Fracture Prevention Clinic Targeting Patients with Fragility Fracture of the Distal Radius: A Pilot Study

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ABSTRACT **Background:** Identifying and treating patients with fragility fractures may be effective in prevention of subsequent fractures because a first fragility fracture often predicts a second fracture.

Objectives: To evaluate a multidisciplinary anti-osteoporotic clinic for patients with prior distal radius fragility fractures (DRFF). To assess whether addressing this early fracture may prevent a second fracture.

Methods: A retrospective case-control study was performed. Cases included patients treated surgically for DRFF who were assessed at a tertiary, multidisciplinary, fracture-prevention clinic. Controls were a series of similarly treated patients who did not attend the clinic. The primary outcome measure was a second fracture.

Results: Average follow-up was 42 months for the treated group and 85 months for the untreated group. The treated group received more treatment for osteoporosis than controls; however, despite one new fracture in the treated group and six new fractures in the control group, there was no significant difference in fracture occurrence.

Conclusions: This pilot study supports the effectiveness of our multidisciplinary anti-osteoporotic clinic in treating osteoporosis but not in reducing subsequent fractures. Further study with larger cohorts and longer follow-up is needed to improve our ability to implement effective prevention of fragility fractures.

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KEY WORDS: distal radius fracture, fragility fracture, multidisciplinary clinic, osteoporosis, prevention

A fragility fracture is one of the major risk factors for a subsequent fracture in osteoporotic patients. Such fractures have been shown to be associated with increased risk for permanent disability and death, and to constitute a major economic burden [1,2]. Multidisciplinary teams have demonstrated effectiveness in osteoporosis prevention, especially when they involve the treating surgeon [3,4]. In 2011, the International Osteoporosis Foundation published a position paper on coordinator-based systems for secondary prevention in fragility fracture patients or Fracture Liaison Services [5]. Since then, a number of studies have demonstrated the efficiency and cost effectiveness of these services in lowering secondary fracture rates and mortality [6,7]. However, despite the clear advantage of early identification and treatment, many osteoporotic patients are still overlooked and remain untreated [8]. Due to this treatment gap, the American Society for Bone and Mineral Research recently published consensus recommendations for the management of osteoporotic fractures and secondary fracture prevention. Strongly supported by the empirical literature, the authors further validate the use of multidisciplinary case management as the most effective means of patient evaluation and treatment.

An evaluation of our medical system demonstrated that patients were unlikely to receive appropriate diagnosis, evaluation, and treatment for secondary prevention of fragility fractures [9]. Since some studies have shown that distal radius fragility fractures increase the risk for vertebral and hip fragility fractures, we initiated a multidisciplinary clinic designed to treat and follow patients with prior fragility fractures of the distal radius [9]. Since these distal radius fragility fractures tend to appear some time prior to vertebral and hip fragility fractures, we believe that targeting this subpopulation of patients with fragility fractures may be more effective in preventing a second fracture [10].

The purpose of this pilot study was to evaluate the effect of a multidisciplinary clinic located in a large health maintenance organization on patients who sustained a distal radius fragility fracture and to compare the results to a similar cohort not treated in the clinic.

PATIENTS AND METHODS

This retrospective case control study included all participants assigned to a tertiary, multidisciplinary, fracture prevention clinic starting in July 2015. Patients over the age of 18 years, treated surgically for distal radius fragility fractures (DRFF) were eligible for inclusion in the clinic. Fragility fractures were defined as fractures sustained following a low kinematic injury. Controls were taken from a series of patients in the same health system undergoing open reduction internal fixation (ORIF) for a DRFF that was not treated by the multidisciplinary clinic.

Table 1. Patient characteristics

	Untreated (n=110)	Treated (n=43)	*P* value
Age, mean years ± standard deviation	63.75 ± 11.23	68.87 ± 11.81)	0.043
Sex, n (%), female	85 (77.27)	36 (83.72)	0.509
Background disease, n (%)	3 (2.78)	0 (0.00)	0.656
Diabetes, n (%)	16 (14.55)	1 (2.33)	0.06
Smoker, n (%)	7 (6.36)	5 (11.63)	0.451
Body mass index kg/m^2	28.08 (4.91)	26.1 (4.98)	0.121
None, n (%)	43 (53.75)	0	
Treatment prior to fracture, n (%)	19 (23.75)	0	
Treatment after fracture, n (%)	18 (22.50)	0	

Comparison between the groups with regard to age, sex, background disease including rheumatoid arthritis and glucocorticoid treatment, renal failure affecting osteoporosis, diabetes, smoking status, treatment for osteoporosis (0 = no treatment, 1 = treatment prior to fracture, 2 = treatment after fracture)

There were a few patients with increased alcohol intake in both groups. Information regarding family history of fracture was available for five patients only.

Table 2. Regression analysis for outcome measures of new fracture, treatment post-fracture, and chart diagnosis of osteoporosis

*Bold signifies significance

	Coefficient	95% confidence interval		*P* value*
	Odds ratio	Lower	Upper	
Outcome: New fracture during follow-up				
Age, years	1.04	0.93	1.18	0.463
Sex, female	3.82	0.22	65.64	0.356
Current smoker	0.29	0.82	1052.0	0.064
Diabetes	7.20	1.71	303.06	0.300
Follow-up time (standardized)	0.79	0.52	1.15	0.215
Body mass index	1.07	0.83	1.37	0.605
Outcome: Treatment post fracture				
Age, years	1.11	0.99	1.24	0.063
Sex, female	0.17	0.01	5.41	0.312
Current smoker	9.30	0.43	200.24	0.154
Diabetes	0.00	0.00	Infinity	0.996
Follow-up time (standardized)	0.74	0.54	1.01	0.059
Body mass index	0.87	0.68	1.12	0.280
Outcome: Diagnosis of osteoporosis				
Age, years	1.09	1.01	1.18	0.029
Sex, female	0.63	0.06	6.36	0.692
Current smoker	0.64	0.05	7.53	0.723
Diabetes	0.70	0.09	5.50	0.737
Follow-up time (standardized)	1.20	1.03	1.40	**0.021**
Body mass index	0.97	0.82	1.15	0.745

The multidisciplinary clinic consisted of a hand surgeon, an endocrinologist and an occupational therapist. The surgeon followed fracture recovery. The endocrinologist evaluated the patient for osteoporosis and used patient history and lab results to administer pharmacological treatment. The occupational therapist focused on independence in activities of daily living (ADL) and fall prevention. At the initial visit, the patient saw all three practitioners. The subsequent appointments were scheduled separately according to the particular needs of the patient.

Patient demographic and clinical characteristics were documented. Evaluation consisted of medical history including former fractures, family history of fractures, past evaluations including dual-energy X-ray absorptiometry (DXA), and prior treatment for osteoporosis. Background diseases or conditions and treatment as well as social history were documented.

Prior to arrival in clinic, serum was obtained for calcium, phosphate, alkaline-phosphatase, vitamin D, B12, and testosterone in men. Liver, kidney, and thyroid function tests were also administered as well as celiac screening test. DXA was performed for bone mineral density if it had not been performed in the past. According to the results, the endocrinologist assigned appropriate pharmacological treatment. The patients were followed every 6 months. The primary outcome measure was a second fracture during the follow-up period.

We compared the outcome measures of this cohort with a previous untreated cohort from the same health system. The categorical data were analyzed using the chi-square test, the Fischer exact test, and the continuous data was analyzed using *t* test or Wilcoxon Rank Sum test, as appropriate. Multivariate logistic regression models were created to measure associations between relevant variables and outcomes of interest while being able to statistically control for other variables. In addition to the demographic and baseline characteristics chosen as covariates, follow up time was also used as a covariate and standardized within groups. All *P* values were two sided and statistical significance was defined as $P < 0.05$. Data analysis was performed using RStudio Version 1.2.1335.

This study was approved by our institutional review board (IRB) prior to study commencement.

Table 3. Medical treatment

	Clinic group	Non-clinic group	*P* value
Bisphosphonates, n (%)	0 (0.00)	14 (32.56)	< 0.0001
Denosumab, n (%)	0 (0.00)	5 (11.63)	0.0017
Teriparatide, n (%)	0 (0.00)	4 (9.30)	0.0074

The distribution of preventive medications
The group seen in the secondary prevention clinic had significantly more medical treatment for the prevention of osteoporosis

RESULTS

A total of 45 patients were seen at the clinic. Two patients did not comply with the suggested treatment and were excluded, thus 43 patients were included in the study. Patient demographic data are summarized and shown to the untreated group in Table 1. Because of the nature of the retrospective review some data were missing, especially from the untreated group. All treatment group patients went through separate post-operative rehabilitation with an occupational therapist according to their physical ability and healing progression.

The age of the patients in the multidisciplinary clinic was significantly higher than the untreated group. New fractures during the follow-up period are shown in Table 2. When comparing the 110 untreated patients with the 43 treated patients throughout the follow-up period, six new fractures (5.45%) were noted in the untreated group, compared to one new fracture (2.44%) in the treated group, a difference that was not significant ($P = 0.43$).

The follow-up period was significantly longer in the untreated group. A sensitivity analysis was performed to assess the effect of follow-up period of new fracture occurrence between groups, using a multivariate logistic regression model that included a treatment group indicator and a standardized follow-up time variable as the predictors. The model found no statistically significant association between treatment group and new fracture occurrence throughout the follow-up period after controlling for follow-up time, consistent with the earlier results [Table 2]. In the untreated group, the 18 patients who received treatment after fracture [Table 3] were given calcium and vitamin D supplements. The pharmacological treatment of both groups is presented in Table 3.

Multivariate logistic regression models were run on three outcomes: new fracture during follow-up, treatment post-fracture, and diagnosis of osteoporosis in charts. Of the three models, only the model predicting diagnosis of osteoporosis in charts showed any predictor with a statistically significant association with the outcome, which was follow-up time (standardized) (odds ratio [OR] 1.19, 95% confidence interval [95%CI] (1.02–1.39), $P = 0.02$) and age (OR 1.09, 95%CI 1.01–1.18, $P = 0.03$). Every one standard deviation increase during the follow-up time was associated with an increase in the odds of a diagnosis of osteoporosis in chart by a factor of 1.19. Every one unit increase in age was associated with an increase in the odds of a diagnosis of osteoporosis in chart by a factor of 1.09.

DISCUSSION

Following an initial fragility fracture, the risk of subsequent fracture increases by 1.6- to 4.3-fold at any given age [11]. Although the 10-year probability of any recurrent fracture after a primary wrist fracture is significantly less than for other primary fractures (spine, 25.7%; hip, 24.9%; humerus, 23.7%), it is still noteworthy(14.2%) and greater than in those without prior fractures[11].Furthermore, DRFFs tend to occur earlier than other fragility fractures. This increases their appeal as a sentinel fracture that can enable early detection; and therefore contribute to improved prevention [12].

Multiple studies have shown the efficacy of a multidisciplinary fracture liaison service [13,14]. A recent prospective study over a 4-year follow-up period reported significant improvement (less consequent fractures) in the treated group, while Van Der Kallen et al. [13] followed their patients for 2 years and found significant differences in fracture rate [14]. The establishment of a multidisciplinary clinic enables early identification of patients at risk, since they are singled out for treatment. Such services likely increase the number of patients treated for osteoporosis and may reduce fracture rates [12,15]. In the current study, patients who attended the clinic received more anti-osteoporotic pharmacological treatment than did patients who did not attend the clinic.

During our follow-up period of 42 months, one of the 43 patients who attended the multidisciplinary anti-osteoporotic clinic had a second fracture. This compares to six new fractures among the 110 patients with the same initial fragility fracture that did not attend the clinic and had a significantly longer follow up period (85 months). Based on these observations, we did not demonstrate any significant difference between the groups ($P = 0.43$) despite an 8% fracture rate in the control group. A sensitivity analysis that investigated the association between new fracture occurrences throughout the follow-up period in the treatment group while controlling for follow-up time supported our finding that there was no significant difference between the two groups. It is likely that as a pilot study, we were underpowered to detect a difference.

Compared to the control group, the treatment group in the current study was characterized by older mean age. This finding would be expected to increase the incidence of fragility fracture compared to the control group, as older age is associated with increased risk of fracture [16]. The treatment group should

therefore have had an increased incidence of consequent fractures and not a similar incidence. This result perhaps explains the lack of significant difference in fracture rate between the treated and untreated groups. A longer follow-up period in the treated group may yield significant differences, especially since we are evaluating DRFFs that tend to occur earlier. However follow-up time was not found to affect the outcome measure of new/second fracture in this study [12,16-19]. In addition, since we saw a significant increase in treatment but no significant decrease in fracture incidence, it is possible this discrepancy is due to the relative ineffectiveness of our preventive treatment at this stage in the condition, rather than due to lack of identification and treatment.

The chart diagnosis of osteoporosis (arguably identification is a first step in preventive treatment) was related to a follow-up period with diagnosis of osteoporosis increasing with time. This result may reflect improving awareness of osteoporosis in our health system, although this still leaves room for improvement since patients should be diagnosed with osteoporosis on intake.

LIMITATIONS

Limitations of the pilot study include its retrospective nature and the limited number of patients and follow-up period. This study was also performed on DRFF alone. While these are known to be fractures that herald subsequent fragility fractures, they generally occur in a younger population, often do not require hospitalization, and may not be brought to the attention of the treating physician. Still, and even due to these characteristics, treatment of a distal radius fracture may serve as an appropriate target for preventing secondary fractures.

We encountered several administrative challenges in setting up the designated clinic. This is likely due to the lack of evidence with regard to the cost-effectiveness of the fracture liaison and highlights the importance of evaluating outcomes to verify effectiveness.

There have been reports in the literature regarding risk of subsequent fracture following an initial fragility fracture. Center and co-authors [10] found that by the end of a 10-year follow-up period, the subsequent fracture risk was no longer different from the first fracture risk. van Geel and colleagues [20] found that a total of 23% of all subsequent fractures occurred in the first year after an initial fragility fracture, 31.3% in the next 4 years, and 25.9% during the next 5 years. Wrist fractures in particular have been associated with a 5 and 10 times greater rate of vertebral fractures in women and men, respectively, a year after initial fracture [10]. Furthermore, Ahmed et al. found that risk of subsequent fracture after DRF is increased in all age groups and had a tendency to precede future hip or other major fractures in the future [16]. Thus, it is imperative to identify these fragility fractures and intervene to reducing further fracture risk. Since it is not clear from this study that treatment is effective in preventing a second fracture, maybe the emphasis should be on early detection to allow for more successful prevention of fractures.

CONCLUSIONS

Improvement in treatment rates following a DRFF treated in a multidisciplinary fracture liaison clinic did not correlate to a reduction in subsequent fractures. It is possible that other factors in our population affect fracture occurrences that are not addressed by the fracture prevention clinic. Further study on a larger cohort is needed to improve our ability to implement effective prevention of fragility fractures.

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Capsule

Coronavirus antibody levels predict vaccine efficacy

Symptomatic COVID-19 infection can be prevented by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccines. A correlate of protection is a molecular biomarker to measure how much immunity is needed to fight infection and is key for successful global immunization programs. **Gilbert** and colleagues determined that antibodies are the correlate of protection in vaccinated individuals enrolled in the Moderna COVE phase 3 clinical trial. By measuring binding and neutralizing antibodies against the viral spike protein, the authors found that the levels of both antibodies correlated with the degree of vaccine efficacy. The higher the antibody level, the greater the protection afforded by the messenger RNA (mRNA) vaccine. Antibody levels that predict mRNA vaccine efficacy can therefore be used to guide vaccine regimen modifications and support regulatory approvals for a broader spectrum of the population.

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Capsule

Structural virology a block to viral cell entry

Crimean-Congo hemorrhagic fever virus is a tickborne virus that can cause severe disease and even death in humans. Disease occurrence is linked to the geographic range of the tick vector, and climate change may increase this range. Infection of host cells requires the fusion glycoprotein Gc, which is the main target of neutralizing antibodies. **Mishra** and co-authors built on previous work that identified a combination of two Gc-targeting antibodies that gave post exposure protection in an animal model. The authors determined the structure of the antigen-binding fragments of the two antibodies bound to a prefusion form of Gc and also the structure of Gc after the conformational change into the trimeric postfusion form. The structures show how the antibodies work together to block membrane fusion.

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Capsule

HIV T_{RM} cells are state of the ART

Recent advances in antiretroviral therapy (ART) and testing have restored the life expectancies of people infected with HIV. However, HIV-positive individuals still show a higher risk for malignancies of the skin and mucosa associated with human papilloma virus (HPV). **Saluzzo** and colleagues reported that HIV-positive individuals who begin ART late show good recovery of circulating CD4 T cells but exhibit an irreversible depletion of CXCR3+ tissue-resident memory T (T_{RM}) cells in the skin. Their skin is instead repopulated by T helper 2-like cells, which appear to foster a permissive immune environment. By contrast, HIV-positive individuals who go on ART shortly after infection reconstitute their cutaneous TRM cells within a year. Thus, early diagnosis and treatment of HIV infection may help to stave off HPV-related cancers.

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