

Cost Savings Associated with the Use of Electrical Bone Growth Stimulation to Treat Diabetic Patients in the U.S. with Fracture Nonunion

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Abstract

Objectives: Diabetic patients can suffer from poor bone quality and impaired vascularity often leading to increased fracture risk, delayed healing and potential fracture nonunion. Therefore, this study assessed healthcare resource utilization by diabetic patients receiving electrical bone growth stimulation (EBGS) versus low-intensity pulsed ultrasound stimulation (LIPUS) or neither (No-stim) for the management of their fracture nonunions.

Methods: Diabetic and non-diabetic patients newly diagnosed with a fracture nonunion were identified using medical and pharmacy claims and stratified by the first treatment received after nonunion diagnosis: EBGS, LIPUS, or No-stim. Patient demographics, comorbidities, fracture characteristics, and healthcare costs were analyzed before and after nonunion diagnosis. Multivariate regression analysis was used to compare healthcare costs incurred during nonunion fracture management for the different treatment cohorts.

Results: After controlling for demographic and clinical characteristics in the diabetic group, EBGS was associated with significantly lower total healthcare costs when compared with the No-stim cohort (marginal difference: -\$11,834, p<0.01) and significantly lower fracture-related costs when compared to both the LIPUS (marginal difference: -\$3,016, p=0.02) and the No-stim (marginal difference: -\$4,783, p<0.01) cohorts. LIPUS was associated with significantly lower total healthcare costs (marginal difference: -\$4,783, p<0.01), but similar fracture-related costs (marginal difference: -\$8,743, p=0.01), but similar fracture-related costs (marginal difference: -\$1,767, p=0.23) when compared to the No-stim cohort. In the non-diabetic group a similar trend was observed as EBGS was associated with significantly lower costs when compared to the other cohorts.

Conclusions: Study results suggest that EBGS is associated with lower healthcare costs in the management of fracture nonunions in both diabetic and non-diabetic patients.

Keywords: Fracture nonunion; Electrical bone growth stimulation; Low-intensity pulsed ultrasound stimulation; Cost savings; Diabetic; Non-diabetic; Healthcare utilization; Economic burden

Abbreviations: CCI: Charlson Comorbidity Index; CPT: Current Procedural Terminology; EBGS: Electrical Bone Growth Stimulation; HCPCS: Healthcare Common Procedure Coding System; ICD-9-CM: International Classification of Diseases Ninth Revision Clinical Modification; LIPUS: Low-Intensity Pulsed Ultrasound Stimulation; No-stim: Neither EBGS or LIPUS; OAD: Oral Antidiabetic Medication; U.S.: United States

Introduction

Diabetes is of significant epidemiological and economic concern in the United States. Approximately 8% of the U.S. population has been diagnosed with diabetes, and that number is expected to double or triple by 2050 [1]. Diabetes is associated with many long-term complications and health risks [2,3], and previous studies have found that the cost of diabetes care totaled \$174 billion in 2007 [4,5]. Furthermore, the direct costs associated with treating type 2 diabetes-related comorbidities alone were reported to be \$22.9 billion in 2006 [6].

Fracture nonunion is another rising health concern in the United States. An estimated 7.9 million fractures occur annually in the U.S., and up to 10% of these fractures develop into a delayed union or nonunion signaling an impaired healing process [7]. Moreover, in addition to the growing prevalence of fracture nonunions in the U.S., the economic impact associated with healing these fractures is of concern. Kanakaris et al. reported that the average direct costs for treating humeral, femoral, and tibial fracture nonunions were £15,566, £17,200, and £16,330,

respectively, in the United Kingdom in 2007. Converted to U.S. dollars, these costs are equivalent to \$31,132, \$34,400, and \$32,660, respectively [8]. Although surgical options for the management of impaired bone healing exist, non-invasive treatment including electrical bone growth stimulation (EBGS) and low-intensity pulsed ultrasound stimulation (LIPUS) are also commonly used to treat fracture nonunions [9-24]. Recently, EBGS was shown to be associated with lower healthcare costs for fracture nonunions in a real world setting when compared to LIPUS or other non-stimulation treatment options (No-stim) [25]. For diabetic patients (types 1 or 2), poorer quality of bone, and impaired vascularity are just some of the factors that lead to increased fracture risk, delayed healing and potential fracture nonunion [2,26-30]. In a retrospective study evaluating diabetic ankle fractures, risk factors for the development of fracture nonunion included previous history of Charcot foot, longer duration of diabetes, use of insulin, and presence of nephropathy or neuropathy [31]. Another retrospective study found that diabetic patients had a higher rate of nonunion in tibial pilon

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fractures than non-diabetic patients (43% vs. 16%) [32]. Additionally, previous studies have shown that bone growth stimulation is efficacious in the treatment of diabetic fractures [19,33-36]. However, the economic benefit of bone growth stimulation in the treatment of fracture nonunions in diabetic patients has not yet been explored.

Diabetes and the risk of fracture nonunion impose a societal and economic burden. Therefore, the purpose of this study was to explore the resource use and healthcare costs associated with EBGS, LIPUS, and No-stim in managing fracture nonunions within both diabetic and non-diabetic patients.

Research Design and Methods

Data source and sample selection

Medical and pharmacy claims data between October 2005 and September 2010 from the Truven Health Analytics MarketScan Commercial Insurance Databases was analyzed. Patients, aged 18-64 with at least one medical claim suggesting a fracture nonunion (ICD-9-CM: 733.82) between July 2006 and September 2009 were included in the study. Patients \geq 65 years old were excluded, as these patients are typically insured by Medicare and Medicaid. The date of the first claim indicating fracture nonunion diagnosis was set as the index date. Only patients with fractures of the appendicular system and at least 9 months of continuous commercial insurance enrollment before and 12 months following the index date were included in this study. Patients with fracture claims indicating EBGS or LIPUS treatment before the index date, cancer metastasis (ICD-9-CM: 198.5) or malignant tumor of bone (ICD-9-CM: 170.xx), or suggesting multiple fractures or fracture nonunion diagnosis in the pre-index period were excluded.

Patients were stratified by the presence or absence of claims suggesting diabetes (ICD-9-CM: 250.xx). Diabetic and non-diabetic patients were further classified by the first treatment received following the index date: EBGS, LIPUS, or No-stim. The use of EBGS was identified when a medical claim had an associated Current Procedural Terminology (CPT) code of 20974 or Healthcare Common Procedure Coding System (HCPCS) code of E0747. The use of LIPUS was identified when a claim had an associated CPT code of 20979 or HCPCS code of E0760. The No-stim cohort included those patients that did not receive EBGS or LIPUS after the index date.

Study measures

Demographic and clinical characteristics including age, gender, insurance plan, geographical region, Charlson Comorbidity Index (CCI) [37], fracture-related comorbidities, and oral antidiabetic medication (OAD) and/or insulin use (diabetic patients only) were reported for each treatment cohort. Fracture characteristics including fracture location, complications during the pre-index period, and fracture treatment before and after the index date were also reported. Observed complications included injury to blood vessels, injury to nerves, hemorrhage, post-traumatic wound infection, traumatic compartment syndrome, septicemia, mechanical complication of internal orthopedic device, infection/inflammatory reaction due to internal device, and blood transfusion. Clinical outcomes were neither reported nor available from the database for analysis.

Total and fracture-related costs before and after the index date were calculated for each treatment group. Total healthcare costs included expenses associated with inpatient care, outpatient care, and medication use. Fracture-related costs included all claims associated with services required to diagnose and treat the patient's fracture. Pharmacy-related costs were excluded from the fracture-related costs as there are no specific medications designated for the treatment of fractures. All costs were adjusted for inflation using the Consumer Price Index and standardized to 2011 U.S. dollars so that cost measures from different years would be comparable. General patterns observed between the diabetic and non-diabetic patients were reported, however, statistical analyses comparing diabetic and non-diabetic patients were not performed as the purpose of this study was to compare patient characteristics and outcomes between the different treatment modalities: EBGS, LIPUS, and No-stim.

Statistical analysis

Descriptive statistics for demographics, comorbidities, treatment patterns, fracture locations, and post-index total and fracture-related healthcare costs were compared among the different treatment cohorts for both diabetic and non-diabetic patients. The mean and standard error were reported for continuous variables, while percentages were reported for categorical variables. Differences in categorical variables were assessed using a Chi-square test. A Student's t-test was used to examine differences in continuous variables. A non-parametric Wilcoxon test was used to compare total and fracture-related healthcare costs between the various treatment cohorts as the distribution of costs associated with the different treatments was not normal.

A generalized linear regression model assuming a gamma distribution with log link function was used to predict total and fracture-related healthcare costs for the different treatment cohorts in both the diabetic and non-diabetic patients after nonunion diagnosis while controlling for fracture location, OAD/insulin use (diabetic patients only), and demographic and clinical characteristics. Predicted total and fracture-related healthcare costs were based on the actual costs observed for the different treatment cohorts and accounted for between cohort differences such that the predicted costs would be comparable.

Results

A total of 11,628 patients diagnosed with a fracture nonunion were included in this study: 1,404 (12.1%) diabetic patients and 10,224 (87.9%) non-diabetic patients. Of the diabetic patients with fracture nonunion (n=1,404), 34.1% received EBGS, 13.0% received LIPUS and 52.9% received No-stim. Among the non-diabetic patients, 28.9% received EBGS, 12.2% received LIPUS, and 58.9% received No-stim (Table 1). Demographic and comorbidity information was analyzed to assess trends in the distribution of patient age, gender, insurance plan type, U.S. region of residence, comorbidity prevalence, and medication use across the different treatment modalities for both diabetic and non-diabetic patients. Similar trends were observed for patient residence and commercial insurance plan as the majority of both diabetic and non-diabetic patients lived in the Southern U.S. and used a preferred provider organization for insurance. Alternatively, there were differences in patient age and comorbidity prevalence between the diabetic and non-diabetic patients. In the diabetic group, over half the patients were aged 55-64 (EBGS: 50.1%; LIPUS: 53.6%; No-stim: 62.1%), while less than one third of non-diabetic patients were in this older patient population (EBGS: 28.7%; LIPUS: 30.9%; Nostim: 26.4%). Furthermore, study results found that diabetic patients had a higher CCI score and a higher proportion of fracture-related comorbidities in comparison to non-diabetic patients. For example, diabetic patients had a higher incidence of anemia: 15.5%, 16.4%, and 18.5% for EBGS, LIPUS, and No-stim treatment, respectively, while the incidence of anemia in non-diabetic patients was 5.4%, 7.3%, and

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	Diabetic							Non-diabetic							
					p-values						p-values				
	EBGS (N=479)	LIPUS (N=183)	No-stim (N=742)	EBGS vs. No-	LIPUS vs. No-	EBGS vs.	EBGS (N=2951)	LIPUS (N=1251)	No-stim (N=6022)	EBGS vs.	LIPUS vs. No-	EBGS vs.			
	%	%	%	stim	stim	LIPUS	%	%	%		stim				
Age				<0.01	0.11	0.51				<0.01	<0.01	0.48			
18–24	1.7	1.1	1.8				11.4	10.5	16.0						
25–34	3.1	1.1	2.0				10.2	9.3	11.5						
35–44	9.4	10.9	9.6				18.7	17.7	17.7						
45–54	35.7	33.3	24.5				30.9	31.6	28.3						
55–64	50.1	53.6	62.1				28.7	30.9	26.4						
Gender				0.10	0.90	0.21				<0.01	<0.01	0.89			
Male	42.2	47.5	47.0				39.9	39.6	49.8						
Female	57.8	52.5	53.0				60.1	60.4	50.2						
Insurance plan type*				0.11	0.10	0.12				0.13	0.02	0.07			
Comprehensive	2.7	0.5	5.5				3.1	2.4	3.7						
EPO	0.6	0.5	0.7				0.4	0.6	0.4						
НМО	17.3	11.5	13.5				14.2	13.7	15.0						
POS	8.1	8.2	6.9				10.2	10.2	8.9						
PPO	67.0	72.7	69.5				65.5	68.9	66.9						
POS w/ capitation+	0.6	0.5	0.4				0.7	0.2	0.6						
CDHP	0.8	2.7	1.5				2.8	1.8	2.2						
Missing/unknown	2.7	3.3	2.0				3.0	2.2	2.3						
U.S. Region				<0.01	0.01	0.10				<0.01	<0.01	<0.01			
Northeast	12.1	10.4	9.3				14.3	9.0	9.5						
NorthCentral	22.5	26.2	31.8				22.4	20.5	28.4						
South	47.2	52.5	42.3				42.5	51.4	40.4						
West	15.2	7.7	15.2				18.7	16.7	19.9						
Unknown	2.9	3.3	1.3				2.0	2.5	1.9						
Charlson comorbidity index‡				0.03	0.37	0.52				0.01	0.02	0.80			
CCI = 2	63.9	61.2	57.5				4.6	4.1	4.3						
CCI >= 3	36.1	38.8	42.5				2.6	2.7	2.8						
Fracture-related Comorbidities		1	1		1										
Diabetes	100.0	100.0	100.0	NA	NA	NA	0.0	0.0	0.0	NA	NA	NA			
Osteoporosis	5.4	6.0	5.3	0.90	0.69	0.77	5.0	4.4	3.9	0.01	0.37	0.42			
Malnutrition	0.0	1.1	0.8	0.05	0.71	0.02	2 0.1	0.2	0.2	0.18	0.62	0.62			
Anemia	15.5	16.4	18.5	0.17	0.51	0.77	5.4	7.3	6.0	0.28	0.09	0.02			
Smoking	0.0	0.6	0.3	0.26	0.56	0.11	0.2	0.3	0.4	0.37	0.87	0.63			
Excessive alcohol drinking	0.8	0.0	0.9	0.84	0.19	0.21	0.8	0.4	0.8	0.80	0.11	0.17			
Received chemotherapy	4.2	3.3	3.2	0.39	0.98	0.60) 2.0	3.0	2.0	0.90	0.03	0.06			
Received steroid	22.1	24.0	22.0	0.95	0.55	0.60) 18.5	5 21.1	18.1	0.69	0.01	0.05			
Received NSAIDs	27.6	27.3	23.7	0.13	0.31	0.95	5 27.4	25.6	23.0	<0.01	0.05	0.23			
OADs and insulin use				0.03	0.57	0.03	}								
Neither	40.7	51.4	47.2												
Insulin only	15.7	10.4	10.8												
OADs only	30.9	23.5	28.4												
Both insulin and OADs	12.7	14.8	13.6												

Table 1: Demographics and comorbidities for the different treatment cohorts among diabetic and non-diabetic patients.

*Acronyms for Insurance Plan Types include: Exclusive Provider Organization (EPO), Health Maintenance Organization (HMO), Point of Service (POS), Preferred Provider Organization (PPO) and Consumer-Directed Health Plan (CDHP)

Capitation pays a physician or group of physicians a set amount for each enrolled person assigned to them, per period of time, whether or not that person seeks care ‡The Charlson Comorbidity Index (CCI) predicts the ten-year mortality rate for individuals diagnosed with a range of co-morbid conditions. Each comorbid condition is assigned a score (1,2,3, or 6) relative to the mortality risk associated with the condition. Higher scores indicate a higher mortality risk. CCI =2 includes hemiplegia, paraplegia, moderate to severe renal disease, diabetes, diabetes with chronic complications, any malignancy, leukemia, lymphoma, cellulitis, and skin ulcers. CCI=3 includes moderate to severe liver disease, AIDS, and metastatic solid tumors

6.0% for the same treatment groups. Similarly, diabetic patients had a higher incidence of osteoporosis and steroid use when compared to non-diabetic patients, although the differences were to a lesser extent.

A comparison of OAD/insulin use for the different treatment groups among diabetic patients revealed that a significantly higher proportion of patients receiving EBGS used either OADs, insulin or both compared

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to the LIPUS (p=0.03) and No-stim (p=0.03) cohorts. However, there was no difference in OAD/insulin use between the LIPUS and No-stim cohorts (p=0.57).

Fracture characteristics and fracture-related treatments in the pre- and post-index periods were analyzed to assess the similarities in patient profiles between the different treatment cohorts (Table 2). Among the diabetic patients, tarsal and metatarsal fracture nonunions were the most prevalent fractures for all three treatment cohorts, although, the proportion of patients with these fractures was higher in the EBGS and LIPUS cohorts than in the No-stim cohort (EBGS vs. No-stim: 60.5% vs. 25.1%; LIPUS vs. No-stim: 52.5% vs. 25.1%). Statistical analysis revealed there was no difference in the distribution of fractures by location for the EBGS and LIPUS cohorts (p=0.13) among diabetic patients. Alternatively, the No-stim cohort had a significantly different distribution of fractures by location when compared to the EBGS and LIPUS cohorts (both p<0.01). Treatments received by diabetic patients in the pre-index period were similar for all treatment groups except for the application of a cast/splint and bone grafting. The EBGS and LIPUS cohorts were more likely to receive a cast/splint prior to fracture nonunion diagnosis than the No-stim cohort (EBGS vs. No-stim: 33.2% vs. 23.5%; LIPUS vs. No-stim: 36.6% vs. 23.5%; both p<0.01). Additionally, the LIPUS cohort was more likely to receive bone grafting prior to nonunion diagnosis than either the EBGS (LIPUS vs. EBGS: 4.9% vs. 1.0%, p<0.01) or the No-stim (LIPUS vs. No-stim: 4.9% vs. 1.8%, p=0.01) cohorts. The proportion of diabetic patients experiencing complications in the pre-index period was similar among the different treatment cohorts. Blood transfusions were the most common complication in the diabetic group during the pre-index period with an incidence of 4.8%, 5.5%, and 8.4% for EBGS, LIPUS, and No-stim, respectively. Interestingly, study analyses found that a significantly higher proportion of patients in the No-stim group had a blood transfusion than in the EBGS group (p=0.02).

During the post-index period, study outcomes revealed that diabetic patients treated with EBGS were less likely to receive invasive treatment than patients treated with either LIPUS or No-stim. For example, after nonunion diagnosis, a significantly lower proportion of diabetic patients in the EBGS cohort received bone grafting than patients treated with LIPUS (EBGS vs. LIPUS: 9.6% vs. 18.0%, p<0.01) or No-stim (EBGS vs. No-stim: 9.6% vs. 25.7%, p<0.01). Additionally, diabetic patients in the LIPUS cohort were also less likely to receive bone grafting than patients in the No-stim cohort in the post-index period (LIPUS vs. No-stim: 18.0% vs. 25.7%, p=0.03). A similar trend was observed among the different treatment groups receiving open reduction with internal fixation in the post-index period (EBGS vs. LIPUS: 7.5% vs. 16.4%, p<0.01; EBGS vs. No-stim: 7.5% vs. 24.8%, p<0.01; LIPUS vs. No-stim: 16.4% vs. 24.8%, p=0.02). The other documented non-stimulation fracture management interventions, which occurred after the index date, included cast/splint, application of external fixation device, closed reduction with and without internal fixation, open reduction with and without internal fixation, and arthroscopy.

Descriptively comparing the fracture characteristics between the diabetic and non-diabetic groups revealed that non-diabetic patients also had more tarsal and metatarsal nonunions (EBGS: 46.5%, LIPUS: 43.9%, and No-stim: 23.6%) than other nonunions. Interestingly, non-diabetic patients were less likely to experience a complication during the pre-index period than diabetic patients, especially with regard to septicemia/bacteremia, mechanical complications with an orthopedic device, infection/inflammatory reaction, and blood transfusion. For example, non-diabetic patients in the pre-index period had a lower incidence of blood transfusion: 2.0%, 4.8%, and 3.0% for EBGS, LIPUS, and No-stim, respectively, when compared to diabetic patients: 4.8%, 5.5%, and 8.4% for the same treatment groups. Despite the differences in observed complications, diabetic and non-diabetic patients received

			Diabet	tic		Non-diabetic						
					p-values					p-values		
	EBGS (N=479)	LIPUS (N=183)	No-stim (N=742)	EBGS vs. No- stim	LIPUS vs. No- stim	EBGS vs. LIPUS	EBGS (N=2951)	LIPUS (N=1251)	No-stim (N=6022)	EBGS vs. No- stim	LIPUS vs. No- stim	EBGS vs. LIPUS
Open fracture (%)	1.7	0.6	4.9	<0.01	0.01	0.26	2.9	2.0	4.4	<0.01	<0.01	0.10
Fracture location (%)				<0.01	<0.01	0.13				<0.01	<0.01	0.12
Clavicle	0.8	3.8	4.5				6.9	7.1	8.8			
Humerus	5.9	7.1	11.6				5.2	4.2	5.7			
Radius and ulna	5.4	7.1	7.8				6.2	6.7	10.5			
Carpal	2.1	1.6	5.5				8.5	8.3	15.8			
Metacarpal	0.4	0.6	1.6				1.5	0.6	2.2			
Phalanges of hand	0.4	0.0	3.4				0.9	0.9	5.6			
Neck of femur	1.3	1.1	5.3				1.0	0.9	2.9			
Other parts of femur	2.3	3.3	4.6				2.3	3.3	2.1			
Tibia and fibula	8.4	7.1	5.7				9.9	11.8	5.5			
Ankle	9.2	14.2	15.6				7.8	8.6	9.5			
Tarsal and metatarsal bones	60.5	52.5	25.1				46.5	43.9	23.6			
Phalanges of foot	1.7	0.0	4.7				2.3	2.6	3.8			
Other	1.6	1.7	4.8				0.9	1.4	4.0			
Fracture-related treatment	ts in the 9 m	onths befo	re the index	date (%)								
Cast/splint	33.2	36.6	23.5	<0.01	<0.01	0.41	32.1	30.1	24.4	<0.01	<0.01	0.20
Application of external fixation device	3.6	4.9	4.0	0.66	0.60	0.42	3.1	4.4	2.6	0.25	<0.01	0.03
Closed reduction without internal fixation	4.4	2.7	6.5	0.12	0.05	0.33	4.4	5.1	4.0	0.35	0.08	0.34

Table 2: Characteristics of the fractures and the fracture-related treatments in the different treatment cohorts for both diabetic and non-diabetic patients.

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Closed reduction with internal fixation	1.3	3.3	2.3	0.19	0.44	0.08	1.8	2.0	3.3	<0.01	0.02	0.60
Open reduction without internal fixation	10.7	10.9	12.8	0.26	0.49	0.92	12.5	10.2	8.2	<0.01	0.02	0.03
Open reduction with internal fixation	20.5	17.5	20.9	0.86	0.30	0.39	20.8	19.3	13.7	<0.01	<0.01	0.28
Bone graft	1.0	4.9	1.8	0.32	0.01	<0.01	2.5	2.4	1.5	<0.01	0.02	0.79
Arthroscopy	1.3	2.7	2.3	0.19	0.73	0.18	2.6	3.2	2.1	0.14	0.02	0.29
Complications during the 9	months b	efore the in	dex date (%)								
Injury to blood vessel of upper or lower limb	0.2	0.0	0.3	0.83	0.48	0.54	0.4	0.5	0.3	0.43	0.43	0.86
Injury to nerve of upper or lower limb	1.0	0.5	0.3	0.08	0.56	0.55	0.3	0.5	0.9	<0.01	0.15	0.39
Secondary and recurrent hemorrhage	0.0	0.0	0.0	NA	NA	NA	0.0	0.0	0.0	NA	NA	NA
Posttraumatic wound infection	0.6	0.5	0.8	0.72	0.71	0.91	0.3	0.4	0.3	0.96	0.71	0.76
Traumatic compartment syndrome	0.2	0.0	0.1	0.75	0.62	0.54	0.3	0.1	0.1	0.05	0.84	0.22
Septicemia/bacteremia	1.9	1.1	2.8	0.29	0.18	0.48	0.4	0.8	0.5	0.64	0.22	0.15
Mechanical complication of internal orthopedic device/ implant/graft	4.4	6.0	6.3	0.15	0.87	0.38	3.4	3.6	3.5	0.72	0.92	0.74
Infection and inflammatory reaction due to internal prosthetic device/implant/ graft	2.5	1.1	3.2	0.46	0.12	0.26	1.1	1.5	1.3	0.44	0.56	0.28
Blood transfusion	4.8	5.5	8.4	0.02	0.19	0.73	2.0	4.8	3.0	<0.01	<0.01	<0.01
Fracture-related treatments	s in the 12 i	nonths afte	er the index	date (%)	-		-				-	
Cast/splint	18.4	16.9	20.0	0.50	0.36	0.67	16.7	19.5	24.7	<0.01	<0.01	0.03
Application of external fixation device	2.3	1.6	3.1	0.40	0.28	0.60	1.3	1.4	2.1	<0.01	0.11	0.63
Closed reduction without internal fixation	1.3	2.2	1.2	0.95	0.32	0.38	1.4	1.4	1.3	0.81	0.86	0.99
Closed reduction with internal fixation	0.0	0.0	0.8	0.05	0.22	NA	0.1	0.2	0.3	0.11	0.66	0.45
Open reduction without internal fixation	4.0	4.9	12.7	<0.01	<0.01	0.59	6.3	6.9	15.8	<0.01	<0.01	0.47
Open reduction with internal fixation	7.5	16.4	24.8	<0.01	0.02	<0.01	11.1	13.5	24.2	<0.01	<0.01	0.02
Bone graft	9.6	18.0	25.7	<0.01	0.03	<0.01	17.3	22.9	32.5	<0.01	<0.01	<0.01
Arthroscopy	1.5	3.8	4.7	<0.01	0.60	0.06	3.4	3.7	5.7	<0.01	<0.01	0.64

similar fracture-related treatments before and after the index date to manage their fracture nonunions.

In order to evaluate the distribution of total and fracture-related healthcare costs for each treatment cohort, insurance claims for the cost of medication, and inpatient and outpatient services were analyzed for both diabetic and non-diabetic patients (Table 3). No significant differences in total or fracture-related healthcare costs were observed for the diabetic patients during the pre-index period for the different treatment cohorts. In the post-index period, however, the total healthcare costs for the diabetic patients were significantly lower (p<0.01) in the EBGS cohort (mean: \$31,277; median: \$18,273) when compared to the No-stim cohort (mean: \$50,256; median: \$23,712). Alternatively, the total healthcare costs in the post-index period were not significantly different between the EBGS and the LIPUS (mean: \$36,270; median: \$20,241) cohorts (p=0.14) or between the LIPUS and the No-stim cohorts (p=0.18) for the diabetic patients. Outpatient costs were the largest component of the total healthcare costs, but were not significantly different between the various treatments in the post-index period. Conversely, the cost of inpatient admissions was significantly lower for the EBGS group (mean: \$6,460, median: \$0) when compared to the LIPUS (mean: \$12,533, median: \$0, p=0.01) and the No-stim (mean: \$22,189, median: \$0, p<0.01) groups in the post-index period. These results suggest that the total healthcare savings associated with EBGS were due largely to differences in required inpatient care. An analysis of fracture-related costs in the post-index period for the diabetic patients found that EBGS (mean: \$8,104; median: \$4,068) was associated with significantly lower fracture-related costs when compared to LIPUS (mean: \$12,531; median: \$4,239) (p=0.01), although differences between No-stim and EBGS or LIPUS were not significant (p=0.49 and p=0.12, respectively).

In the non-diabetic patients, the observed differences in costs between the various treatment cohorts were not as substantial as those reported for the diabetic patients; however, statistically significant differences still existed. Overall, the total healthcare costs in the nondiabetic group (EBGS: mean: \$19,033, median: \$10,453; LIPUS: mean: \$21,370, median: \$11,434; No-stim: mean: \$21,119, median: \$11,400) were on average \$9,929 to \$29,137 lower than the total healthcare costs in the diabetic group (EBGS: mean: \$31,277; median: \$18,273; LIPUS: mean: \$36,270; median: \$20,241; No-stim: mean: \$50,256; median: \$23,712) in the post-index period. Interestingly, in the post-index

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	Diabetic												
				Trea	atment coh	nort	p-values						
	E	EBGS (N=4	79)	LIF	PUS (N=18	33)	No	o-stim (N=	742)		LIPUS	EBGS	
	Maan	(05)	Madian	Maan		Madian	Maan	(05)	Madian	EBGS vs.	vs. No-	VS.	
	Mean	(SE)	weatan	wear	(3E)	Median	wear	(3E)	Median	NO-SUM	Sum	LIPU5	
Costs in 9 months before index date (\$)	00.070	(4.007)	40.004	00.000	(4 750)	44.000	00.400	(0, 400)	44.000	0.57	0.77	0.00	
	26,872	(1,867)	13,684	26,638	(4,759)	14,283	33,198	(2,480)	14,286	0.57	0.77	0.86	
Cost of inpatient admissions	9,852	(1,368)	0	9,620	(2,123)	0	13,999	(1,529)	0	0.02	0.30	0.52	
Cost of outpatient services	13,493	(867)	7,820	14,182	(2,873)	8,321	16,009	(1,574)	7,535	0.39	0.39	0.81	
Cost of medications	3,528	(244)	1,770	2,836	(305)	1,372	3,191	(158)	1,736	0.30	0.44	0.14	
Fracture-related healthcare costs	8,625	(1,277)	1,133	6,827	(1,258)	1,170	12,153	(1,418)	1,238	1.00	0.73	0.78	
Cost of inpatient admissions	6,312	(1,223)	0	4,757	(1,234)	0	9,426	(1,368)	0	0.02	0.08	0.90	
Cost of outpatient services	2,313	(171)	1,000	2,070	(236)	990	2,726	(204)	884	0.11	0.59	0.54	
Costs in 12 months after index date (\$)													
Total healthcare costs	31,277	(1,915)	18,273	36,270	(3,628)	20,241	50,256	(3,276)	23,712	<0.01	0.18	0.14	
Cost of inpatient admissions	6,460	(792)	0	12,533	(2,447)	0	22,189	(1,932)	0	<0.01	<0.01	0.01	
Cost of outpatient services	19,984	(1,400)	11,947	19,688	(1,634)	12,851	23,644	(2,040)	13,116	0.74	0.28	0.21	
Cost of medications	4,834	(338)	2,987	4,049	(397)	2,358	4,423	(214)	2,606	0.26	0.48	0.14	
Fracture-related healthcare costs	8,104	(535)	4,068	12,531	(1,492)	4,239	17,689	(1,409)	6,103	0.49	0.12	0.01	
Cost of inpatient admissions	2,529	(460)	0	6,117	(1,355)	0	12,934	(1,352)	0	<0.01	<0.01	<0.01	
Cost of outpatient services	5,575	(255)	3,897	6,415	(449)	4,092	4,755	(317)	1,990	<0.01	<0.01	0.03	
		Non-diabetic											
				Trea	atment col	nort				p-values			
	E	BGS (N=2	951)	LIPUS (N=1251)			No-stim (N=6022)				LIPUS	EBGS	
										EBGS vs.	vs. No-	VS.	
	Mean	(SE)	Median	Mean	(SE)	Median	Mean	(SE)	Median	No- stim	stim	LIPUS	
Costs in 9 months before index date (\$)													
Total healthcare costs	15,106	(770)	7,157	18,388	(976)	7,797	14,286	(427)	4,920	<0.01	<0.01	0.09	
Cost of inpatient admissions	5,434	(709)	0	7,955	(807)	0	5,914	(341)	0	0.43	<0.01	<0.01	
Cost of outpatient services	8,441	(195)	5,045	9,147	(374)	5,308	7,192	(165)	3,664	<0.01	<0.01	0.52	
Cost of medications	1,231	(51)	198	1,286	(179)	180	1,180	(46)	110	<0.01	0.23	0.13	
Fracture-related healthcare costs	7,192	(713)	1,228	9,030	(824)	1,079	6,510	(313)	870	<0.01	<0.01	<0.01	
Cost of inpatient admissions	4,469	(699)	0	6,478	(773)	0	4,425	(297)	0	0.27	<0.01	0.01	
Cost of outpatient services	2,723	(86)	1,093	2,552	(167)	913	2,085	(53)	790	<0.01	<0.01	<0.01	
Costs in 12 months after index date (\$)													
Total healthcare costs	19,033	(621)	10,453	21,370	(912)	11,434	21,119	(456)	11,400	0.95	<0.01	<0.01	
Cost of inpatient admissions	4,468	(485)	0	5,648	(640)	0	7,580	(356)	0	<0.01	<0.01	<0.01	
Cost of outpatient services	12,785	(260)	8,436	13,838	(424)	9,223	11,911	(180)	8,151	<0.01	<0.01	<0.01	
Cost of medications	1,781	(76)	274	1,884	(230)	284	1,628	(63)	193	0.04	0.85	0.24	
Fracture-related healthcare costs	8,102	(248)	4,076	9,374	(356)	4,326	10,157	(274)	4,677	<0.01	<0.01	<0.01	
Cost of inpatient admissions	2,089	(209)	0	2,737	(296)	0	5,029	(261)	0	<0.01	<0.01	0.01	
Cost of outpatient services	6,013	(111)	4,032	6,638	(180)	4,152	5,129	(85)	3,051	<0.01	<0.01	<0.01	

Table 3: Healthcare costs before and after the index date among diabetic and non-diabetic patients with fracture nonunion in the different treatment cohorts* †.

*A non-parametric Wilcoxon test was used to compare the total and fracture-related costs between the various treatment cohorts as the distribution of costs associated with the different treatments was not normal

†All costs presented are in U.S. dollars and represent raw, unadjusted costs observed in the medical claims dataset

period the fracture-related costs among diabetic patients were similar to the fracture-related costs reported for the non-diabetic patients (diabetic: mean: \$8,104, median: \$4,068 vs. non-diabetic: mean: \$8,102, median: \$4,076) in the EBGS cohort. Alternatively, the fracture-related costs appeared to be lower for the non-diabetic patients when compared to the diabetic patients for the LIPUS (diabetic: mean: \$12,531, median: \$4,239 vs. non-diabetic: mean: \$9,374, median: \$4,326) and No-stim (diabetic: mean: \$17,689, median: \$6,103 vs. non-diabetic: mean: \$10,157, median: \$4,677) cohorts. These results suggest that EBGS may be effective in managing some of the additional costs typically associated with diabetic healing. Statistical analyses showed that the EBGS cohort had significantly lower total healthcare costs in the non-diabetic patients when compared to the LIPUS cohort (p<0.01), although the total healthcare costs were not significantly different between the EBGS and the No-stim cohorts (p=0.95). Interestingly, during the post-index period, the LIPUS cohort had significantly higher total healthcare costs when compared to the No-stim cohort (p<0.01) in the non-diabetic patients. Furthermore, fracture-related costs were the lowest in the EBGS cohort, followed by the LIPUS and then the No-stim cohorts (p<0.01 for all pair-wise comparisons) for the non-diabetic patients.

Predicted total and fracture-related healthcare costs were calculated based on the actual costs observed for the different treatment cohorts for both diabetic and non-diabetic patients while controlling for intercohort differences in fracture location, demographics, OAD/insulin use (diabetic patients only) and clinical characteristics. For the diabetic patients, study results revealed that the EBGS cohort was associated with significantly lower total healthcare costs when compared to the No-

stim cohort (marginal difference: -\$11,834, p<0.01) and significantly lower fracture-related costs when compared to both the LIPUS (marginal difference: -\$3,016, p=0.02) and the No-stim (marginal difference: -\$4,783, p<0.01) cohorts in the post-index period (Figure 1). Alternatively, when compared to the No-stim cohort, the LIPUS cohort was associated with significantly lower total healthcare costs (marginal difference: \$8,743, p=0.01) but similar fracture-related costs (marginal difference: -\$1,767, p=0.23). For the non-diabetic patients, the EBGS cohort had significantly lower total and fracture-related healthcare costs when compared to the No-stim (marginal difference: -\$1,537, p<0.01 and -\$839, p<0.01, respectively) and the LIPUS (marginal difference: -\$2,112, p<0.01 and -\$901, p=0.01, respectively) cohorts (Figure 2). Conversely, there was no significant difference in total (marginal difference: \$575, p=0.37) or fracture-related (marginal difference: \$62, p=0.86) costs between the LIPUS and the No-stim cohorts for the non-diabetic patients. Notably, a comparison between the diabetic and non-diabetic groups revealed that the cost benefit of EBGS compared to LIPUS and No-stim treatment was greater for diabetic patients suggesting that EBGS is particularly successful in managing the costs related to obtaining successful fracture repair in these high-risk patients.

Discussion

Diabetes is an epidemiological burden in the U.S. with its growing prevalence and known association with long-term healthcare complications. Research has shown that diabetic patients have reduced bone strength and vascularity issues that lead to an enhanced risk of delayed fracture healing and fracture nonunion [2,26-30]. With nonunion rates as high as 43% in diabetic patients [32] and the costs associated with the treatment of diabetes and nonunions rising, identifying cost-effective treatments to manage these conditions is important.





In this study, EBGS treatment resulted in fracture-related healthcare savings of approximately \$4,800 per diabetic patient when compared to No-stim treatment and approximately \$3,000 per diabetic patient when compared to LIPUS treatment suggesting that EBGS may result in lower healthcare costs in the management of difficult to heal patients. Furthermore, consistent with a previous cost-benefit study in a real-world patient population [25], EBGS also resulted in significantly higher fracture-related savings in non-diabetic patients as compared to LIPUS or No-stim treatment.

The higher fracture-related costs observed for diabetic patients compared to non-diabetic patients is most likely a result of the increased complications associated with diabetic healing that lead to a higher risk of nonunion [2,26-30]. For example, higher overall complication rates (71% vs. 35%) and significantly higher overall infection rates (71% vs. 19%, p<0.001) associated with pilon fractures were reported for diabetic patients as compared to non-diabetic patients [32]. Interestingly, the diabetic complication rates (<10%) observed in this database study were lower than the complication rates reported in the literature [38]. It is possible that the observed differences in complication rates is due to the use of administrative claims in this study where the identification of any complication is dependent on the specificity of the claim (for instance, the use of a diabetes-related code) and/or the completeness of the coding for the claim. Although diabetic patients were found to have higher fracture-related costs than non-diabetic patients, EBGS resulted in much higher cost savings for diabetic patients versus non-diabetic patients when compared to both LIPUS and No-stim treatment. These results suggest that EBGS may be effective in mitigating some of the complications associated with diabetic fracture healing.

It is possible that the observed cost differences between the diabetic and the non-diabetic groups in this study may be partially due to the age difference between these two groups. In this study, 56.9% of the diabetic patients were 55-64 years old and 29.5% were 45-54 years old. Alternatively, 27.6% of the non-diabetic patients were 55-64 years old and 29.5% were 45-54 years old. Due to the age discrepancy between the diabetic and the non-diabetic patients, a sensitivity analysis was conducted to determine if the differences in healthcare costs between the diabetic and the non-diabetic patients were due to differences in age or the presence of diabetes. Cost savings for the older non-diabetic patients (\geq 45 years old) were found to be higher than those reported for all non-diabetic patients suggesting that age may have an effect on required healthcare utilization to obtain successful fracture nonunion repair. However, the cost savings for the older non-diabetic group were still lower than the costs savings observed for the diabetic patients. Moreover, when a similar analysis was performed with the older diabetic patients (\geq 45 years old), the cost savings for the older diabetic patients were lower than the costs savings for the overall diabetic group suggesting that factors other than patient age may have a larger impact on the resultant cost savings. Most importantly, when accounting for demographic (including age) and clinical characteristics, the outcome for the study remained the same for both diabetic and non-diabetic patients: EBGS was associated with the lowest total and fracture-related healthcare costs.

Study Limitations

Limitations to this study include the inability to measure the severity of diabetes through the claims database. Alternatively, the use of OADs/ insulin was used as a surrogate measure for the severity of diabetes. The reported use of OADs/insulin in the diabetic patients was highest for the EBGS cohort and could suggest the severity of diabetes was greater for the EBGS cohort than for the LIPUS or No-stim cohorts. Similarly, fracture severity was also unable to be determined. Post initial fracture management data including wound-related complications served as an alternate indicator for fracture severity. The prevalence of these conditions was generally very low (<1%) and comparable between the different treatment cohorts.

Additionally, as there are no clinical endpoints to indicate fracture healing in claims data, the fracture-related inpatient stays and/or additional invasive procedures were assessed as surrogate endpoints to signify on-going fracture management. Although this study did not assess healing, previous clinical studies report successful fracture nonunion healing with EBGS in a wide range of patients [9-18,20,22-24], including those with diabetes [19,26-29]. Another limitation to claims data is that the location of the fracture nonunion is not always documented and the fracture related treatment is not always associated with a specific fracture location. Therefore, the analysis performed in this study was limited to patients with a single fracture. Notably, the identified study limitations apply to all treatment cohorts and consequently impart no bias toward a specific cohort that could impact the validity of the outcomes reported.

Conclusions

Given the growing prevalence of diabetes and the increased risk of impaired healing for diabetic patients, the costs associated with obtaining successful fracture repair will continue to be substantial for patients and payers alike. Thus, it is important to consider treatment options that may reduce those costs associated with obtaining fracture consolidation. This study confirmed the cost of care (both total and fracture-related) is higher in diabetic patients than in non-diabetic patients. More importantly, EBGS was shown to significantly reduce the costs associated with successful fracture nonunion repair in both diabetic and non-diabetic patients when compared to LIPUS or Nostim treatment. Overall, the cost benefit of EBGS was highest in diabetic patients. Therefore, EBGS should be strongly encouraged as a fracture management treatment, particularly in high risk patients including those with diabetes.

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