Mechanical load and primary guinea pig osteoarthrosis

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Hartley guinea pigs spontaneously develop knee osteoarthrosis. The reproducible course, the changes first appearing at the central medial condyle and then progressing peripherally and laterally, makes this animal a suitable model for intervention studies. We studied the effect of load, and randomized 9-month-old male animals into 4 groups: immediate killing, mid-femoral 30°-valgus osteotomy, sham operation or below-knee amputation. After 3 months, the proximal tibia was step-sectioned and examined stereologically by light microscopy. Local load-redistribution from the medial to the lateral condyle (osteotomy) reduced cartilage fibrillation by 22% medially and increased it 27% laterally. Subchondral bone thickness decreased by 36% in the medial condyle. In contrast, general load-redistribution (amputation) did not affect the progress of fibrillation, despite pronounced bone atrophy. Cartilage thickness, however, did not change; calcified cartilage thickness remained remarkably constant, and it was always higher on the lateral side. Therefore tidemark advancement does not appear to be an important mechanism in early guinea pig osteoarthrosis. Thus, when the natural course of guinea pig osteoarthrosis is interfered with surgically, in the early phase, changes in bone are more conspicuous than those in cartilage, which further indicates that mechanical load and stiffness gradients are important pathogenetic mechanisms.

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For ethical reasons, invasive studies of early human osteoarthrosis (OA) are not feasible. Therefore, various animal models have been designed. Many noxious agents can damage synovial joints, but load seems to be a common denominator and a necessary pathogenic factor (Radin et al. 1984). Most models concern a graded intraarticular injury that causes a rapidly progressing condition, resembling secondary OA more than the rather slowly evolving human primary OA. Other models use extraarticular approaches, changing the mechanical load in a more physiological range by osteotomy or repetitive impulsive loading (Table 1). Finally, there are naturally occurring slowly progressive non-inflammatory OA-like arthropathies in animals, e.g., in guinea pigs (Bendele and Hulman 1988).

Most OA studies have focused on cartilage changes (Goodman et al. 1991, Lovász et al. 1995) and few on bone (Radin et al. 1991). Wu et al. (1990) showed that subchondral bone changes were an integral part of OA, induced by malalignment (tibia osteotomy) in adult rabbits. However, primary rabbit OA is rare. Since osteotomy is used clinically to prevent/treat OA, we investigated whether extraarticular surgical load redistribution could affect the natural history of guinea pig OA.

Animals and methods

Thirty-three 9-month-old male Hartley guinea pigs (Møllegård, Copenhagen, Denmark) were randomized into 4 groups. Group 1 (n 7, body weight 1.1 (1.0–1.2) kg), killed immediately when 9-months-old, was used as a baseline; group 2 (n 10, 1.2 (1.2–1.4) kg) underwent a mid-femoral valgus osteotomy to induce a load shift from the medial to the lateral condyle, internally fixed with a 30° prebent stainless steel plate; group 3 (n 8, 1.3 (1.2–1.4) kg) underwent a unilateral tibia amputation through the proximal third of the diaphysis; and group 4 (n 8, 1.3 (1.2–1.5) kg) had a soft tissue sham operation at the mid-femoral level. More animals were allocated to the intervention groups because of expected larger variations and the risk of postoperative complications. The animals were anesthetized by intramuscular injections of atropine (0.1 mL/kg), diazepam (0.5 mL/kg) and fentanyl-fluanison (1 mL/kg). They were allowed free mo-

Table 1. Survey of mechanical extraarticular OA animal models

First author	Year	Species	Model	Main findings
Palmoski	1980	Dog	Immobilization	Causes disuse atrophy
Kiviranta	1987	Dog	Immobilization	Causes disuse atrophy
Behrens	1989	Dog	Immobilization	Motion has protective effect
Johnson	1988	Dog	Osteotomy	Induces OA
Reimann	1973	Rabbit	Osteotomy	Induces OA
Videman	1982	Rabbit	Exercise	No OA induction
Radin	1984	Rabbit	Repetitive impulsive load	Induces changes in bone before those in cartilage
Wu	1990	Rabbit	Osteotomy	Induces bone and cartilage OA
Lovász	1995	Rabbit	Osteotomy	Causes mild degenerative changes
Dekel	1978	Rabbit	Repetitive impulsive load	Induces bone and cartilage changes
Takasu	1992	Mouse [a]	Exercise	Accelerates OA
Bendele	1991	Guinea pig [a]	Body weight restriction	Reduces OA
Radin	1982	Sheep	Exercise	Induces bone and cartilage changes
Ghosh	1990	Sheep	Exercise	Induces osteophytosis and cartilage hyperplasia

[a] spontaneous OA.

bilization and kept in separate cages. Radiographs were taken immediately after surgery, as well as 4 and 12 weeks later. Two osteotomy animals died postoperatively, another one was killed because of failure to thrive. After the immediate postoperative period, the animals were allowed to move freely in their cages. Ground force distribution was measured with a 4" × 4" force distribution sensor (I-scan, Tehscan, Boston, MA, USA) pre- and postoperatively.

Groups 2–4 were killed with intraperitoneal injections of pentobarbital after 3 months at 12 months of age. The proximal tibia was dissected free, fixed in neutral-buffered 4% formalin for 72 h, decalcified for 5–7 days in 40% formic acid and then embedded in paraffin. With random start, excluding the cruciate ligament area, 11–13 histological sections were cut through each condyle with a constant interval of 250 mμ, and stained with hematoxylin and eosin. Macroscopic findings were defined as "cartilage destruction, subchondral bone eburnation and osteophyte formation". The 744 histological sections were coded and read blindly by a single observer, using a random stratified sampling technique (de Bri et al. 1995). The central (not meniscus-covered) compartment, comprising about one third of the joint surface, and the peripheral compartment (meniscus-covered) were recorded separately. Thus, volume fractions of epiphyseal bone, articular cartilage, cysts and osteophytes were measured by point and intersection counting (about 200 hits per item and condyle) with a projection light microscope at a final magnification of ×50 and ×125, using a multipurpose test system. The absolute volumes were calculated using Cavallieri's principle (Gundersen et al. 1988). Cysts were defined as cavities larger than 100 mμ, devoid of marrow cells; osteophytes as osteocartilaginous tissue extending beyond the original cortex; fibrillation as the ratio between the observed, rough surface and the smooth articular surface. Horizontal splitting at the tidemark—i.e., separation at the border between calcified and uncalcified cartilage—was measured by intersection counting, using a cycloid grid for vertical sections and expressed as percentages of the entire joint surface (de Bri et al. 1995). Thickness of the uncalcified/calcified articular cartilage and subchondral bone was measured at right angles to the joint surface. The thickness of subchondral bone was measured from the osteocartilaginous border to the first distal occurrence of non-osseous tissue. For statistical analysis, we used a Dunnet test for multiple comparisons at a rejection level of 5%.

Results

After wound healing, the osteotomy animals appeared to move unhindered, and the healing of osteotomies was confirmed radiographically (Figure 1). Hartley guinea pigs are naturally somewhat bowlegged, but we could not reproducibly measure the functional varus/valgus angle on video recordings or take standardized radiographs during loading. However, the ratio between pre- and postoperative force measurements showed that the osteotomy animals bore nearly equal loads on their hindlegs: mean 0.97 (SD 0.1) on the osteotomy side and 0.94 (0.1) on the contralateral side. The amputated animals were able to walk tripedally. Ground force measurements showed that these animals overloaded their remaining hind leg: 1.6 (0.5). None of the 12-month-old animals showed a restricted range of knee motion.

At 9 months, no gross OA changes were seen macroscopically or radiographically. Histologically, however, cartilage fibrillation had already developed in

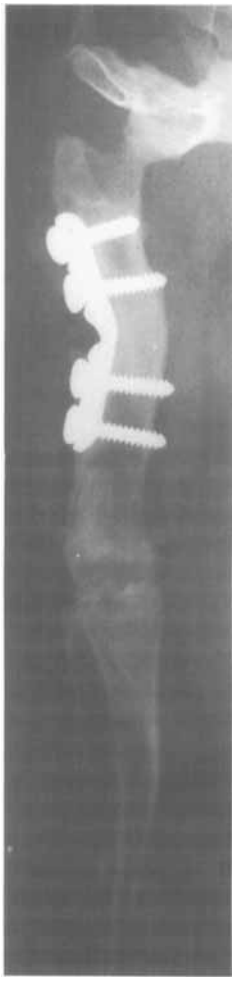


Figure 1. Radiograph of a guinea pig hind-limb 12 weeks after 30° mid-femoral valgus osteotomy.

Table 2. Mean (SD) absolute volumes of bone and cartilage of the entire proximal tibial epiphysis (mm^3). Entire epiphyseal volume defined as extending from cartilage surface to inactive physes, anteriorly and posteriorly by cortical bone

	Entire epiphyseal volume	Subchondral bone		Articular cartilage	
		Medial condyle	Lateral condyle	Medial condyle	Lateral condyle
9 month [a]	33 (2.8)	7.8 (0.5)	5.4 (0.5)	7.1 (0.7)	6.1 (0.7)
Sham	41 (2.9)	11 (1.1)	6.1 (0.5)	9.6 (1.5)	7.4 (0.6)
Osteotomy	41 (2.3)	8.7 (1.0) [b]	7.8 (1.3) [b]	8.3 (0.6) [b]	7.6 (1.0)
Amputation	34 (1.6) [b]	5.1 (1.1) [b]	4.6 (0.9) [b]	7.1 (0.7) [b]	7.1 (0.7)

[a] as a baseline.
[b] $p < 0.05$ compared with the sham-operated group.

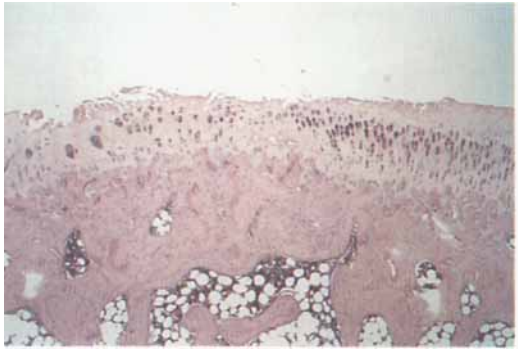
Table 3. Absolute volumes of cysts (central compartment) and osteophytes (peripheral compartment) in proximal tibial epiphysis (mm^3), mean (SD)

	Cysts		Osteophytes	
	Medial condyle	Lateral condyle	Medial condyle	Lateral condyle
9 month [a]	0.01 (0.01)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)
Sham	0.30 (0.25)	0.00 (0.00)	0.25 (0.01)	0.01 (0.02)
Osteotomy	0.03 (0.06) [b]	0.01 (0.02)	0.05 (0.11) [b]	0.00 (0.00)
Amputation	0.01 (0.01) [b]	0.00 (0.00)	0.07 (0.11) [b]	0.01 (0.01)

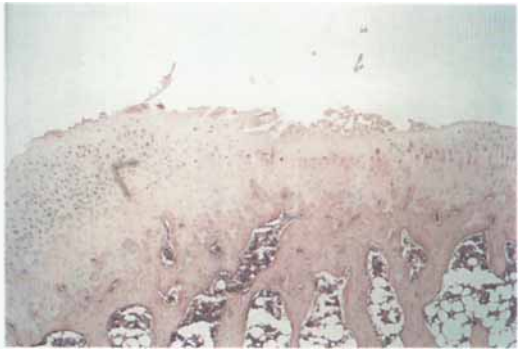
[a] as a baseline.
[b] $p < 0.05$ compared with the sham-operated group.

the part of the medial condyle not covered by meniscus. In the osteotomy group, the valgus malalignment caused a reduction in fibrillation medially and an increase laterally. Concomitantly, the thickness of the subchondral bone decreased medially and increased laterally (Tables 2–5, Figure 2). However, in the amputated animals, non-weight bearing induced obvious bone atrophy, which was more pronounced medially, but the development of fibrillation was not affected (Tables 2–5, Figure 3). At 12 months, the sham-operated animals had developed a rough articular surface and osteophytes on the medial side. Histologically, fibrillation, cartilage destruction, subchondral bone

Figure 2. Hematoxylin and eosin, ×47



Histological section from the proximal medial tibial condyle of an osteotomized guinea pig. OA changes were less pronounced than in the controls.



Laterally, however, OA changes had developed with cartilage fibrillation and subchondral bone sclerosis.

Table 4. Cartilage fibrillation of central compartment (ratio between the involved surface and smooth contour) and horizontal splitting of central compartment (%), mean (SD)

	Fibrillation		Horizontal splitting	
	Medial condyle	Lateral condyle	Medial condyle	Lateral condyle
9 month [a]	1.1 (0.1)	1.0 (0.0)	0.4 (0.6)	0.0 (0.0)
Sham	1.8 (0.2)	1.1 (0.0)	16 (7.0)	0.0 (0.0)
Osteotomy	1.4 (0.1) [b]	1.4 (0.2) [b]	7.1 (4.9) [b]	0.0 (0.0)
Amputation	1.5 (0.1)	1.1 (0.0)	10 (7.6)	0.0 (0.0)

[a] as a baseline.
[b] $p < 0.05$ compared with the sham-operated group.

Table 5. Thickness of cartilage and subchondral bone (mm). Mean (SD)

	Uncalcified cartilage		Calcified cartilage		Subchondral bone	
	Medial condyle	Lateral condyle	Medial condyle	Lateral condyle	Medial condyle	Lateral condyle
9 month [a]	0.24 (0.01)	0.19 (0.01)	0.09 (0.02)	0.13 (0.01)	0.43 (0.05)	0.31 (0.05)
Sham	0.27 (0.06)	0.23 (0.04)	0.10 (0.02)	0.16 (0.02)	0.49 (0.05)	0.30 (0.05)
Osteotomy	0.23 (0.04)	0.20 (0.04)	0.11 (0.03)	0.16 (0.02)	0.30 (0.03) [b]	0.31 (0.04)
Amputation	0.23 (0.03)	0.21 (0.03)	0.10 (0.02)	0.15 (0.02)	0.19 (0.04) [b]	0.18 (0.03) [b]

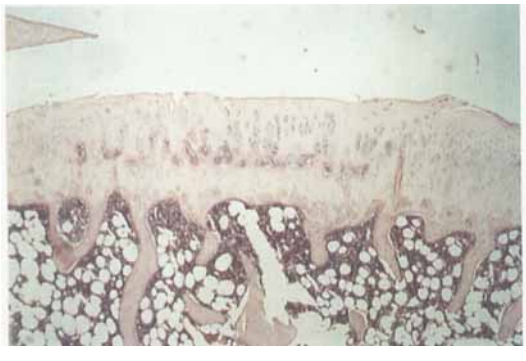
[a] as a baseline.
[b] $p < 0.05$ compared with the sham-operated group.

sclerosis and cysts were evident on the medial side, more severe centrally than peripherally. The lateral condyle was virtually unaffected (Figure 4).

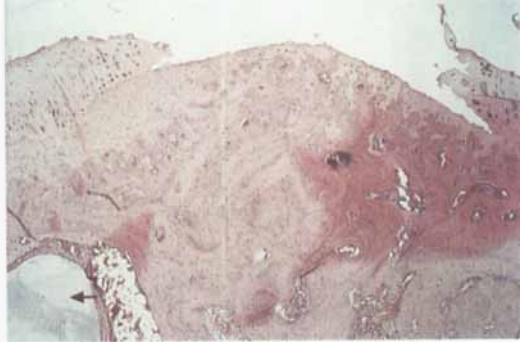
Discussion

The characteristic natural course of guinea pig OA—starting at the medial central compartment and progressing laterally and peripherally—may have a simple mechanical explanation, i.e., that load is the predominant pathogenic factor. Our main finding in this study—that one can change the natural history by surgically altering the load—supports this idea. In many species, load and wear mainly affect parts not covered by menisci (Seedholm et al. 1974), the medial compartment presumably taking up most of the load in the knee joint (Kettelkamp and Chao 1972), a likely oc-

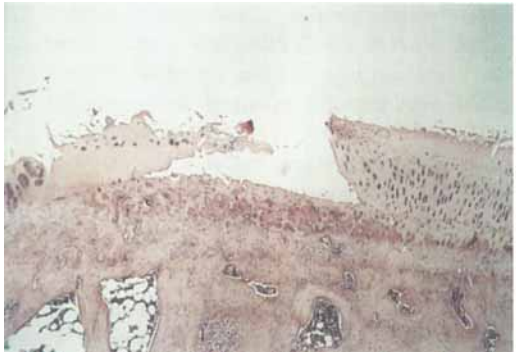
Figure 3. HE, ×47



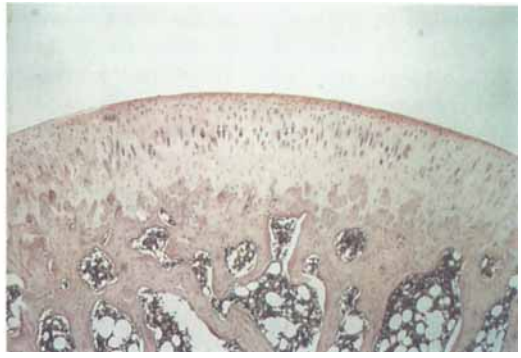
The proximal medial tibial condyle of a below-knee amputated guinea pig. OA changes were somewhat less severe than in the controls, but bone atrophy was the most striking finding.



The medial condyle of the non-amputated side showed cartilage destruction, subchondral bone sclerosis and cysts (arrows).



The proximal medial tibial condyle of a sham-operated guinea pig. Note the articular cartilage fibrillation and destruction in the central "non-meniscus-covered" compartment. Subchondral bone sclerosis occurred concomitantly with the cartilage changes.



The lateral condyle had no morphological signs of OA.

currence in the bow-legged guinea pig as well. Although we did not directly measure load, the consistent pattern of fibrillation and subchondral bone thickness in the lateral and medial condyles after osteotomy means that a substantial change in the load actually took place.

The fact that changes were apparent even in the 9-month-old animals and that it progressed in the amputated and the osteotomy animals also, shows that the disease process had started early. At 12 months, guinea pigs may be considered to be middle-aged, and although the animals were apparently not impaired, the pathological changes roughly correspond to those found clinically in patients with early symptomatic OA. In primary OA, in man as well as in guinea pigs, the natural course involves concomitant changes in bone/cartilage. However, in this experiment, when the load was altered during the early phases of OA, the bone change was more marked than those in cartilage, further showing the importance of stiffness gradients in the pathogenesis of OA (Radin et al. 1984, 1991). Wu et al. (1990) observed an increase in subchondral bone turnover within a few weeks of a rabbit tibia osteotomy.

In malalignment models, the closer to the joint the osteotomy is made and the larger the angle, the larger the load change (McKellop et al. 1991). Most workers have used 30° osteotomies, an angle that may seem to be excessive from a clinical point of view, but a substantial malalignment is obviously necessary to cause reproducible structural changes in a few months; still larger osteotomies probably induce unloading of the joint. Moreover, in rabbit malalignment models, transtibial osteotomy has generally been used; since it is distal to the joint, this means a change in the direct load on the knee. Guinea pigs, however, are smaller, and as the tibia is subcutaneous, its healing after plate fixation is precarious. In addition, surgical trauma near the metaphysis may affect the epiphyseal bone. We therefore performed a femoral osteotomy and placed it at the mid-diaphyseal level to minimize periarticular adhesions. This procedure probably causes less load change on the knee than a proximal tibia osteotomy does, particularly since the animals walk with their knees somewhat flexed, but the local and general bone changes observed indicate that the procedure actually changed the load. Similar results have been reported using a femoral osteotomy (Lovász et al. 1993). In a sham operation, we performed a soft tissue operation instead of an undisplaced osteotomy. Although the surgical trauma was less than in the intervention group, it seems very unlikely that a mid-diaphyseal bone lesion per se would appreciably affect the joint, particularly since the osteotomy group loaded their hind legs fairly equally postoperatively.

The lesions in malalignment models appear to differ from those caused by repetitive impulsive loading, where the extremity is subjected to numerous point loads which are within the physiologic range but presumably larger than the load changes caused by malalignment models. After repetitive impulsive loading, the first cartilage lesions occur in the deep and middle layers of the uncalcified cartilage but, as in malalignment models, bone changes occur simultaneously (Radin et al. 1984).

After amputation, the subchondral bone thickness became half that in the sham group and the bone also changed more medially than laterally. This may indicate that, before intervention, an ongoing mechanical stimulus was necessary to sustain the local bone stock and that it differed between the medial and lateral sides. The changes in cartilage thickness, being much

less conspicious, may mean that the avascular cartilage simply cannot react so rapidly as bone. Animal models (Table 1) and clinical studies (Burke et al. 1978, Lemaire and Fisher 1994) have previously shown structural effects of general load change.

Clinical fibrillation, although it may precede OA, is not always progressive (Freeman 1972). In guinea pigs, however, fibrillation is found mainly in the central medial condyle, a site that invariably develops advanced OA, including bone changes (de Bri et al. 1995).

Most morphological OA studies have used qualitative or semiquantitative methods (Mankin et al. 1971, Bendele and Hulman 1988). However, because of the large intra- and interanimal variations, single histological sections are not valid samples of an entire joint or of a disease process. Therefore, the structural heterogeneity in OA makes it rational to use stereological methods (Gundersen et al. 1988). One should remember, however, that stereologic data are averages and therefore may differ from qualitative scores which tend to emphasize the most severe changes in a specimen. However, isolated circumscribed lesions are rarely clinically important and statistical averages are therefore probably more relevant.

The importance of stress concentration at the tidemark in the pathogenesis of OA has been highlighted by the reportedly high clinical incidence of horizontal splitting in this area (Meachim and Bentley 1978). In our study, the decrease in horizontal splitting in the medial condyle was associated with a decreased load in the osteotomy group. Moreover, in a computer simulation, Anderson et al. (1993) described a model in which thickening of the calcified cartilage is balanced by thinning of the uncalcified layer. In man (Vignon et al. 1974) and in guinea pigs (de Bri et al. 1996), one finds a slowly progressive thickening of the calcified layer. However, during the present experiment, the amount of calcified cartilage remained remarkably constant and, since it did not change on intervention and was also always thicker on the lateral side, it seems unlikely that tidemark advancement is a prominent early pathogenetic factor in guinea pig OA, which develops more rapidly than its human counterpart. Rodents also differ from humans since they never completely close their physes, but longitudinal growth is small in adult animals (de Bri et al. 1995).

The volume of osteophytes and cysts in the medial condyles decreased in the amputated and osteotomized legs. These changes therefore seem to be related to load (de Bri et al. 1996), but not necessarily directly to OA.

Clinically, osteotomy is used to correct congenital and acquired deformities in order to improve function and prevent OA. In manifest knee OA, osteotomy also often relieves pain (Rudan and Simurda 1991, Odenbring et al. 1992). Previously, a study on transarthroscopic cartilage biopsies suggested that normalization occurred after proximal tibia osteotomy, although it was difficult to take samples (Bergenudd et al. 1992). In the present model, a surgically altered load caused more marked changes in bone than in cartilage. Such structural changes may contribute to the sometimes puzzling beneficial clinical effect of osteotomy in knee OA; but since surgery in these cases is performed closer to the joint, nonspecific effects triggered by fracture healing are perhaps also involved.

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