

Delayed Fracture Healing in Alcohol Abusers—A Preliminary Retrospective Study

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Abstract: A retrospective study of 30 patients (12 alcoholics and 18 nonalcoholics) was performed to determine whether the fracture healing time (T) was longer in alcoholics and smokers. Fracture healing time (mean \pm standard error) was longer in alcoholics (24.1 \pm 5.8 weeks vs. 11.4 \pm 1.1 weeks in nonalcoholics, $p=0.001$) and in 21 smokers (15.8 \pm 2.9 weeks) vs. 9 nonsmokers (18.2 \pm 5.9 weeks) ($p=0.045$). Delayed union, defined as $T > 26$ weeks, was more prevalent in alcoholics (4 out of 12) than in nonalcoholics (0 out of 18) ($p = 0.018$). Experimental evidence from fracture healing studies in ethanol-fed rats indicates that ethanol adversely affects the early stages of fracture healing. Findings in this preliminary study are consistent with this hypothesis, but are based on small number of patients. Nevertheless, they suggest that standard orthopedic treatments may not be sufficient to prevent delay of fracture healing in alcoholics.

Keywords: Alcohol abuse, biological deficiency in fracture healing, delayed union, fracture healing time, intertrochanteric femur fractures, nonunion, oral steroid use, smoking, subtrochanteric femur fractures, tibia diaphyseal fractures.

INTRODUCTION

Clinical and experimental studies provide significant evidence for disruption of bone remodeling associated with excessive and chronic consumption of alcohol [1]. This disruption is mainly due to suppression of new bone formation along with relatively small changes (increase or decrease) of bone resorption. The cumulative bone loss occurring over several remodeling cycles leads to the frequent finding of low bone mass, decreased bone formation, and increased fracture incidence in alcoholics [2,3]. In addition to the increased fracture risk initiated by bone loss, a significantly higher frequency of complications of fracture healing also occurs in patients with a history of alcohol abuse compared with nonalcoholic patients [4-9]. However, it has not been well established in the literature whether patients abusing alcohol are at risk for delayed fracture healing when compared with non-alcoholics. If in fact alcoholism is established as a risk factor for delayed fracture healing, this will provide the rationale to investigate the mechanism and highlight the need to develop appropriate prevention and treatment.

Nyquist *et al.* [4] found that it took longer to heal transverse tibia fractures in alcoholics than in nonalcoholics. But they did not find such difference in patients with oblique tibia shaft fractures. The purpose of this study is to determine whether alcoholics experienced a longer healing time than nonalcoholics among fracture patients who were treated

operatively at the Omaha Veterans Affairs Medical Center during a six-year period. This study was undertaken to provide the rationale to initiate experimental studies at Omaha VAMC to investigate biological mechanisms that may be responsible for the problems in fracture healing experienced by alcoholics.

MATERIALS AND METHODOLOGY

The study was approved by the Human Studies Subcommittee of Omaha VA Medical Center. Fifty-four patients between the ages of 28 and 89 were treated operatively at the Omaha Veterans Affairs Medical Center between 1994 and 2000 for fractures of the femur (intertrochanteric, subtrochanteric, and periprosthetic) and tibia shaft. Only 30 of the patients (12 alcoholics and 18 nonalcoholics) could be included in the study. Twenty-four patients were excluded for the following reasons: 10 (2 alcoholics, 8 nonalcoholics) were lost to follow up, 10 (4 alcoholics, 6 nonalcoholics) died prior to fracture healing (range: 1 to 6 weeks post surgery), and 4 patients with pathological fractures (2 alcoholics, 2 nonalcoholics) were excluded. The types of fractures in the 30 patients in the study were as follows: 20 intertrochanteric (7 alcoholics, 13 nonalcoholics), 6 tibia shaft (3 alcoholics, 3 nonalcoholics), 2 subtrochanteric (1 alcoholic, 1 nonalcoholic), and 2 periprosthetic (1 alcoholic, 1 nonalcoholic). All but one patient was male.

A retrospective chart review was performed to determine fracture healing time, alcohol use, history of smoking, and oral corticosteroid use. Fracture healing time was defined as the period of time from the operative treatment of the fracture to the time at which full painless weight bearing was resumed. Radiographic evidence of callus was present in all

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of the patients at the time of clinical healing, but this was not the end point for fracture healing. Non-unions were defined as fractures taking greater than 12 months (52 weeks) to achieve painless ambulation, even in the setting of a persistent fracture line. Delayed unions were defined as taking greater than 6 months (26 weeks) for healing. Patients with documented alcohol use of at least two drinks per day and clearly documented history of long-standing alcohol abuse were defined as alcoholics. The charts of the control patients were reviewed and had no indication of alcohol abuse. In the VA healthcare system, "alcohol misuse" is defined as a score of ≥ 4 points for men and ≥ 3 for women

on the Alcohol Use Disorders Identification Test – Consumption (AUDIT-C) scale (0-12 points) and more than 20% of the VA patients screen positive on AUDIT-C. Our definition of alcohol abuse corresponds to a score between 4 and 5 on the Alcohol Use Disorders Identification-Consumption (AUDIT-C) Screening Test [10].

RESULTS

The demographic data and fracture healing times for the 12 alcoholic and 18 nonalcoholic patients are given in Tables 1 and 2, respectively. The average age at operative treatment

Table 1. Fracture Healing Time and Demographic Data for 12 Alcoholic Subjects. There were 7 Intertrochanteric Femur Fractures, One Subtrochanteric Femur Fracture, One Periprosthetic Femur Fracture and 3 Diaphyseal Fractures of the Tibia

Subject	Age (yr)	Diagnosis	Treatment	Healing Time (wks)	Smoking History	Oral Steroid Use
A1	56	Intertrochanteric	DHS	31.6	YES	YES
A2	80	Intertrochanteric	ORIF/DHS	7.3	YES	NO
A3	72	Intertrochanteric	DHS	15.6	YES	NO
A4	78	Intertrochanteric	DHS	67.2	YES	NO
A5	71	Intertrochanteric	DHS	10.1	YES	NO
A6	67	Intertrochanteric	Gamma Long	9.1	YES	NO
A7	76	Intertrochanteric	DHS	8.7	YES	NO
A8	53	Subtrochanteric	ORIF/DCS	34.3	NO	NO
A9	61	Periprosthetic Femur Fracture	RETROGRADE NAIL	14.6	YES	YES
A10	45	Tibia—Segmental	ORIF/ILIZAROV	58.7	NO	NO
A11	65	Tibia midshaft	CLOSED CAST	14.1	YES	YES
A12	47	Distal Tibia	CLOSED CAST	18.3	YES	NO

Table 2. Fracture Healing Time and Demographic Data for 18 Nonalcoholic Subjects. There were 13 Intertrochanteric Femur Fractures, One Subtrochanteric Femur Fracture, One Periprosthetic Femur Fracture and 3 Diaphyseal Fractures of the Tibia. Patients N5, N7, N8 and N15 had Quit Smoking before Fracture for Periods Ranging from 5 to 20 Years. Patient N17 had Stopped Alcohol Abuse 10 Years before Fracture

Subject	Age (yr)	Diagnosis	Treatment	Healing Time (wks)	Smoking History	Oral Steroid Use
N1	62	Intertrochanteric	ORIF	6.1	NO	NO
N2	81	Intertrochanteric	ORIF	9.1	YES	NO
N3	69	Intertrochanteric	ORIF/DHS	11.7	YES	NO
N4	76	Intertrochanteric	ORIF/DHS	18.1	YES	NO
N5	75	Intertrochanteric	ORIF/DHS	9.7	YES	YES
N6	86	Intertrochanteric	ORIF/DHS	18.6	NO	NO
N7	83	Intertrochanteric	DHS	7.3	YES	NO
N8	88	Intertrochanteric	DHS	11.9	YES	NO
N9	89	Intertrochanteric	DHS	15.6	NO	NO
N10	83	Intertrochanteric	DHS	6.1	NO	NO
N11	81	Intertrochanteric	DHS	6.3	NO	NO
N12	50	Intertrochanteric	DHS	21.9	YES	NO
N13	77	Intertrochanteric	DHS	11.7	NO	NO
N14	70	Subtrochanteric	ORIF	7.1	YES	NO
N15	57	Periprosthetic Femur Fracture	ORIF/Plate/Cable	14.4	YES	NO
N16	28	Tibia Segmental	IM Nail	9.6	YES	NO
N17	64	Tibia	ICBG/CLOSED ROD	13.7	YES	NO
N18	38	Tibia/Fibula	IM Nail	6.6	NO	NO

Table 3. Fracture Healing Time for Specific Categories of Fracture, Reported as Mean ± Standard Error (n)

Subgroups	Fracture Healing Time in Alcoholics, wks	Fracture Healing Time in Nonalcoholics, wks	P-values
Intertrochanteric Femur Fracture	21.4±8.3 (7)	11.8±1.5 (13)	0.298
Tibia shaft Fracture	30.4± 14.2 (3)	10.0±2.1 (3)	0.287
Subtrochanteric Femur Fracture	34.3 (1)	7.1(1)	_____

of fracture was 64.3 yrs for alcoholics and 69.8 yrs for controls. The data were analyzed using an analysis of covariance (ANCOVA) model with group, smoking history, oral steroid use as factors and an interaction term (group * smoking history), and age as a covariate. Other interaction terms did not show a significant effect and hence were removed from the model. The analysis showed that there were statistically significant differences in the data ($p = 0.025$). The mean fracture healing time ± standard error (SE) for various groups and subgroups are reported below along with the number of patients (n). Differences were regarded as statistically not significant for $p > 0.05$.

The average fracture healing time was significantly longer for alcoholics: 24.1 ± 5.8 weeks ($n = 12$) compared to 11.4 ± 1.1 weeks ($n = 18$) in nonalcoholics ($p = 0.001$). None of the controls developed non-unions, whereas 2 of the 12 alcoholic patients developed non-unions. No patients in the control group developed a delayed union compared to 2 of the 12 alcoholic patients. The combined delayed and non-union rate in alcoholics (4 out of 12) was significantly higher than in nonalcoholics (0 out of 18) ($p = 0.018$, Fisher's Exact Test).

Although the total numbers of alcoholics (12) and non-alcoholics (18) in this study are small, we performed statistical analysis of various subgroups mainly to provide some insights for designing future studies of the variables that influence fracture-healing time in alcoholics vs. nonalcoholics. The fracture healing times for different categories of fracture are given in Table 3. For intertrochanteric femur fractures, the mean fracture healing time in alcoholics is 9.5 weeks longer than in nonalcoholics, but the 95% confidence interval for this difference in mean values is $\{-10.7392, 29.7897\}$, which includes zero. This is mainly due to the combination of small number of alcoholics and the relatively large standard deviation (21.8 weeks, compared with the mean value of 21.4 weeks in this subgroup). A similar situation is encountered in the subgroup of tibia shaft fractures with even smaller sample sizes.

Differences in fracture healing time between alcoholics and nonalcoholics in patients with and without a smoking history are given in Table 4. The difference was not significant for smokers. The small p value for the comparison of alcoholics vs. nonalcoholics among nonsmokers cannot be considered valid because there were only 2 alcoholic patients in the subgroup, (alcoholics, nonsmokers). Comparison between smokers and nonsmokers among alcoholics would also be invalid for the same reason.

The fracture healing time for all smokers (alcoholics and nonalcoholics) as a group was 18.2 ± 5.9 weeks ($n=9$) compared with 15.8 ± 2.9 weeks ($n=21$) for all nonsmokers

($p = 0.045$). Interaction term, Group*Smoking History, was also significant ($p = 0.022$). Normally, the presence of a significant interaction term would mean that the difference in fracture healing time between alcoholics and nonalcoholics could not be attributed solely to alcohol abuse. As discussed below, the known effects of smoking on fracture healing suggests that with a sufficient number of patients in the subgroup (alcoholics, nonsmokers), we may find that the fracture healing time for this subgroup, namely, 46.5 ± 12.2 weeks ($n=2$), may change drastically and become less than that for the subgroup (alcoholics, nonsmokers), which is 19.7 ± 5.7 weeks ($n=10$) in the present study. If this proves to be true, the interaction term is likely to be insignificant. These issues must be resolved in future studies.

Table 4. Fracture Healing Time (weeks) for Smokers and Nonsmokers, Reported as Mean ± Standard Error (n). The Comparison between Alcoholics and Nonalcoholics among Nonsmokers is Inconclusive because of the Small Sample Size (n = 2)

Subgroups	Alcoholics	Nonalcoholics	P-values
Smokers	19.7 ±5.7 (10)	12.2 ± 4.6 (11)	0.1906
Nonsmokers	46.5 ±12.2 (2)	10.1 ±2.0 (7)	0.0019

DISCUSSION

The alcoholic patient population is notoriously difficult to study because of poor compliance with follow up, as well as other practices that serve as confounding factors when investigating treatment outcomes. However, in the present study, fewer alcoholic patients were lost to follow up (2 out of 20) or due to death (4 out of 20) than nonalcoholic patients: 8 out of 34 and 6 out of 34, respectively. We were able to demonstrate that the average fracture healing time was significantly longer for alcoholics (24.1 wks) compared to non-alcoholics (11.4 wks) ($P = 0.001$). The average fracture healing time in alcoholics was slightly less than the time we defined as delayed union (26 weeks). We found that alcoholic patients had significantly higher frequency of fracture healing delays (delayed union and nonunion combined) than nonalcoholic patients.

Eighty three percent of alcoholics were smokers compared with 61 percent among nonalcoholics. In the entire study, fracture healing was most delayed in the 2 alcoholic patients who were not smokers, although the number of patients is too small to make a statistically valid conclusion. Nevertheless this is a surprising result since it is known that smoking is a contributory factor in delayed fracture healing [11] and that cessation of smoking following fracture

treatment decreases the risk of postoperative complications [12]. The average fracture healing time was not significantly different between smokers (12.2 wks) and non-smokers (10.1 wks) among nonalcoholics. It was not possible to make the corresponding comparison for alcoholics, since there were only 2 patients who were nonsmokers (Table 4).

Our results are similar to those found by Nyquist *et al.* [4] in a study of patients (18 y to 60 y) treated between 1980 and 1990 at Malmö University Hospital in Sweden: alcoholics (22.3 wks, n = 49, average age 44 y) and nonalcoholics (16.3 wks, n = 150, average age 37 y) who sustained transverse tibia shaft fractures ($p = 0.035$). But they found no difference in those with oblique fractures of the tibia shaft. Transverse fractures are caused by high-energy forces, whereas oblique fractures result from low-energy events, e.g. from falls. Transverse fractures are known to take longer to heal than oblique fractures [13]. Nyquist *et al.* [4] did not find any difference in the rate of non-unions and delayed unions.

The study has several limitations mainly due to the small numbers of alcoholics (12) and nonalcoholics (18). In spite of the very small number of patients in subgroups according to the type of fracture, statistical analysis was performed as a basis for power analysis in future studies. As pointed out in the "Results" and "Discussion" sections the tentative findings from this analysis need to be confirmed or refuted in future studies with a larger cohort of patients. We did not distinguish between transverse and oblique fractures as was done by Nyquist *et al.* [4] for fractures of the tibia shaft fractures in their study. The statistical analysis of fracture healing time in subgroups according to smoking history was also performed for providing guidance for future studies and has the same limitation as mentioned above. In addition, two of the findings are anomalies in the context of existing knowledge that are likely to be modified in future studies: (1) fracture healing was most delayed in 2 alcoholics who were not smokers, and (2) there was a significant interaction term between alcohol abuse history and smoking. The latter is not valid since there were only 2 patients in the subgroup of alcoholics who were nonsmokers with mean fracture healing time that was more than double that of the subgroup of 10 alcoholics who are smokers. If an interaction is found in future studies with a larger cohort, it is likely that this relationship may be reversed, i.e. with alcoholics who are smokers having a longer fracture healing time. Another limitation of the study is that our definition of alcohol abuse, while a reasonable one, agrees with criteria used in only some of the published studies, but not all. Similarly, there is no standard or consensus in published studies on the length of fracture healing time that would be considered delayed healing. Moreover, a precise definition of delayed healing needs to take into account the differences in normal fracture healing time among various long bones. Nevertheless, our definition of delayed healing, namely, fracture healing time longer than 26 weeks, is valid since it is at least 50% greater than the longest normal fracture healing time for any type of human long bone with single fractures [13].

Fracture healing problems in alcoholics are often attributed to their noncompliance with the standard orthopedic treatment protocols. However, recent animal studies have provided significant evidence for an alcohol-induced bio-

logical deficiency that is manifested as suppression of new bone formation in the fracture site [14-21]. Several in vitro studies support the hypothesis that alcohol has a direct toxic effect on bone cells [1]. Inhibition of new bone formation in the fracture site may also be mediated by elevated or extended expression of proinflammatory cytokines such as interleukin 1 beta and tumor necrosis factor alpha [19, 22]. Normal expression of these cytokines during the inflammatory phase following bone injury support the onset of osteogenesis, whereas the abnormal expression is associated with delay or inhibition of new bone formation.

CONCLUSIONS

The mean fracture healing time in alcoholics was approximately twice that in nonalcoholics and this difference was highly significant. The frequency of delays in fracture healing in alcoholics was also significantly greater than in nonalcoholics. The mean fracture healing time in smokers, regardless of alcohol abuse status, was only 15% longer than in nonsmokers, but this difference was significant. The findings of the present study support the hypothesis that interventions in addition to the standard fracture treatment protocols may be necessary to obtain prompt fracture healing in alcoholics. However, studies using a larger cohort of patients are needed to determine whether the trends observed in the present study would become statistically valid conclusions to provide unambiguous directions for changes in the current clinical practice.

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ABBREVIATIONS

T	=	Fracture healing time
AUDIT-C	=	Alcohol use disorders identification test-consumption
SE	=	Standard error

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