# Regeneration of the donor side after autogenous fibula transplantation in 53 patients

## Evaluation by dual X-ray absorptiometry

Dieter Bettin[1], Holger Böhm[4], Mark Clatworthy[2], David Zurakowski[3] and Thomas Marc Link[4]

Department of [1]Orthopedic Surgery and [4]Institute of Radiology, University of Münster, Germany, Departments of [2]Orthopedic Surgery and [3]Biostatistics, Brigham and Woman's Hospital, Harvard Medical School, Boston, Massachusetts.
Correspondence: Dieter Bettin, Department of Orthopedic Surgery, Marienkrankenhaus Aschendorf-Papenburg, Marienstr. 8, DE-26871 Aschendorf, Germany. bettin@uni-muenster.de
Submitted 01-08-05. Accepted 02-09-03

**ABSTRACT We determined the degree of fibular regeneration at the donor site, using radiographs and dual x-ray absorptiometry, in 53 patients who underwent autogenous nonvascularized fibular transplantation for tumor reconstruction in long bones (mean follow-up 15 (3–26) years). Logistic regression was used to determine whether gender, age at transplantation, time since transplantation, bone mineral density (BMD), and length of the graft were associated with fibular regeneration.**

**26 patients had spontaneous complete bone regeneration. Younger age at transplant was the only predictor of fibular regeneration. In predicting fibular regeneration, sensitivity was 96% and specificity 74%, using 15 years of age as a cut-off. In the long-term follow-up, we found only gradual changes in the BMD and the values ranged from 24% to 217%. We found no correlations of bone mineral density with age, gender, length of the graft, or time since transplantation.**

In many cases, an autogenous fibula graft is used to reconstruct large segmental bone defects of the extremities (Enneking et al. 1980, Shaffer et al. 1985, Enneking and Mindell 1991). Previous studies have focused on the outcome of the transplant (Shaffer et al. 1985). However, failure to regenerate the donor fibula may be clinically important because of knee or ankle instability (Ganel and Yaffe 1990). In 53 patients, we evaluated the amount of fibula regeneration and assessed variables that may be associated with regeneration.

## Patients and methods

We examined 53 patients (43 men) who underwent autogenous fibula transplantation as part of the reconstruction of a limb-sparing procedure for a bone tumor. Patients who had received intra- and postoperative chemotherapy, local radiation therapy, had osteoporosis or were on steroid medication were not included since these factors may affect bone mineral density (Burchardt 1983). The grafting was performed between January 1974 and March 1994 and the mean follow-up was 15 (3–26) years. The diagnoses were juvenile bone cysts (16), aneurysmal bone cysts (10), osteoid osteomas (7), fibrous dysplasia (5), giant cell tumor of bone (5), and miscellaneous bone tumors (10).

The mean age at transplantation was 16 (2–51) years. 32 patients were below and 21 patients above 15 years of age. The fibular segment was removed subperiosteally from the middle third and divided with an oscillating saw while being irrigated with Ringer's solution. The remaining proximal and distal fibula measured 5–10 cm and protected the proximal and distal tibiofibular joints. The average fibular graft was 12 (4–28) cm long. The donor and recipient sites were always in the same extremity. Patients were immobilized, on average, for 10

(0–36) weeks after surgery. Full weight bearing of the involved extremity was achieved at an average of 42 (9–208) weeks postoperatively.

All patients were recalled for a physical and radiographic examination. Bone mineral density at the location of the resected and contralateral fibula was determined by dual x-ray absorptiometry (Lunar DPX-L), expressed in terms of g/cm$^2$. Accuracy was determined by repeated measurements at the same location. The method was accurate within 2.5% in our study (data not shown). A minimum follow-up of 2 years was chosen to avoid changes in bone mineral density on the contralateral unharvested side related to additional weight-bearing, since the donor site was protected by partial or complete nonweightbearing after surgery. For reproducibility, the extremities were always placed in a frame, which held the lower leg at 25 degrees of inward rotation. In very young children, an additional fixation device was used for secure positioning (Faulkner et al. 1995). Anteroposterior and lateral radiographs of the lower leg were taken to show the length of the resected graft. In the operated children, we evaluated proportional growth of the remaining fibula. Therefore we scaled the measurement of the postoperative radiograph to the proportion of the follow-up control. This radiograph was used to determine the site of the DXA scan. If the gap was completely filled with newly formed bone, we determined the bone mineral density of the donor site and the corresponding region of the unaffected, contralateral fibula. The bone mineral density of the newly formed bone was expressed as a percentage of the corresponding part. Although the regenerated bone was not always homogeneous, we determined total bone mineral density. No analysis was done concerning the bone density profile in the newly formed bone. If no continuous osseous link between the fibula stumps was seen, it was classified as a pseudarthrosis. The capability for spontaneous repair was analyzed as regards the patient's age at the time of harvesting, the duration of time since resection, the size of the gap, and gender.

### Statistics

Age at transplantation and length of the graft were evaluated in patients who had or had not had fibular regeneration, using a two-sample Student t-test. The proportion of males and females in the groups were compared with Fisher's exact test. Stepwise multiple logistic regression was used to determine multivariate predictors of fibular regeneration (Hosmer and Lemeshow 1989). The Pearson product-moment correlation coefficient (r) was calculated to assess the relationship of age, bone mineral density and fibular gap in patients who regenerated. Sensitivity and specificity for predicting fibular regeneration were calculated, using standard formulas (Weinstein and Fineberg 1980), and the 95% confidence intervals determined by Pratt's method (Blythe 1986). The statistical analysis was done using the SAS software package (version 6.12, SAS Institute, Cary, NC). Two-tailed $p < 0.05$ was considered statistically significant. Power analysis showed that the sample size provided 90% power (alpha = 0.05, beta = 0.10) to detect a difference of 1 SD in age at transplant and length of the graft between patients with or without fibular regeneration (version 4.0, nQuery Advisor, Statistical Solutions, Boston, MA).

## Results

A continuous bridge of newly formed bone was found at the donor site in 26 of 53 patients. In all of them, the defect filled within 8–16 months. Radiographically, the bone density and structure of the regenerate differed from the contralateral fibula. Hypertrophic and hypodense areas were irregularly distributed (Figures 1 and 2). The bone mineral density of the regenerated fibula averaged 108 (24–217)%. In 14 patients, the bone mineral density of the newly formed bone was greater than that in the unaffected fibula. In 27 patients, we found incomplete ossification. Their bone regeneration was usually irregular, with an average bridging of 25 (0–85)% of the former defect. Patients with fibular regeneration were younger than those without it—i.e., mean 10 vs. 21 years ($p < 0.001$, unpaired Student t-test, Table). Multiple logistic regression confirmed that age at transplantation was the only predictor of fibular regeneration ($p < 0.001$). The lower limit of the 95% confidence interval showed that patients less than 15 years of age who underwent autogenous fibula transplantation as a limb-sparing procedure were 8 times more likely

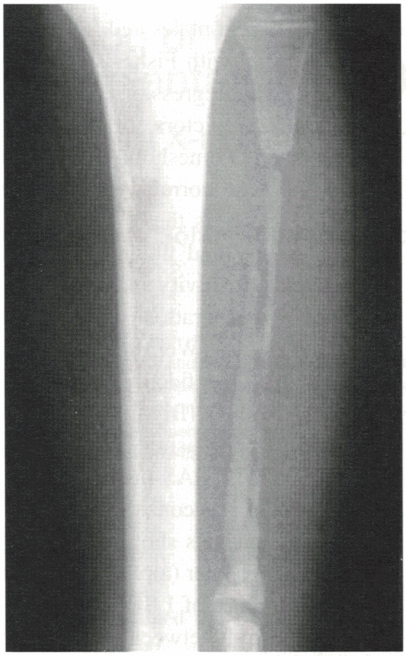

Figure 1. Fibula regenerate in a 7-year-old boy 2 months after fibula resection (10 cm) used for autogenous bone transplantation. Hypertrophic bone formation can be seen at the distal regeneration side with initial signs of early gap fusion.

Figure 2. The same patient 3 years after fibula resection. Complete regeneration of the resected fibula with cortical hypertrophy at the proximal regenerate and partial restoration of the medullary canal at the distal regenerate.

to have fibular regeneration than those 15 years of age or more. When using age as a predictor, a cut-off value of 15 years gave a sensitivity of 96% and a specificity of 74%. Thus, in our study, 25 of the 26 patients who had fibular regeneration were less than 15 years of age, and 20 of the 27 patients who had no fibular regeneration were 15 years of age or more. In extending this finding to the general population, the 95% confidence intervals for sensitivity and specificity were 80–100% and 58–90%, respectively.

A comparison of patients with or without fibular regeneration, showed no significant differences as regards to gender, time since grafting, size of the fibular gap, or bone mineral density (Table).

No major complications occurred after fibular resection. In 3 patients, slight pain was reported, depending on the amount of physical activity. No patient developed tibial stress fractures or infections. The superior tibiofibular joints were nearly always stabile and showed a full range of knee motion. Apart from that group, 3 patients had mild instability of the lateral collateral ligament of the knee, all of whom had an incomplete fibular regeneration. No dislocation of the superior tibiofibular joint was seen on the radiograph.

**Study population according to fibular regeneration**

| Variable | Fibular regeneration Yes (n = 26) | No (n = 27) | P-value |
|---|---|---|---|
| Age, years [a] | 9.8 (3.5) | 21 (12.3) | < 0.0001 |
| Gender | | | 0.5 |
| Male | 22 | 20 | |
| Female | 4 | 7 | |
| Length of graft, cm [a] | 11 (3.6) | 13 (4.6) | 0.3 |
| Years since grafting [a] | 16 (5.1) | 14 (5.5) | 0.3 |

[a] mean (SD)
Gender was compared by Fisher's exact test. Age at grafting and length of graft compared with the unpaired Student's t-test.

## Discussion

After an extensive review, we found only a few publications dealing with regeneration of a resected fibula (Edelman and Barbacci 1992, Vielpeau et al. 1993, Vandeweyer and Gebhart 1996). Most of the studies are case reports in young children. We found a physiological cut-off since spontaneous fibular repair had occurred only in patients whose age at the time of grafting was less than 15 years. This may be explained by the high osteogenic potential of the juvenile periosteum or sources of mesenchymal stem cells (Rockwood et al. 1991). In 7 of our 32 patients below this age who had no osseous bridging, damage to the periosteal tissue during the harvesting operation was probably responsible for the failure, because other possible factors were excluded by a strict patient selection. In accordance with other studies, we routinely found atrophy of the fibula stumps in the adult patients. In those showing no continuous osseous bridging of the fibular gap, no statistical relationship was found between their age and the time of grafting and the mineral density of the newly formed bone, although the reunion seemed to be age-dependent. In patients whose defect did not heal within 2 years, the defects never filled. Bone mineral density is caused by factors that affect the individual postoperative profile—e.g., differences in the patients' activity level or bone metabolism that may influence late bone remodeling which we did not evaluate in our study (Kannus et al. 1994).

According to the mechanisms of bone repair, the main process of initial fibular regeneration takes place within the first 2 postoperative years (Burchardt 1983). We found rapid healing in younger patients, with a complete repair in an 8-year-old patient after 8 months. This accords with the findings of other investigators, who described a complete fibular regeneration in a 1-year-old patient within 8 weeks. The physiological mechanism of epiphyseal bone growth may accelerate bone repair. Among the patients whose defect did not heal within 1.5–2 years in our study, it never filled in. 19 patients showed no regenerate after 10 years. To explain this observation, it may be hypothesized that the remodeling process can take place only after the defect has been bridged and the fibula has regained its physiological biomechanical function.

In our study, the density of the reformed fibula varied from 24% to 217%, as compared to the contralateral fibula. Bone density may be changed by extremely asymmetrical physical activity, immobility, or pain related inactivity (Dalén et al. 1985, Del Puente et al. 1996). In such cases of immobilization the density varied between 10% and 56% (Donaldson et al. 1970, Faulkner et al. 1995), but only a few of our patients complained of pain and none are immobilized. Surprisingly, side-to-side differences have persisted for over 10 years since surgery. By this time, the bone structure and, hence, the bone mineral density of the fibular regenerate should, according to Wolff's law, be similar to its counterpart (Enneking et al. 1980, Burchardt 1983). In addition, for patients with a complete fibular regeneration, the remodeling processes seem not to be complete. This hypothesis is uncertain and needs to be verified in micromorphological studies. A prospective controlled study design would be needed to detect time-dependent processes of bone remodeling (Burchardt 1983).

To quantify the fibular regeneration in our study, we chose the method of dual x-ray absorptiometry to measure bone mineral density. Among the advantages of this method, artifacts near the metallic implants are rare, radiation levels are low, and regenerated and contralateral fibulas can be compared (Hansen et al. 1990). Of the numerous studies on the relationship between mineral density in bone and the incidence of fractures, most have been done using osteoporosis analysis to predict the risk of fracture of vertebrae; no comparable data have been reported for the fibula (Casez et al. 1994, Jergas and Genant 1995). Dual x-ray absorptiometry alone can not measure internal changes taking place in the regenerated bone concerning the amount of new bone. In this respect, more invasive biopsy techniques for histomorphological analysis would be required.

No competing interests declared.

Blythe C R. Approximate binomial confidence limits. J Am Stat Assoc 1986; 81: 843-55.

Burchardt H. The biology of bone graft repair. Clin Orthop 1983; 174: 28-42.

Casez J P, Troendle A, Lippuner K, Jaeger P. Bone mineral density of distal tibia using dual-energy x-ray absorptiometry in normal women and in patients with vertebral osteoporosis or primary hyperparathyroidism. J Bone Min Res 1994; 12: 1851-7.

Dalén N, Lafman P, Ohlsen H, Ströberg L. Athletic activity and human diaphyseal bone. Orthopedics 1985; 8 (9): 1139-41.

Del Puente A, Pappone N, Mandes M G, Mantova D, Scarpa R, Oriente P. Determinants of bone mineral density in immobilization: a study on hemiplegic patients. Osteop Int 1996; 6 (1): 50-4.

Donaldson C L, Hulley S B, Vogel J M, Hattner R S, Bayers J H, Mcmillan D E. Effect of prolonged bed rest on bone mineralization. Metabolism 1970; 19: 1071-84.

Edelman R, Barbacci, D. Fibular regeneration. J Foot Surg 1992; 31 (49): 368-71.

Enneking W F, Mindell E R. Observations on massive retrieved human allografts. J Bone Joint Surg (Am) 1991; 73: 1123-42.

Enneking W F, Eady J L, Burchardt H. Autogenous cortical bone grafts in the reconstruction of segmental skeletal defects. J Bone Joint Surg (Am) 1980; 62: 1039-57.

Faulkner K G, Genant H K, McClung M. Bilateral comparison of femoral bone density and hip axis length from single and fanbeam DXA scans. Calcif Tissue Int 1995; 56: 26-31.

Ganel A, Yaffe B. Ankle instability of the donor site following removal of vascularized fibula bone graft. Ann Plast Surg 1990; 24: 7-9.

Hansen M A, Hassager C, Overgaard K, Marslew U, Riis B J, Christiansen C. Dual-energy X-ray absorptiometry: A precise method of measuring bone mineral density in the lumbar spine. J Nucl Med 1990; 31 (7): 1156-62.

Hosmer D W, Lemeshow S. Applied logistic regression. New York: John Wiley and Sons, 1989.

Jergas M, Genant H K. Quantitative bone mineral analysis. In: Diagnosis of bone and joint disorders (Ed. Resnick D). W.B. Saunders Co., Philadelphia 1995.

Kannus P, Haapasalo H, Sievänen H, Oja P, Vuori I. The site-specific effects of long-term unilateral activity on bone mineral density and content. Bone 1994; 15 (3): 279-84.

Rockwood C A, Wilkins K E, King R E. Fractures in children. Third Edition. J. B. Lippincott Company, Philadelphia 1991.

Shaffer J W, Field G A, Goldberg V M, Davy D T. The fate of vascularized and nonvascularized autografts. Clin Orthop 1985; 174: 87-95.

Vandeweyer E, Gebhart M. Complete fibular regeneration following removal of the fibula for bone grafting. Acta Chir Belg 1996; 96 (4): 182-4.

Vielpeau C, Mons P, Locker B, Bouamra K. Bone regeneration in the distal third of the fibula after resection of aneurysmal bone cyst using on original technique. Rev Chir Orthop Réparatrice Appar Mot 1993; 79 (7): 594-7.

Weinstein M C, Fineberg H V. Clinical decision analysis. W. B. Saunders Co., Philadelphia 1980.