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The Impact of Patient Age on Foot and Ankle Arthrodesis Supplemented with Autograft or an Autograft Alternative (rhPDGF-BB/β-TCP)

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Background: A recent survey of orthopaedic surgeons asking about risk factors for nonunion following foot and ankle arthrodesis revealed that patient age is considered to be a relatively low risk factor, despite the potential for autologous graft quality to deteriorate with increasing age. The purpose of the current study was to evaluate the impact of patient age and graft type on fusion rates following hindfoot and ankle arthrodesis.

Methods: In this study, we analyzed data from a previously published clinical trial, comparing fusion success in 397 subjects who underwent hindfoot or ankle arthrodesis (597 joints) supplemented with either autograft or an osteoinductive autograft alternative, recombinant human platelet-derived growth factor-BB homodimer carried in beta-tricalcium phosphate (rhPDGF-BB/β-TCP). The odds of fusion success were compared among subjects older or younger than age thresholds of 55, 60, 65, 70, and 75 years. The odds of fusion success were also compared between autograft and rhPDGF-BB/β-TCP among subjects older than each age threshold.

Results: In the autograft group, the joints of subjects who were younger than the age thresholds of 60 and 65 years had >2 times the odds of successful fusion compared with those of older subjects. There was no significant difference in the odds of fusion success between the older and younger subjects at the age threshold of 55 years. In the rhPDGF-BB/β-TCP group, there was no significant difference in the odds of successful fusion between older and younger subjects at any age threshold. When the odds of fusion success were compared between the 2 graft materials in subjects who were older than each age threshold, rhPDGF-BB/β-TCP had approximately 2 times the odds of fusion success compared with autograft for all thresholds, except 55 years.

Conclusions: The presented evidence suggests that age is an identifiable and concerning risk factor for hindfoot and ankle arthrodesis nonunion, a finding in contrast to the wider perception in the surgeon community. Notably, patients ≥60 years of age had significantly lower odds of fusion success with the use of autograft. The data reveal that use of rhPDGF-BB/β-TCP as an alternative bone-healing adjunct may help mitigate the risk of nonunion when these procedures are performed in the elderly population.

Level of Evidence: Prognostic Level II. See Instructions for Authors for a complete description of levels of evidence.

Nonunion rates for hindfoot and ankle arthrodesis remain high, with some reported rates nearing 30% for patients undergoing primary triple arthrodesis[1]. A recent survey of 100 international foot and ankle surgeons revealed that smoking, lack of arthrodesis site stability, poor vascularity, and diabetes are perceived by surgeons to be risk factors most closely associated with nonunion[2]. A patient age of >60 years was perceived as a less important risk factor. While some patient factors, like diabetes[3] and smoking status[3,4], have been shown with reasonable evidence to be

Disclosure: The original trial was funded by Biomimetic Therapeutics (Franklin, Tennessee), which has since become a wholly owned subsidiary of Wright Medical Group N.V. (Memphis, Tennessee) and which is the manufacturer of the rhPDGF-BB/β-TCP evaluated in the study. Multiple authors are employees of Wright Medical Group N.V. On the **Disclosure of Potential Conflicts of Interest** forms, *which are provided with the online version of the article*, one or more of the authors checked "yes" to indicate that the author had a relevant financial relationship in the biomedical arena outside the submitted work (http://links.lww.com/JBJSOA/A221).

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associated with reduced union rates, most remain largely unstudied.

One such potential risk factor is patient age as it relates to the effectiveness of graft material. While surgeons in the aforementioned survey perceived patient age to be of lesser concern than other factors, it is nonetheless important to explore because bone-healing is highly dependent on mesenchymal stem cell (MSC) activity and the ability of MSCs to differentiate into osteoblasts. Recent research has shown that MSCs collected from older patients exhibit decreased osteogenic potential[5,6] and migration capacity[6-8]. This suggests that autograft, one of the most common grafting materials used during arthrodesis surgery, may not be as effective in older patients as in younger patients.

The objective of this study, therefore, was to determine whether autograft has the same effectiveness in younger and older patients who undergo hindfoot and ankle arthrodesis. The hypotheses were (1) the use of autograft would result in lower odds of fusion success in older subjects compared with younger subjects; (2) an osteoinductive autograft alternative, recombinant human platelet-derived growth factor-BB homodimer carried in beta-tricalcium phosphate (rhPDGF-BB/β-TCP), would have similar odds of fusion success in younger and older subjects; and (3) rhPDGF-BB/β-TCP would have higher odds of fusion success than autograft when used in older subjects.

Materials and Methods

Study Design, Setting, and Location

In this study, we used data from a previously published prospective, randomized controlled trial[9]. The trial was registered at ClinicalTrials.gov (NCT00583375).

Full details of the study design, including a patient disposition flowchart, are available in the previous article[9]. Briefly, the investigation was conducted across 37 centers in Canada and the United States. Subjects were eligible for inclusion if they were ≥18 years of age and had an arthritic condition in the hindfoot or ankle requiring arthrodesis. All subjects underwent arthrodesis using an open surgical technique with use of either supplemental autologous bone graft or an autograft alternative, rhPDGF-BB/β-TCP. Arthrodesis procedures involving the tibiotalar (ankle), subtalar, calcaneocuboid, and talonavicular joints were included; talonavicular, subtalar, and calcaneocuboid arthrodeses were performed as either single, double, or triple arthrodesis procedures.

Subjects were randomized to treatment at a 2:1 ratio of rhPDGF-BB/β-TCP to autograft. Subjects in the rhPDGF-BB/β-TCP group received an rhPDGF-BB/β-TCP bone-graft substitute. Subjects in the autograft group received autologous bone harvested from the proximal part of the tibia, the distal part of the tibia, the calcaneus, or the iliac crest, at the discretion of the individual surgeon. Surgical techniques were identical in the 2 groups except for the randomly assigned graft material. All subjects were non-weight-bearing for 6 weeks following surgery.

End Points

The primary end point for the current analysis was the odds of arthrodesis success, based on computed tomography (CT) analysis, at 24 weeks postoperatively. Arthrodesis success was defined as evidence of at least 50% osseous bridging as determined by an independent radiographic reviewer. The interrater reliability of these measurements was previously determined by having a second independent radiographic reviewer retrospectively rate the CT scans. In 87% of the cases, there was agreement on whether a joint satisfied the arthrodesis success criteria (i.e., evidence of at least 50% osseous bridging) between the assessments of the original radiologist and the second reviewer. This corresponded to a kappa statistic of 0.717, which is considered "substantial" strength of agreement[10].

Statistical Methods

Demographics and clinical factors for the 2 treatment groups were compared via the Fisher exact test, for categorical variables, and 2-sample t test, for continuous variables. Rates of fusion as evidenced on CT and estimates of odds ratios are presented. CT-fusion rates for subjects younger and older than 55, 60, 65, 70, and 75 years of age were compared based on a parametric test of 2 proportions. For these age thresholds, all joints in subjects at or older than the threshold were compared with all joints in subjects younger than the threshold. As an example, for the age threshold of 65 years, subjects 0 to 64 years of age would be considered younger than the threshold and subjects ≥65 years of age would be considered older than the threshold. To evaluate whether rhPDGF-BB/β-TCP would result in higher odds of fusion success than autograft when used in older subjects, odds ratios were estimated for joints in subjects at or older than each threshold age.

Results

A total of 597 joints underwent arthrodesis in 397 enrolled subjects. Demographics were similar between the 2 groups, with a mean subject age of 55.8 and 57.3 years in the rhPDGF-BB/β-TCP and autograft groups, respectively (Table I). There was a higher percentage of male subjects in the autograft group compared with the rhPDGF-BB/β-TCP group (57.7% versus 48.1%), but this did not reach significance ($p = 0.073$).

In the autograft group, joints in younger subjects had higher odds of fusion success than those in older subjects for each age threshold (Table II). This difference was significant at the age thresholds of 60 and 65 years, where joints in younger subjects were 2.24 and 2.74 times more likely, respectively, to have CT-confirmed evidence of fusion compared to those in older subjects. Similar but nonsignificant trends were seen at the age thresholds of 70 and 75 years. In the rhPDGF-BB/β-TCP group, joints in younger subjects had odds of fusion success similar to those in older subjects for each age threshold (Table III). There were no significant differences at any age threshold.

When the odds of fusion success were compared between the 2 graft materials for older subjects only, joints in the

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TABLE I Demographics by Group

	Overall	Autograft	rhPDGF-BB/β-TCP	P Value*
No. of subjects	397	137	260	
Sex *(no.)*				0.073
Male	204	79	125	
Female	193	58	135	
Age† *(yr)*	56.3 (20-86)	57.3 (20-82)	55.8 (20-86)	0.332
BMI†,‡ *(kg/m²)*	30.9 (19-45)	30.6 (19-45)	31.3 (20-44)	0.246
Diagnosis				0.201
Primary arthritis	143 (36.0%)	54 (39.4%)	89 (34.2%)	
Rheumatoid arthritis	25 (6.3%)	5 (3.7%)	20 (7.7%)	
Posttraumatic injury/deformity	192 (48.4%)	62 (45.3%)	130 (50.0%)	
Other	37 (9.3%)	16 (11.7%)	21 (8.1%)	
Risk factors				
Smoking history within last 5 yr	96 (24.2%)	32 (23.4%)	64 (24.6%)	0.807
Obesity (BMI ≥30 kg/m²)‡	181 (45.6%)	57 (41.6%)	124 (47.7%)	0.289
Previous revision surgery	92 (23.2%)	32 (23.4%)	60 (23.1%)	0.999
Diabetes history (type 1 or 2)	44 (11.1%)	18 (13.1%)	26 (10.0%)	0.401
Arthrodesis location				0.915
Ankle	152 (38.3%)	52 (38.0%)	100 (38.5%)	
Subtalar	104 (26.2%)	38 (27.7%)	66 (25.4%)	
Calcaneocuboid	3 (0.8%)	0 (0.0%)	3 (1.2%)	
Talonavicular	23 (5.8%)	9 (6.6%)	14 (5.4%)	
Double arthrodesis	30 (7.6%)	10 (7.3%)	20 (7.7%)	
Triple arthrodesis	85 (21.4%)	28 (20.4%)	57 (21.9%)	

*Fisher exact test for categorical variables; 2-sample t test for continuous variables. †The values are given as the mean, with the range in parentheses. ‡BMI = body mass index.

rhPDGF-BB/β-TCP group were approximately twice as likely to have evidence of fusion success as those in the autograft group for each age threshold, with the exception of the 55-year threshold (Table IV). The trends were similar for the 70 and 75-year thresholds, but the differences did not reach significance. This comparative analysis was also repeated for joints in subjects younger than 55 years, with joints in the autograft and rhPDGF-BB/β-TCP groups having fusion rates of 68.0% and 64.6%, respectively. This difference did not reach significance (p = 0.699).

Discussion

Nonunion following hindfoot and ankle arthrodesis is an important adverse event that carries substantial economic

TABLE II Odds of Fusion (≥50% Osseous Bridging on CT) at the Joint Level: Younger Vs. Older Subjects with Autograft

Age Threshold	Younger*	Older*	Odds Ratio	P Value
55 yr	51/75 (68.0%)	76/128 (59.4%)	1.45	0.106
60 yr	72/100 (72.0%)	55/103 (53.4%)	2.24	0.003†
65 yr	89/124 (71.8%)	38/79 (48.1%)	2.74	<0.001†
70 yr	108/167 (64.7%)	19/36 (52.8%)	1.64	0.096
75 yr	119/189 (63.0%)	8/14 (57.1%)	1.28	0.335

*The values are given as the number of joints with at least 50% osseous bridging/total number of joints from patients with ages either younger (Younger) or at least the age of the specified age threshold (Older), with the percentage in parentheses. †A p value of <0.05 indicates a significant difference.

TABLE III Odds of Fusion (≥50% Osseous Bridging on CT) at the Joint Level: Younger Vs. Older Subjects with rhPDGF-BB/β-TCP

Age Threshold	Younger*	Older*	Odds Ratio	P Value†
55 yr	102/158 (64.6%)	160/236 (67.8%)	0.87	0.747
60 yr	146/224 (65.2%)	116/170 (68.2%)	0.87	0.739
65 yr	185/276 (67.0%)	77/118 (65.3%)	1.08	0.367
70 yr	216/326 (66.3%)	46/68 (67.6%)	0.94	0.588
75 yr	240/364 (65.9%)	22/30 (73.3%)	0.7	0.809

*The values are given as the number of joints with at least 50% osseous bridging/total number of joints from patients with ages either younger (Younger) or at least the age of the specified age threshold (Older), with the percentage in parentheses. †No significant differences were found.

and personal consequences. A recent study evaluated patients with nonunion following ankle arthrodesis within the Canadian health-care system. The authors found that additional care related to nonunion represented a financial burden equivalent to 10 nights of an acute inpatient stay[11]. This did not account for loss of productivity for the patient or the impact on family dynamics associated with revision surgery and the subsequent recovery.

Nonunion rates in hindfoot and ankle arthrodesis have remained consistently high over the past 50 years despite the evolution of surgical techniques and internal-fixation hardware. Arthrodesis techniques are technically demanding and are normally attempted after the implementation of joint-preserving options. Typical considerations prior to arthrodesis include the general health of the patient, the technical experience of the surgeon, and the ability of the patient to comply with the needs of a long recovery.

An equally important consideration is the patient's bone quality and healing potential. This component of arthrodesis is more difficult to define, however, with limited published literature available to guide care teams. Bone quality has been defined as the sum of osseous characteristics that affect resistance against fracture[12]. The U.S. National Institutes of Health (NIH) defined bone strength as the integration of bone mineral density plus bone quality[13]. Increased bone density has been associated with improved clinical outcomes in orthopaedic surgery, as evidenced in spinal arthrodesis[14]. Furthermore, studies using cadaveric models have demonstrated an important role of bone density regarding implant fixation strength in the tibial plateau and the proximal part of the humerus[15,16].

There is also a need to further investigate the impact of patient age on bone-healing potential. This might be related to the quality of bone, the diminished activity of osteoprogenitor cells, or a combination of both. When a bone is injured, a key component of the healing cascade is the release of signals, such as PDGF, that attract MSCs to the injury site through chemotaxis. These MSCs then multiply and differentiate into osteoblasts or scavenger cells. Recent investigative work has shown that MSCs undergo functional decline with age, with the authors of 1 study specifically reporting that MSCs isolated from patients ≥60 years of age display impaired migration ability compared with those from younger patients[8]. This research supports the hypothesis that increased patient age, even as young as 60 years, may play a larger role in bone-healing potential than previously thought.

The data from the current study also appear to support this hypothesis, with subjects in the autograft group who were younger than the age threshold of 60 years having twice the odds of fusion success as those older than this threshold. While these data confirm that age can be an independent risk factor

TABLE IV Odds of Fusion (≥50% Osseous Bridging on CT) at the Joint Level with Either rhPDGF-BB/β-TCP or Autograft, Stratified by Subject Age Threshold

Age Threshold	rhPDGF-BB/β-TCP*	Autograft*	Odds Ratio	P Value
≥55 yr	160/236 (67.8%)	76/128 (59.4%)	1.44	0.056
≥60 yr	116/170 (68.2%)	55/103 (53.4%)	1.87	0.007†
≥65 yr	77/118 (65.3%)	38/79 (48.1%)	2.03	0.008†
≥70 yr	46/68 (67.6%)	19/36 (52.8%)	1.87	0.070
≥75 yr	22/30 (73.3%)	8/14 (57.1%)	2.06	0.148

*The values are given as the number of joints with at least 50% osseous bridging/total number of joints from patients with either rhPDGF-BB/β-TCP or autograft who were at least as old as the specified age threshold, with the percentage in parentheses. †A p value of <0.05 indicates a significant difference.

for hindfoot and ankle arthrodesis nonunion, it also contradicts the general impression of the foot and ankle surgical community. The previously mentioned survey of 100 international foot and ankle surgeons revealed that a patient age of >60 years was perceived as a less important risk factor in potential nonunion[2]. Our findings show that age is an important factor to consider.

In contrast, the odds of fusion success were similar for older and younger subjects when rhPDGF-BB/β-TCP was used as an alternative to autograft. Comparing the odds of fusion success between rhPDGF-BB/β-TCP and autograft in older subjects, joints in the rhPDGF-BB/β-TCP group had approximately twice the odds of a successful fusion result as those in the autograft group for each age threshold, except 55 years. These results suggest that the use of rhPDGF-BB/β-TCP may reduce some of the age-related healing variability and comorbidities associated with autologous bone. When comparing fusion rates of joints in subjects younger than the age threshold of 55 years, there was no significant difference between the 2 graft materials. This suggests that rhPDGF-BB/β-TCP and autograft may perform similarly well in joints in younger subjects.

The current data set has strength in methodology as a large, multicenter randomized controlled trial in which CT imaging was used to confirm arthrodesis success. However, there were limitations. The study was not originally designed for the ad hoc odds-ratio analysis performed in the current work, and thus this was an extrapolation of the data. This also resulted in lower numbers of joints for the older age thresholds (70 and 75 years), making it difficult to draw conclusions for these thresholds. For this reason, the conclusions of this manuscript focus on the age thresholds of 60 and 65 years. In addition, the use of CT imaging is a more critical and accurate assessment for success in arthrodesis, and thus comparing these data to historical research often incorporating radiographic assessment may lead to inaccuracies in comparative analysis. Defining nonunion as a binary outcome remains challenging, as union rate is a continuous variable. Subjects also had autograft harvested from multiple locations, which has been shown to result in different concentrations of hematopoietic marrow and osteoblastic progenitor cells[17,18]. This suggests that patients receiving calcaneal or tibial autograft could possibly have received graft with lower osteoinductive potential than that harvested from the iliac crest. Finally, longer follow-up is needed to determine whether the relationship between age, graft material, and fusion status holds beyond 24 weeks.

In conclusion, the presented evidence suggests that age is an identifiable and concerning risk factor for hindfoot or ankle arthrodesis nonunion, a finding in direct contrast to wider perception in the surgeon community. Notably, patients ≥60 years of age had significantly higher odds of nonunion when autograft was used as the grafting material. The data reveal that use of an osteoinductive bone-graft alternative to autograft as an adjunct may help mitigate the risk of nonunion when these procedures are performed in the elderly population.

In an era of cost containment, it is imperative that surgeons consider the risk factors for nonunion as part of their decision-making process. When a candidate for hindfoot or ankle arthrodesis exceeds 60 years of age, our data suggest that using an autograft alternative, such as rhPDGF-BB/β-TCP as demonstrated in this analysis, may dampen the negative impact on healing that comes with aging. This may have implications for more individualized patient management in the years ahead. ■

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