($n = 17$), 10 patients exhibited a callus formation, in 7 patients, no callus formation was visible. A Fisher's exact test showed no significant difference between diabetic and non-diabetic patients, ($p = 0.067$), which would suggest a delayed callus formation in diabetics.

The fracture morphology had no influence on fracture healing. In the framework of the 6 weeks follow-up, radiographs demonstrated no change of the fracture gap in 9 diabetic patients (52.9%) as well as in 51 non-diabetic patients (29.1%). On the other hand, after six weeks, the radiographs did no longer indicate any fracture gap in one diabetic (5.9%) and in 6 non-diabetic patients (3.4%).

Regarding the beginning bone remodeling, the tendency for bone remodeling was around 70% lower in diabetics than in non-diabetics (odds ratio: 0.310; 95% CI: 0.11-0.89; $p = 0.029$). After having performed the age standardization, no significance was detected. Regarding the changes of the fracture gap, no direct correlation to the timepoint of the surgery was found. At the 6 weeks follow-up, 7 (41.2%) diabetic and 39 (22.3%) non-diabetic patients exhibited no signs of consolidation. On the other hand, 9 (52.9%) diabetic patients and 130 (74.3%) patients belonging to the control group demonstrated clear signs of consolidation.

Finally, in 1 (5.9%) diabetic patient and in 6 (3.4%) non-diabetic patients out of the control group, the consolidation had already been completed by the time of the six-week follow-up ($p = 0.118$). The chance of a successful fracture consolidation is 60% lower in diabetics than in non-diabetics (odds ratio: 0.410; 95% CI: 0.15–1.15; $p = 0.089$). If an age adjustment is carried out however, the prognosis for a successful fracture consolidation tends to be lower for diabetics than for non-diabetics, but this is only a tendency. Nevertheless, no correlation was found between the consolidation and the time span between the accident and the surgery.

DISCUSSION

In the retrospective single-center study at hand, a tendency for delayed fracture healing in patients suffering from diabetes type 2 and a radius fracture in comparison to the non-diabetic control group was found. Interestingly, the fracture morphology does not offer any radiologically recognizable influence on fracture healing. Furthermore, no differences were found neither in the signs of consolidation, nor in the changes of the fracture gap according to the fracture types of the AO classification. However, the diabetic patients exhibited a delayed callus formation and their tendency for bone remodeling was reduced by 70% in comparison to the non-diabetic patients.

This increased fracture risk in diabetics (30) and the associated fracture healing and wound healing are due to multiple factors which have been intensively investigated. However, it depends on the duration of diabetes and on the comorbidities, like e.g. retinopathy, and on the diabetic neuropathy (18, 21).

Contrary to the reduced bone mineral density of patients with type 1 diabetes, type 2 diabetics exhibit normal to elevated values of bone mineral density (BMD), (29). In a study with a duration of twelve years, no loss of bone mineral density was detected in type 2 diabetics in comparison to the range of the normal population (14). In a prospective cohort study with a mean follow-up of 9.8 years, intra-articular fractures occurred more than twice as frequently in women with diabetes mellitus as in non-diabetic women (32).

The bone mineralization is regulated by the parathormon, the growth hormone, by calcitriol, the bone morphogenetic protein (BMP), and the vitamin D3 protein, as well as by IGF (insulin-like growth factor), TGF- β (tumor growth factor-beta), and other cytokines (14). The influence of the systemic factors circulating in the blood, like e.g. TGF- β , and of the blood glucose reducing medication on the bone mineralization is of peculiar interest (27). The influence of elevated TGF- β levels on human osteoblasts has already been proven in vitro. It has been demonstrated that glucose and the additional administration of insulin lead to a stimulation of TGF- β , which does not depend on its concentration. Due to the elevated levels of TGF- β , an increased proliferation of the osteoblasts as well as a decrease of the AP activity and a reduced matrix formation occur, which probably have a negative effect on bone formation (6).

Further research has demonstrated a correlation between insulin and glucose levels on the one hand and the expression of osteocalcin, a key protein of the bone-forming cells (osteoblasts) on the other hand (9, 13, 31).

The time of the initial diagnosis of the diabetes mellitus, and consequently the duration of the chronic metabolic disease, is not known for all patients. Moreover, the quality of the blood glucose control cannot be traced in the patient sample neither throughout the years, nor during the treatment period of the radius fracture.

In type 2 diabetics, a lower bone turnover is characterized by reduced bone markers, like e.g. osteocalcin, and C-terminal telopeptide (12). The hyperglycemia also contributes to the formation of high concentrations of advanced glycation end-products (AGE) in the collagen, which, in turn, leads to changes in the bone density (26). AGEs accumulate with increasing age, but are also considerably elevated in patients suffering from diabetes, and contribute to the diabetes-related complications (3, 4). In the analysis of the cell lines. The authors have been able to show that osteoblastic cells, isolated out of fetal rat ovaria, cultured on AGE-modified type I collagen, these AGEs could be inhibited dose-dependently (11). Furthermore, advanced glycation end-products have lead to an increase of the bone resorption which has been induced by osteoclasts (22).

The authors suppose that the quality of the blood glucose control and the physiological blood glucose have a considerable effect on fracture healing. On this premise, a routine determination of the HbA1c level has to be stipulated. In this way, an early optimization of the blood glucose level can be carried out immediately after the surgery, if the individual HbA1c target value has not been reached. Thereby it might be an advantage to optimize the blood glucose level pre- and perioperatively by changing the oral antidiabetic treatment into insulin therapy.

For the treatment of type 2 diabetes, there already exists a multitude of oral antidiabetics with different modes of action. Furthermore, the skeletal effects of the treatment of diabetes have only been fragmentarily investigated so far. At this time, there exist no prospective studies analyzing if the patients benefit from the treatment with oral antidiabetics (OAD) as a monotherapy, as a combination of different OADs or in conjunction with insulin, as a basally supported oral therapy (BOT) or as an exclusive insulin therapy (CT, ICT) with regard to diabetic osteopathy.

Glitazones have a negative influence on bone quality, as they cause an “unbalanced bone remodelling” which is characterized by a decrease of the bone resorption and an increase of the bone formation (16). In a meta-analysis, glitazones and PPARgamma-receptor agonists have exhibited an increased fracture risk. Nevertheless, the fracture risk has remained unchanged in combination with other oral antidiabetics (20). Metformin has had a positive influence on the osteoblasts, which is possibly due to that it triggers the activation of Runx2/Cbfa1 and AMPK, and has a subsequent influence on the bone marrow progenitor cells (BMPCs), (23). In comparison with the glitazones and sulfonyl urea, lower CTX (C-terminal cross-linked telopeptide of type-I collagen) levels have been measured in metformin and the higher PINP levels indicated an increased activity of osteoblasts (35).

The diabetic patients have received different antidiabetic treatment. Therefore, it is not allowed to carry out a direct comparison by assuming a direct influence of the medication on the fracture healing.

Another factor, which influences the delayed fracture healing are the probable differences of the vitamin D status among the individual patients. This assumption is supported by the different stages of chronic renal disease that have been documented in the sense of the limited glomerular filtration rate, as estimated by prediction equations based on serum creatinine concentration, age, race, sex, and body size. The severity of the chronic renal disease and the vitamin D status are well-known influencing factors of the bone quality. A lack of vitamin D is an established risk factor for osteoporosis and is often detected in older patients (24).

It is useful for detecting chronic kidney disease, classifying its severity, estimating its progression, managing its complications (19), and for supplementing vitamin D prematurely, if necessary. An early intervention with supplements that are rich in proteins and energy, in ad-

dition to a therapy with calcium, vitamin D, and bisphosphonate therapy has had positive effects on total body BMD and total hip BMD among elderly hip fracture patients (5).

CONCLUSION

Due to the delayed fracture healing, an intensified and multidisciplinary treatment is necessary in order to ensure a treatment with as little complications as possible. This concerns the soft tissue management as well as the fracture treatment and the follow-up, together with an optimized regulation of the blood glucose level. This could cause a change in the assessment and the treatment of fractures in diabetics, as the fracture no longer has to be regarded as such, but only as the symptom of an existing systemic disease, which still has to be treated with an osteosynthesis, whereas the success of the therapy depends on the complex treatment of the underlying disease.

In order to corroborate the authors' thesis of the delayed fracture healing in patients suffering from diabetes, prospective studies, which take into consideration the factors mentioned above, are currently carried out.

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