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Collagen Fibril Populations in Human Anterior Cruciate Ligament Allografts

Electron Microscopic Analysis*

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ABSTRACT

We studied human anterior cruciate ligament allograft specimens by quantitative electron microscopy to analyze their collagen fibril populations. The specimens were procured at the time of second-look arthroscopy from the superficial region of the midzone of the anterior cruciate ligament grafts after synovial clearage. The grafts used for the anterior cruciate ligament reconstructions were from fresh-frozen allogenic Achilles, tibialis anterior or posterior, or peroneus longus or brevis tendons and had been implanted 3 to 96 months previously. By 12 months after surgery, the anterior cruciate ligament allografts consisted predominantly of small-diameter collagen fibrils (30 to 80 nm), which resulted in a unimodal pattern in the collagen fibril profile. The number of large-diameter fibrils (90 to 140 nm) within the allogenic tendon grafts had decreased. This predominance of small-diameter collagen fibrils persisted in almost all specimens older than 12 months. The anterior cruciate ligament allografts had collagen fibril profiles that did not resemble normal tendon grafts or normal anterior cruciate ligaments, even several years after surgery.

Anterior cruciate ligament reconstructions using allogenic tendon grafts have become increasingly popular because they provide satisfactory results without sacrificing normal tissues.[6,11] We previously reported an arthroscopic and histologic study of the remodeling process of allogenic tendons transplanted into the human knee as ACL substitutes.[12] This study showed that the arthroscopic macroappearance of the ACL allografts remained unchanged from 11 months postoperatively onward, and that the grafts reached histologic maturity within the first 18 months.[12] However, neither the size nor the density of collagen fibrils within the allogenic tendon graft were investigated. Little is known about the collagen remodelling process for allogenic tendons used as ACL grafts. The objective of this study was to observe the ACL graft remodeling process by quantification of collagen fibril population profiles as a function of time in patients who had undergone ACL reconstruction using fresh-frozen allogenic tendons.

MATERIALS AND METHODS

Forty-five patients (45 knees) who had undergone allograft ACL reconstruction from 3 to 96 months previously, and whose anterior stability had been adequately restored, were randomly selected. The restored stability of the involved knees was carefully confirmed by negative to trace-positive Lachman and pivot shift results. It was also confirmed with our apparatus to quantitate objectively knee instability. This apparatus was designed to perform an anterior-posterior (AP) drawer test by applying a gear-amplified manual force of 200 to 250 N to the proximal tibia with the knee flexed 20° to 30°. Simultaneously, AP displacement of the tibia with respect to the femur was measured with two linear variable differential transformers, one of which was set on the center of the patella and the other on the tibial tubercle. Tibial rotation coupled with AP translation of the tibia was not limited.[8] This made it possible to obtain the response curve for the AP force compared with AP displacement between the femur and the tibia. The parameter of anterior laxity, or anterior displacement of the proximal tibia at 200 N anterior force, was calculated

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from the curves of the bilateral knee, and side-to-side difference represented residual instability. Side-to-side difference in anterior laxity at 200 N force was less than 4.5 mm in all 14 patients who were examined 18 months or more after surgery (less than 1.0 mm side-to-side difference, 7 patients; 1.1 to 2.0 mm, 3 patients; 2.1 to 3.0 mm, 2 patients; 3.1 to 4.5 mm, 2 patients).[13] None of the patients experienced giving way of the knee postoperatively.

All 45 patients were subjected to second-look arthroscopy as a part of the procedure to remove hardware installed for graft fixation. This allowed us to procure a biopsy specimen from the superficial region of the ACL graft's midsubstance after careful synovial clearage. Two grafts could not be seen because of abundant scar tissue in the intercondylar notch. One other graft was regarded as a "failure" because of poor revascularization at 3 months after surgery. Therefore, only 42 of the 45 grafts were used for this study. The patients were 19 men and 23 women whose average age was 21 years, ranging from 15 to 37, at the time of reconstruction. The biopsy specimens were obtained at different periods from 3 to 96 months: 9 at 3 to 4 months; 5 at 6 to 7 months; 12 at 12 months; 7 at 13 to 24 months; 4 at 25 to 48 months; and 5 at 49 to 96 months.

Anterior cruciate ligament reconstruction technique

Fresh-frozen allografts, 8 to 10 mm in diameter, were used. Allografts were formed from the Achilles tendon, the anterior or posterior tibialis tendons, the peroneal longus or brevis tendons, or a few thick flexor tendons without any bone attached to their ends. The Achilles tendons were used for a third of the patients (14); tibialis anterior or posterior tendons for a third (14); and the peroneus or other tendons for the remaining third (14). The allografts were fixed into drill holes made at the anatomic ACL attachment sites on the femur and the tibia. They were fixed with 3 or 4, No. 2 braided polyester sutures and buttons (40 cases) or staples (2 cases). The procedure was accomplished by conventional medial parapatellar arthrotomy in the first 11 cases and by closed technique under arthroscopic control in the remaining 31 cases. All of the procedures were performed or strictly supervised by the primary author (KS). Postoperatively, the knees were immobilized for 2 to 33 days, full weightbearing was allowed at 5 to 12 weeks, jogging was recommended at 4 to 7 months, and full activity was allowed at 8 to 12 months.[11,15,16]

Biopsy procurement, processing for electron microscopy, and quantification

A 4-mm straight arthroscope was introduced into the joint under local or spinal anesthesia. After routine observation revealed that the ACL graft was taut and functional, the synovium was carefully cleared from the graft at the biopsy site and a 2-mm wide curette punch was introduced through the anteromedial portal to procure a cylindrical biopsy specimen (2 to 3 mm in length, 5 to 6 mm^3 in volume) from the graft's midsubstance.[12]

The specimens were fixed in 10% neutral formalin, embedded in Epon-Araldite (Agar Scientific, Essex, UK), cut at a 90° angle to the collagen fibril axis by ultramicrotomy, and stained with lead citrate and uranyl acetate for electron microscopy. Suitable areas on the grids were then photographed at a magnification of ×20,000. A calibration grid was always included to determine accurately the magnification at each sitting. The negatives were directly analyzed using an MD-20 Image Analyzer (Finders Imaging, Adelaide, Australia), and a constant inclusion grid area of 2.25 μm^2 was analyzed for each photomicrograph. At least two photomicrographs per biopsy were analyzed to quantitate the collagen fibril profiles. Analysis consisted of collagen fibril diameter measurement recorded as the number of fibrils with a diameter in a specific size range and the percentage of area covered by each fibril diameter group.

RESULTS

Biopsies of 3-month ACL allografts (N = 9)

The collagen fibril profile was barely bimodal. Although small-diameter fibrils (30 to 80 nm) were seen predominantly, there were a small number of large-diameter fibrils (90 to 140 nm), which accounted for this bimodal distribution (Fig. 1).

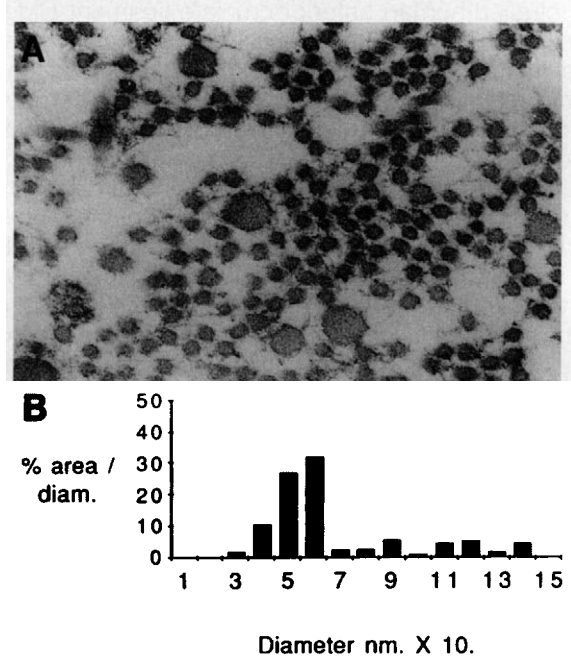

Figure 1. A, electron photomicrograph of a typical 3-month ACL allograft biopsy (×80,000). Note that small-diameter fibrils (30 to 80 nm) predominate, and that there are a small number of large-diameter fibrils (90 to 140 nm), which accounts for the bimodal distribution. B, histogram of the 3-month allograft showing the percentage cross-sectional area covered by collagen fibrils of various diameters. Note the collagen fibril profile is almost unimodal and the maximum cross-sectional area of fibrils is at 60 nm and that the small fibrils now occupy about 70% of the total cross-sectional area. Large-diameter fibrils now occupy approximately 20% of the total cross-sectional area of collagen.

Biopsies of 6-month ACL allografts (N = 5)

The collagen fibril profile was almost unimodal and the maximum number of fibrils was in the 60 nm diameter group. Large fibrils (maximum number in the 110 nm diameter group) appeared less frequently than in the 3-month specimens (Fig. 2).

Biopsies of 12-month ACL allografts (N = 12)

Most of the collagen fibrils were in the small-diameter groups (<80 nm), resulting in the unimodal pattern observed in the collagen fibril population profile. At this stage, there was almost complete absence of large-diameter fibrils (Fig. 3).

Biopsies of 13- to 96-month allografts (N = 16)

Collagen fibril profiles were equivalent to those seen in the 12-month allografts (Fig. 4).

These findings in collagen fibril profiles were very consistent regardless of the tissues used as ACL grafts. However, there were two exceptions to the above. One 12-month and one 59-month biopsy specimen had a significant number of large-diameter fibrils (approximately 125 nm), in contrast to the above-mentioned 12-month and older grafts. In these two specimens the large-diameter fibrils accounted for approximately 40% of the total cross-sectional area of collagen fibrils in the visual field (Fig. 5). However, the large-diameter collagen fibrils in these exceptional grafts were smaller and more irregular on their surface than those in the allografts before implantation (Figs. 6 and 7).

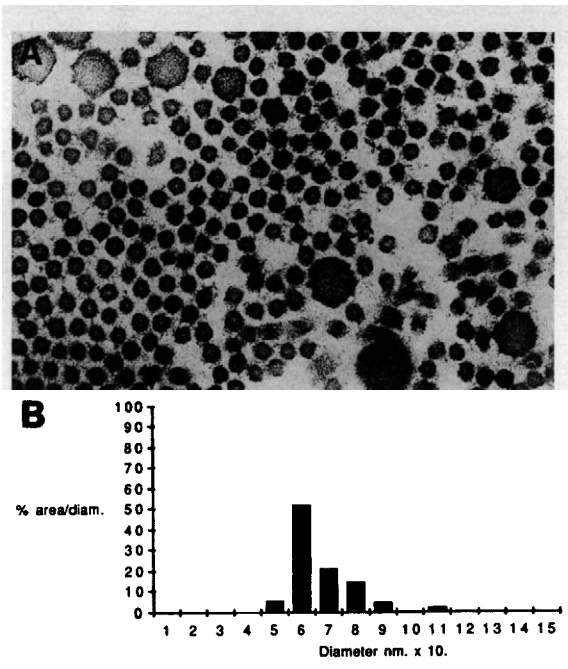

Figure 2. A, electron photomicrograph of a typical 6-month ACL allograft biopsy (×80,000). Note that small-diameter fibrils (30 to 80 nm) are seen predominantly. Also, there are still a small number of large-diameter fibrils (90 to 140 nm). B, histogram of the 6-month ACL allograft biopsy showing the percentage cross-sectional area covered by collagen fibrils of various diameters. Note the collagen fibril profile is almost unimodal and the maximum cross-sectional area of fibrils is seen at 60 nm diameter. Large fibrils of 90 nm and larger in diameter account for less than 10% of the total cross-sectional area (compare with Fig. 4B).

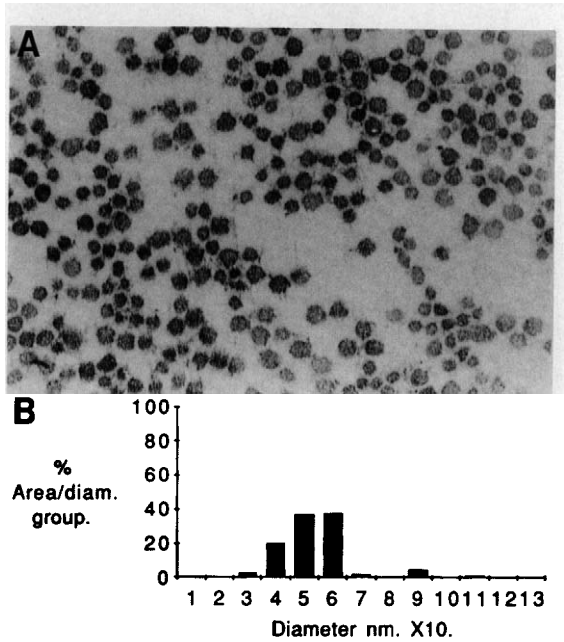

Figure 3. A, electron photomicrograph of a typical 12-month ACL allograft biopsy (×80,000). Note that small-diameter fibrils (30 to 80 nm) predominate. Also, there are very few large-diameter fibrils (90 to 140 nm). B, histogram of a typical 12-month ACL allograft biopsy showing the percentage cross-sectional area covered by collagen fibrils of various diameters. Most of the cross-sectional area is represented in the small-diameter collagen fibril groups (<80 nm), which results in a unimodal pattern in the collagen profile.

DISCUSSION

This is the first study that used quantitative collagen fibril population analysis to demonstrate both the collagen remodeling process within allogenic tendon transplants used as an ACL substitute in the human knee and the period during which this occurs. Most ACL graft biopsies, until 6 months after implantation, demonstrated a bimodal distribution of large- and small-diameter fibrils similar to the normal reconstituted tendons (Figs. 6 and 7). However, after 6 months the distribution consistently became more unimodal such that there was an increasing predominance of small-diameter fibrils (<80 nm) with a concomitant and progressive loss of the large-diameter fibrils, which are moderately well packed but not as "tight" as in the normal ACL or even the normal tendon from which these grafts originated. This predominance of small-diameter fibrils persists even several years after implantation. The older

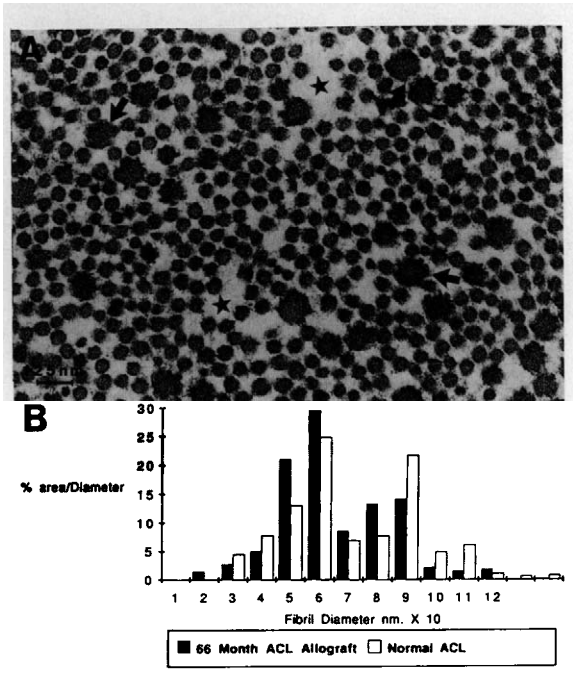

Figure 4. A, electron photomicrograph of a typical 66-month ACL allograft biopsy (×80,000). Note a predominance of small-diameter fibrils (30 to 80 nm). The largest fibrils (arrows) have an irregular surface and measure approximately 125 nm in diameter. Fibril packing is almost normal, but large spaces (★) among fibrils, which are not seen in the normal ACL, are present. B, histogram of the 66-month ACL allograft biopsy showing the percentage cross-sectional area covered by collagen fibrils of various diameters in comparison with that of the normal ACL. Note the different pattern from that of the normal ACL as most of the cross-sectional area is represented in the small-diameter collagen fibril groups (< 80 nm).

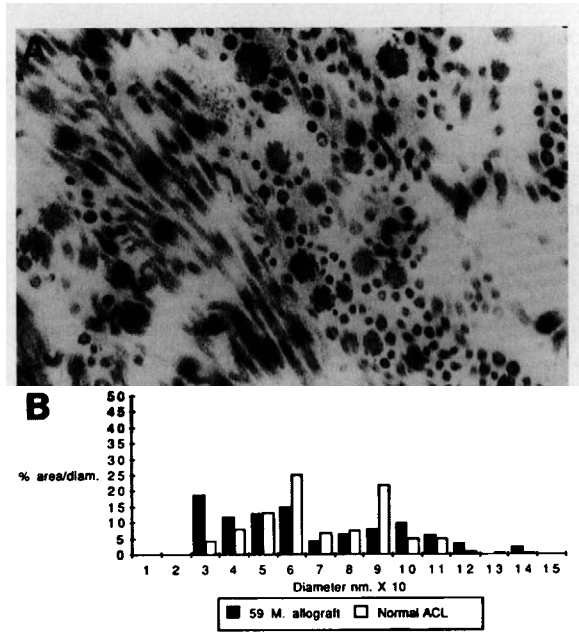

Figure 5. A, electron photomicrograph of an atypical ACL allograft biopsy older than 12 months (59 months, ×80,000) Note that the small-diameter fibrils (30 to 80 nm) predominate and that some large-diameter fibrils (90 to 140 nm) are still present. Also note that the large-diameter collagen fibrils in this exceptional graft are smaller and more irregular on their surface than those in the allografts before implantation. B histogram of the atypical ACL allograft biopsy showing the percentage cross-sectional area covered by collagen fibrils of various diameters in comparison with that of the normal ACL Note the similar pattern to that of the normal ACL with a significant number of large-diameter fibrils accounting for approximately 40% of the total cross-sectional area still present in this atypical graft.

biopsies we studied showed little increase in the number of large-diameter fibrils. These observations suggest that most of the original large-diameter fibrils in the ACL allografts are replaced by newly synthesized small-diameter collagen fibrils (or undergo disaggregation).

The loss of large-diameter collagen fibrils within 6 months after implantation or later has also been observed in human patellar tendon, goat ACL autografts, and posterior cruciate ligament autografts in a sheep model (O. W. Deacon et al., unpublished data, 1991; B. W. Oakes et al., unpublished data, 1991; Refs. 1, 3, 8). Since Parry et al.[9] reported that adult mature tendon or ligament has a bimodal distribution of collagen fibrils (Figs. 6 through 8), it has been assumed that these large-diameter fibrils in the normal tendon, representing a large percentage of the tendon collagen cross-sectional area, are probably responsible for the very high tensile strength of these tendons because of the high density of intermolecular collagen cross-links. This assumption has recently been confirmed with quantitative analyses by Shadwick,[10] who demonstrated a clear correlation between the presence of large-diameter collagen fibrils and the tensile strength of the developing swine flexor and extensor tendons in the extraarticular environment. The loss of large-diameter fibrils in the allografts 6 months or older, and their less tight packing of collagen fibrils as shown in this study, could be one potential explanation for the dramatic reduction of tensile strength of ACL allografts observed in previous experimental studies However, there is still little evidence that elaborately healed ACL grafts with small-diameter collagen fibrils are significantly weaker than the ligaments with both large- and small-diameter fibrils.[2,3,14,17,19]

Although orthopaedic surgeons have hoped that reconstructed ACLs mimic the original ACL in terms of microstructure, this study has shown that the grafts are totally different from the original ACLs in collagen fibril profile and density of collagen fibril packing. To ensure a stronger reconstructed ACL, therefore, a larger diameter graft may be necessary to increase the collagen mass and cross-sectional area. Walz et al.[18] observed a correlation between anterior-posterior laxity and graft cross-sectional area in ACL grafts from various species. Our recent clinical study has also revealed that the ACL allograft procedure in which a larger diameter graft had been used was significantly better than an autograft procedure in terms of restored anterior stability measured with instrumented testing.[1

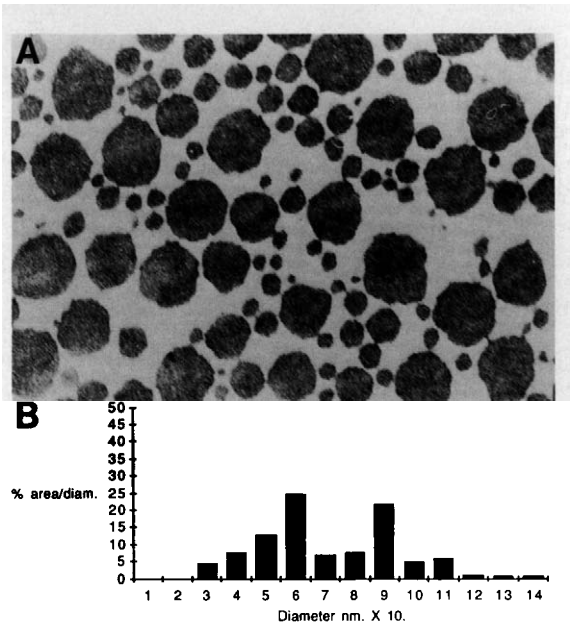

Figure 6. A, electron photomicrograph of a reconstituted fresh-frozen human Achilles tendon. Note that there are many large-diameter collagen fibrils (90 to 140 nm) as well as a small number of small-diameter fibrils (30 to 80 nm). Also note there is more space between the fibrils compared with a normal tendon (×80,000). B, histogram of the reconstituted fresh-frozen human Achilles tendon showing the percentage cross-sectional area of collagen fibrils of various diameters. Note the large-diameter collagen fibrils form a large proportion (approximately 40%) of the percentage cross-sectional area of collagen fibrils.

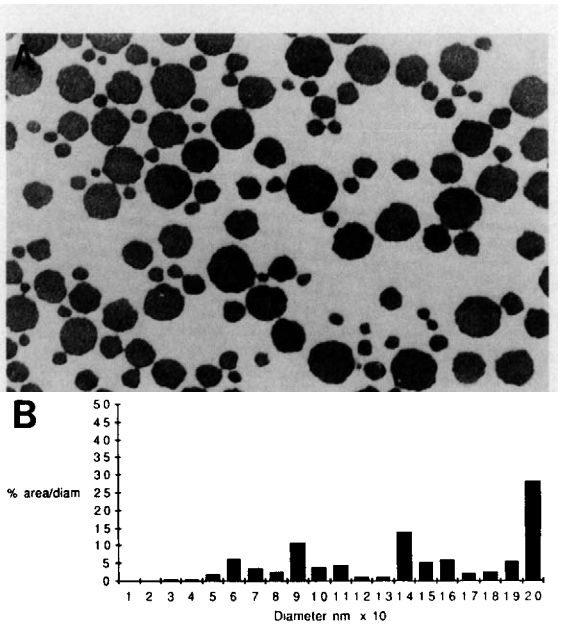

Figure 7. A, electron photomicrograph of a reconstituted fresh-frozen human tibialis anterior tendon. Note that there are more large-diameter fibrils and less small-diameter fibrils than those in the Achilles tendon (×80,000). B, histogram of the reconstituted tibialis anterior tendon showing the percentage cross-sectional area covered by collagen fibrils of various diameters. Note that large-diameter collagen fibrils form a larger proportion (approximately 80%) of the percentage cross-sectional area of collagen fibrils.

Therefore, the use of an allograft procedure may be more advantageous in terms of restoring anterior stability than the popular patellar tendon autograft in which a larger diameter graft cannot always be used, even though there is little evidence in humans that mechanical properties of the ACL allografts are equivalent to those of the autografts.[16] Unfortunately, previous experiments with ACL allografts have never proven this optimistic theory; the transplanted ACL grafts in animals' knees are probably subjected to excessive overload in the early postoperative phase leading to their stretching out.[3,9,14,17]

Two grafts in our study were atypical in that they contained significant numbers of large-diameter fibrils (approximately 125 nm). These fibrils were still smaller and more irregular on their surface than those seen in the allografts before implantation. The presence of these fibrils could be attributed to a delay in the remodelling process and degradation of the large-diameter fibrils of the allograft or to the transformation of small-diameter fibrils to large ones with graft maturation. The latter possibility is regarded as unlikely because there was no gradation of fibrils from the small-diameter to the large-diameter fibrils, which would be expected if small-diameter fibrils were undergoing normal appositional surface growth as is seen in the normal development of tendons or ligaments. The cross-sectional area of the allograft (approximately 9 mm in diameter) is usually much larger than a patellar tendon autograft from the central part of the patellar tendon (normally 10 mm in width) and this in itself may account for the possible delay in the remodelling process in these particular allografts.[7]

A criticism for this study could be that all of the biopsies were obtained from the superficial region of the grafts and that this may not represent the bulk of the collagen of the graft. Biopsies were obtained from the middle of the autografts in previous autograft studies (O. W. Deacon et al., unpublished data, 1991; Ref. 8). Because the remodeling process of canine ACL allografts was more pronounced in the superficial region than in the core region after implantation in our previous experiment, the superficial region from which the biopsies were taken in this study should represent the most advanced region of the graft in terms of the remodeling process toward maturation.[14] Considering that hypercellularity in human ACL allografts subsides by 18 months after implantation, differences in collagen fibril profiles between the superficial and core portions should disappear within 18 months as well because cellular responses in the superficial portion are activated by necrosis in the core.[12] Further studies are required to determine when the allograft as a whole reaches a plateau in terms of the graft remodeling.

It seems surprising that the various tendons used as ACL allografts were uniformly transformed into newly synthesized collagen fibrils of small diameter, regardless of the

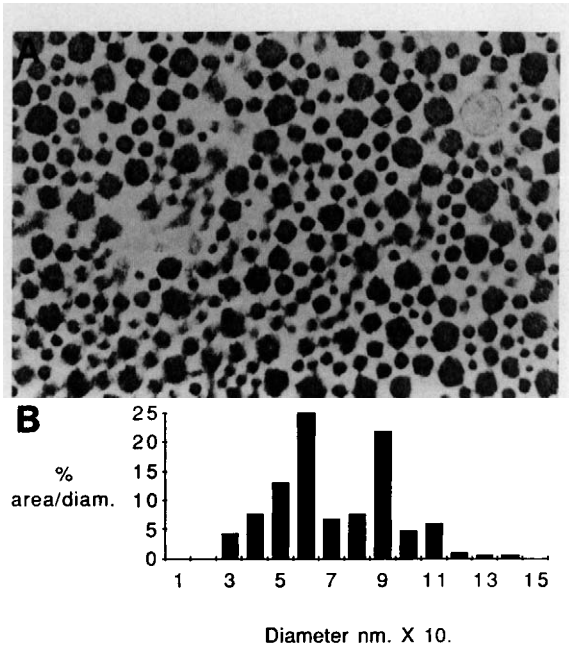

Figure 8. A, electron photomicrograph of a normal human ACL from a 17-year-old judo wrestler (×80,000). Note that there are many small-diameter fibrils and a significant number of relatively large-diameter fibrils (90 to 110 nm). B, histogram of the normal ACL showing the percentage cross-sectional area of collagen fibrils of various diameters. Note that small-diameter fibrils form a large proportion (approximately 70%) of the percentage cross-sectional area of the collagen fibrils in contrast to the reconstituted allograft tendons before implantation.

tissues transplanted. Therefore, it could be assumed that the original collagen fibril profiles of the allografts before implantation, which depend on the donor's age, sex, and activity level, as well as harvest site, have little effect on the final collagen fibril profiles of the reconstructed ACLs. This assumption could also be supported by the fact that the cells within the ACL allografts transplanted 3 to 4 months previously were identified at DNA level as those not from the donors but from the recipients.[5] From a clinical point of view, this means one safe (free from any kind of infections) donor could supply over 20 ACL allografts if surgeons do not stick to a single tissue such as the patellar or the Achilles tendon.

Finally, it should be mentioned that the discussions here are based on the assumption that large-diameter collagen fibrils of the allograft tendons do not undergo a process of disaggregation into small-diameter fibrils similar to that described in mature collagen fibrils after glycerol treatment, in which case the effect is reversible.[4] This is a possibility that must be seriously considered, but it is very difficult to verify experimentally without rigorous immunoelectronmicroscopy.

CONCLUSION

Six months after surgical implantation, the collagen remodeling process occurring within allogenic tendon grafts used for ACL reconstruction in the human knee joint reached a phase where the allografts contained predominantly small-diameter collagen fibrils (<80 nm). This closely parallels a previous study that also demonstrated the loss of large-diameter collagen fibrils of the patellar tendon within 6 months after use as ACL patellar tendon autografts.

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DISCUSSION

Peter A. Indelicato, MD, *Gainesville, Florida:* The results of this study clearly define some of the limitations that occurred in a normal biologic remodeling process. In other words, smaller diameter fibers replacing larger ones. I agree with the authors that this may explain the resulting biomechanical weaknesses seen in the reconstruction grafts in animal models. In both autogenous and allogenic tissue it appears that the fibrocytes that eventually inhabit the graft, for some unknown or yet to be defined reason, are "programmed" to produce a different type of collagen fiber with different cross linking characteristics. One could speculate that by manipulating the environment surrounding the graft during the early part of ligamentization, either mechanically or chemically, one could alter this evolutionary pattern, resulting in a more normal histologic occurrence. I encourage these authors to continue to pursue this approach to enhance the ultimate mechanical strength of the ACL reconstruction. I disagree, however, with the authors' suggestion of compensating for the resulting mechanical weakness currently experienced by increasing the initial diameter of the graft. My perception is that the volume of the intercondylar notch can only accommodate a certain diameter graft and that postoperative impingement or an overaggressive notchplasty are undesirable solutions to this dilemma.

Authors' Reply: We thank Dr. Indelicato for his thoughtful comments. We agree that a graft of too large a diameter can cause significant impingement against the intercondylar notch without an aggressive notchplasty. Considering the unfavorable remodeling process of biologic grafts inside the human knee joint as shown in this study, however, a graft with a slightly larger diameter than the normal ACL would be preferred with an adequate notchplasty to ensure better outcome or a stronger reconstructed ACL.