Nonunions. Surgery and low-intensity ultrasound treatment

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Introduction
Introduction

1.1 Bone biology

Bone is a living tissue and not some lifeless scaffold! This is one of the first facts the aspirant orthopedic surgeon learns. The remodeling capacity of living bone is tremendous. Bearing in mind the long cascade of processes needed for uneventful bone healing makes one marvel that bone healing so often goes well. If a delayed union or even nonunion develops, multiple co-acting causes have to be taken into account.

The unique quality of bone is that it has the tensile strength of cast iron and twice the energy absorption capacity of oak. Bone can remodel itself and adapt to physiological and pathological stimuli as a result of cellular activity. On the one hand, woven or primary bone is disorganized; it contains disorrientated collagen fibers and is hypercellular. The mechanical behavior of woven bone is similar no matter from what direction force is applied. Woven bone formation occurs rapidly in embryonic or fetal conditions and in adult bone at ligament and tendon insertions. Apart from embryonic bone in healthy conditions, woven bone is produced in pathological conditions such as bone injury (metabolic/traumatic) and as a result of dramatic changes in mechanical stimulation. Lamellar bone on the other hand behaves in the opposite way. It is highly organized and relatively hypocellular. The mechanical behavior of lamellar bone is orientated such that it is at its strongest parallel to the longitudinal axis. Lamellar bone is formed after birth and replaces woven bone. The diaphysial and metaphysial regions of the long bones and the small bones consist of a hyperdense outer shell, the cortex, surrounding the inner structure of cancellous bone. As in trabeculae the inner structure of lamellar bone is found around the struts in cancellous bone. In cortical bone the lamellar structure is mainly osteonic. An osteon is made up of small concentric lamellar cylinders, with osteocytes embedded (in lacunae and canaliculi), surrounding a central vascular channel, similar to the rings of a tree trunk. This structure of bone as just described maximizes both the stiffness and toughness of bone.

Bone consists of cells and the extracellular matrix. The extracellular matrix is composed of 35% organic material, and 65% inorganic material. The inorganic component is largely hydroxyapatite, which is a crystalline calcium phosphate mineral. The organic part of bone is made up of collagen and noncollagenous matrix. The protein collagen is organized in polypeptide chains, and a double helix of chains and molecules form the collagen fibrils. The collagen fibrils are grouped in bundles to produce the collagen fiber. The holes in between the fibrils are filled with proteins and mineral deposits, through which mineralization
Collagen Type I is the major structural protein component of bone, and provides its tensile strength. Although small in number, the biological impact of noncollagenous proteins is important. Noncollagenous proteins include osteocalcin, osteonectin, osteopontin, phosphoproteins, thrombospondin, and bone growth factors. Osteocalcin and osteonectin possess specific calcium binding properties and initiate hydroxyapatite crystal production during mineralization. The phosphoproteins are capable of binding to bone cells (osteoclasts) and of regulating bone resorption. Bone growth factors are low molecular weight glycoproteins. They play an important role in the differentiation of mesenchymal precursor cells into chondrocytes, osteoblasts, and osteoclasts. Bone growth factors can affect both the cells that produce them (autocrine) or other cells (paracrine).

The osteoclasts compromise 1% of all bone cells and originate from hematopoietic stem space cells. The osteoclasts' function is to resorb bone. The osteoblasts (5% of bone cells) produce bone. They originate from mesenchymal progenitor cells, similar to osteocytes and bone lining cells (94% of all bone cells). Bone lining cells line the bone surfaces, and osteocytes are situated inside the bone. The orchestrated co-operation of osteoblasts and osteoclasts forms a basic multicellular unit, through which bone modeling and remodeling takes place. Until relatively recently the function of the osteocytes has been unclear. Within the last decade, however, significant progress has been made in understanding how bone cells may sense and transduce mechanical signals derived from bone loading. These studies emphasize the role of osteocytes as the 'professional' mechanosensory cells of bone, and the lacuno-canalicular porosity as the structure that mediates mechano-sensing. Strain-derived flow of interstitial fluid through this porosity seems to be sensed by the osteocytes. The osteocytes are thereby informed about the mechanical adequacy of the surrounding tissue. Overuse as well as disuse produces abnormal canalicular flow, which is translated into bone forming or bone resorbing cell signals. This concept facilitates an explanation of local bone gain and loss during adaptation, as well as remodeling in response to fatigue damage as processes supervised by mechano-sensitive osteocytes. Burger et al. have postulated an attractive theory. According to Wolff's law, bone tissue adapts its mass and structure to the prevailing mechanical loads resulting from gravity and muscle function. The mechanical loads applied to bone causes flow of interstitial bone fluid in the lacunar canalicular porosity (not the Haversian or Volkmann channels, through which blood vessels run). The fluid flow (fluid shear stress) is sensed by the osteocyte, which communicates through the syncytium to the bone cells on the surface (bone lining cells, osteoblasts and osteoclasts). They in turn respond with bone resorption (osteoclasts) and/or deposition of bone (osteoblasts). In addition, another possible explanation for bone adaptation is the stress generated electrical potential, which causes streaming potentials, and which the
osteocytes might sense. The organism itself is largely dependant on hormones such as parathyroid hormone, vitamin D, calcitonin, and the glucocorticoids for bone mineral metabolism.

Bone growth factors play a significant role in fracture healing. These factors can stimulate cellular proliferation and the bone cell's biosynthetic activity. The transforming growth factor-β (TGF-β) superfamily of proteins, function in many tissues in the human body. Among them are bone morphogenetic protein (BMP) 2-6 and 7-9 (= osteogenic protein 1-3), which have osteoconductive properties. The recombinant human TGF-β1 incorporated in calcium phosphate cement, stimulates bone cell differentiation in vitro and osteotransductivity in animal bone defects. BMPs can induce ectopic bone formation.

1.2 Fracture healing

Fracture healing or regeneration is a complex process, the ultimate goal of which is to recreate a bone that can withstand normal mechanical loads. Unlike other tissues which form scars, bone is regenerated and the properties of the pre-existing bone are restored. Many of the cellular and biochemical actions that occur during fracture healing are similar to those that take place in the growth plate and endochondral ossification during bone development. Animal studies give us the opportunity to examine these processes in detail. The fracture healing response can be seen as four distinct responses that take place in the bone marrow, cortex, periosteum, and soft tissue (Figure 1). Within a few hours after fracture, there is loss of normal architecture of the bone marrow as well as a decline in the

Tissue differentiation during fracture healing

Figure 1. Histology of callus tissue, showing tissue differentiation during fracture healing. (Figure kindly donated by dr. M.C.M. van der Meulen, PhD, Cornell University, UK)
number of blood vessels and a reorganization of the cells of the bone marrow of high and low density. In high cellular density regions of the medullary callus endothelial cells are transformed into polymorphic mesenchymal cells. These cells differentiate into osteoblasts and start to form bone. These rapid, early processes occur independent of environmental circumstances, i.e. there is high tolerance of movement. Histologically, fracture healing is divided into primary, cortical bone healing, and secondary bone healing, which occurs in the periosteum and soft tissue. Primary bone healing (in which the cortices at both ends at the fracture site unite without external callus) can only take place if there is maximal stability, usually through rigid internal fixation. The response of the periosteum is the opposite. It is enhanced by motion and inhibited by rigid fixation. Secondary bone healing occurs through a combination of intramembranous and endochondral ossification. Secondary bone healing goes through distinctive stages. The first stage of the regenerative process is inflammation. The hematoma, which develops immediately after fracture, consists of a fibrin clot and platelets, polymorphonuclear neutrophils, monocytes, and macrophages. New blood vessels grow into this site and osteoblasts appear in the cambium layer of the fracture ends. The enzyme endothelial cell nitric oxide synthetase (ecNOS) mediates blood flow to the fracture site. This unique shear-stress activated enzyme produces effect in endothelial cells, and osteocytes.

The second stage of fracture healing is soft callus formation. Cartilage is formed in the peripheral region of the callus. Bone formation occurs closer to the bone ends. This phase is marked by an increase in vascularity at the fracture site. Stage three is when hard callus formation occurs. Woven bone is formed from cartilaginous tissue. Intramembranous ossification, in which bone is formed in the periosteal callus directly from mesenchymal cells, occurs simultaneously with endochondral ossification. Here the chondrocytes differentiate into bone producing cells. The fourth stage is the bone remodeling phase. During this stage, woven bone is converted in lamellar bone.

During fracture repair, four new bone formation processes occur: endochondral ossification, intramembranous ossification, appositional new bone formation, osteonal migration (creeping substitution). Dependent on many factors, one or more of these processes occurs during fracture repair.

1.3 Disturbed fracture healing
1.3.1 Definition of nonunions

The clinical definition of a delayed union of a fracture is dependent on its localization, but arbitrarily is normally between 3 and 6 months post fracture. The time span post-fracture of a nonunion is between 6 and 9 months. Nonunion is uncommon and is a serious and
debilitating condition. About 5-10% of all fractures have a delayed union and 1% end in a nonunion or pseudarthrosis. The definition of a nonunion is a failure of the bone to unite and all healing processes have stopped. Histologically there is fibrous and cartilaginous tissue between the ends of the fracture. Sometimes there is fluid in the gap, with the histological appearance of a pseudo-joint (synovial pseudarthrosis or neo-arthrosis).

1.3.2 Classification of nonunions

Nonunions or pseudarthroses are classified as hypertrophic, normotrophic/oligotrophic and atrophic. The radiological appearance of a hypertrophic nonunion is known as an 'elephant's foot' (Figure 2). Abundant callus is formed at the fracture ends. Normotrophic nonunion is characterized by some callus formation. Both normotrophic and hypertrophic nonunions are considered hypervascular. Conversely atrophic nonunion presents as sclerotic or necrotic bone ends without any callus formation. The distinction between viable and non-viable nonunions is made on the understanding that the hypertrophic and normotrophic forms are viable whereas atrophic is non-viable. Atrophic pseudarthroses are certainly not always non-vital. Bone activity can be measured by the uptake of radioactive strontium, calcium or technetium. This technique is called scintimetry or scintigraphy. Weber and Cech reported that on scintimetry most atrophic nonunion showed activity. Only the rare, longstanding cases of atrophic defect nonunion showed no activity.

Figure 2. Radiograph of a hypertrophic diaphyseal nonunion of the fibula one year after fibular osteotomy. The configuration of a so called 'elephant's foot' is seen.
1.3.3 Pathophysiology of nonunions

Classically, the three disturbances in primary bone healing that lead to the development of a nonunion are instability, devitalization of fragments and infection. Factors that further determine the disturbed healing of a fracture are biomechanical counteractive forces, loss of bone substance, bone tumor, and necrotic bone. The factors that predispose to a disturbed fracture healing can be divided in fracture (treatment) characteristics and patient characteristics.

Fracture and fracture treatment characteristics:

The shaft or diaphyseal fractures take more time to heal than extra-articular metaphyseal fractures. The occurrence of diaphyseal nonunions is more frequent in all long bones. Hypovascularity or hypoxia at the fracture site seems to be very important. The localization of the fracture in relation to the nurture blood vessel is important especially in humerus, scaphoid, femoral neck, tibia, and talus fractures. Fractures distal to the vessel have a higher risk of impaired bloodflow and delayed union. Recently enhanced dynamic magnetic resonance imaging (MRI) findings in scaphoid fractures however show that poor proximal pole vascularity is not an important factor in the development of a nonunion. High energy traumas are prone to delayed bone healing. Local conditions predisposing the development of a nonunion are extensive damage to the bone and surrounding tissues, leading to bone cell death and loose fragment formation. Theories include soft tissue damage, skin necrosis, interposition of soft tissue and vascular damage. Others have concluded that nonspiral fractures are prone to develop delayed union, however the soft tissue damage was not addressed to in this study. The blood flow pattern after fracture with blunt trauma differs from the pattern after osteotomy. This might have to do with more periosteal stripping caused by the blunt trauma resulting in a delayed blood flow. The presence of a compartment syndrome doubles the time to bony consolidation. Time to fasciotomy did not affect the delay in union. The importance of intact neural structures to bone healing has been established by animal studies. Damage to the proprioceptive neural structures leads to the development of an atrophic nonunion. The presence of nerve fibers in the periosteum after fracture may be the factor that induces angiogenesis.

Iatrogenic conditions contributing to delayed healing are soft tissue and periosteal damage and excessive debridement in a noninfected situation. The persistence of a fracture gap after treatment is a contributing factor for delayed healing. A diastasis of more than 2mm in internal fixation results in an inferior healing process. Furthermore, gross instability and torsion instability disturb normal bone healing. On the contrary, mild axial instability, promotes bone healing. Despite achieving better screw fixation in
the osteosynthesis of osteoporotic fractures by using bone cement, the toxic effect of polymethylacrylate and heat it produces during the hardening process contraindicates its standard use in fracture treatment.55

Patient characteristics:
Both the condition of the patient sustaining a fracture and the nature of the fracture are both important factors in the development of a nonunion. Women are reported to have a higher incidence of tibial nonunions.90 No comparative study on gender differences exists, but gender does not seem to play an important role in fracture healing. The effects of aging on bone healing have not been examined in detail. Scintimetric evaluation of a group of patients with a fracture of the femoral neck treated by osteosynthesis revealed a higher incidence of disvascularity and nonunion when compared to lower age groups.148,149 Older patients who have undergone a distraction osteogenesis using the Ilizarov method showed decreasing density of the newly formed bone.57 The age related decline of cellular response to growth factor, due to a decreased sensitivity, 6,102 might be one of the underlying mechanisms. The thinner periosteum and the lower cellularity of adults compared to children is another explanation for the slower rate of bone healing in adults.

Nutritional status is a well established factor in fracture healing. The metabolic requirements of a person sustaining a fracture are increased up to 55% in multiple injury cases.39,80 Electrolyte deficiency, calcium and phosphorus in particular, will lead to a delayed callus formation due to impaired mineralization. Protein deficiency due to catabolic reaction after fracture can lead to diminished callus strength.50 Concomitant diseases like Diabetes Mellitus (DM), anemia or hormone deficiencies have a negative influence on bone healing. Badly regulated insulin dependent DM delays fracture healing because of malnutrition, neuropathy or vascular problems. Insulin administration resulted in the reversal of mechanical defects in a DM animal model.56 It has been proposed that insulin works like a growth factor. Animal experiments on iron deficiency anemia and fracture healing showed impaired tensile strength of the callus and a 33% increase in the incidence of nonunion probably due to decreased oxygen tension at the fracture site.132 Deficiency of growth hormone and estrogen are associated with delayed union of fractures. Administration of growth hormone in the early phase of fracture healing evens out the negative effect.114,115 Osteoporosis predisposes bone to fracture easily after even minimal trauma, but normal bone healing is not hampered. All addictive drugs, the use of which may lead to malnutrition or anemia can, by the same token, lead to impaired bone healing. Chronic alcoholism with accompanying malnutrition, hematopoietic depression and polyneuropathy has a negative effect on fracture healing.112,91 Several studies have associated the addictive habit of tobacco smoking with impaired fracture healing.35,40,68,89,90 Vasoconstriction or decreased vascular
ingrowth,\textsuperscript{131} inhibition of cell proliferation and greater risk of low energy fracture due to decreased bone density\textsuperscript{125} are the causes of delayed union. An increased incidence of nonunion due to smoking in spinal fusion\textsuperscript{15,24,65} and ankle arthrodesis\textsuperscript{23} is reported. As well as causing osteoporosis, use of corticosteroids can result in an impaired fracture healing as their use may result in inhibition of osteoblast differentiation.\textsuperscript{38} The administration of anticoagulants (heparin and coumarin) to patients with fractures and in animal experiments\textsuperscript{166} has been observed to lead to delayed union. The proposed mechanisms are blood clot inhibition and/or the diminishing number and metabolic activity of calcifying cells. Some antibiotics, for example ciprofloxacin, one of the fluoroquinolones, delay bone healing in its early phases.\textsuperscript{76} In a retrospective study a marked association was found between non-steroidal anti-inflammatory drugs (NSAIDS) and delayed bone healing.\textsuperscript{61} Although the effect of NSAIDS on bone healing is not conclusive because of the retrospective study design, there are numerous data on the prostaglandin inhibitor effect of NSAIDS.\textsuperscript{1,110} NSAIDS prevent the prostaglandin E2 activating effect on bone formation.\textsuperscript{78} The condition of bone and soft tissue pre injury is important. Damage from previous surgery or trauma, irradiation,\textsuperscript{121} vascular diseases, pre-existing edema and pathological condition of the bone can all affect the normal bone healing.

### 1.3.4 Treatment of nonunions

Stability, a healthy microenvironment and an adequate blood supply\textsuperscript{78} are the principles of normal bone healing.\textsuperscript{154,166} Primary union of a fracture can be achieved by anatomical reduction of the viable fragments and stable osteosynthesis.\textsuperscript{161} If mechanical stability and good vascularity are present bone healing can occur, even in a case of infected pseudarthrosis.\textsuperscript{162,108} Secondary union of a fracture is achieved by intramedullary or external osteosynthesis. The treatment for a hypertrophic nonunion is a stable fixation in order to correct the insufficient mechanical precondition.\textsuperscript{161,123} This is the most important factor, which unfortunately is often not emphasized enough. Additional measures that may be taken are removal of devitalized fragments, decortication and drilling of sclerotic bone (Beck's procedure). All these procedures are aimed at improving vascularization.

#### Biomechanical principle

A special biomechanical solution for a femoral neck nonunion is a Pauwels intertrochanteric abduction osteotomy.\textsuperscript{120} Ununited femoral neck fracture in a series of 50 patients under 70 years of age was treated by intertrochanteric osteotomy.\textsuperscript{99} After a follow-up of mean 7 years, a prosthetic replacement was necessary in 7 patients for persistent nonunion or severe collapse of the femoral head. All other nonunions united in an average of 3.6 months (range 2 to 8 months). The outcome of the patients who underwent an intertrochanteric
osteotomy was good with a mean Harris hip score (HHS) of 91. Despite radiological signs of vascular disturbances of the femoral head in twenty-two patients, only three of them needed a prosthetic replacement. The others continued to function well with an average HHS of 85. The continuation report of this series is a consecutive series of 70 patients, all under the age of 70, with an ununited fracture of the femoral neck treated by Pauwels intertrochanteric abduction osteotomy. The average follow-up period was 12 years, range 1-20 years. The nonunion healed in 61 patients (87%). At the most recent check-up, 90% of the 61 patients were satisfied, with an average Harris hip score (HHS) of 91. A femoral head necrosis developed in 35 cases (57%). Twenty patients underwent a total hip arthroplasty (mean 8.5 years after osteotomy); the remaining 15 patients were functioning very well (HHS 79) after mean of 14 years. In total 41 of 70 patients (59%) had no further treatment after valgisation osteotomy and had a mean HHS of 79. Results of comparable series are the same. The low-risk, although technically demanding valgisation osteotomy should be the first step in the treatment of femoral neck nonunions, even in the presence of femoral head necrosis; secondary operations are not compromised. The ideal implant for the valgisation osteotomy is the AO 120° fixed angled blade plate. An alternative is the 95° condylar plate which can be bent to any desired angle, creating a similar shape to the 120° plate. The standard procedure is wedge resection in stages, allowing several osteotomy reductions using the seating chisel as a handle with which to check the clinical adduction possibility. After removal of the seating chisel, the blade of the 120° angled blade or adapted condylar blade plate is introduced. The osteotomy is reduced by closing the wedge and applying the plate to the femoral shaft with a clamp. This action leads automatically to compression of the osteotomy. Fixation of the plate to the femur using the asymmetric DC-holes for additional compression concludes the procedure (Figure 3).

Compression principle
As stated by Weber in 1976 the compression osteosynthesis, due to tension band effect of the plate in subtrochanteric nonunion is the treatment of choice. An incomplete wedge osteotomy additional plating, and autogenous bone graft are added if necessary. In 31 of 32 cases (97%) union was achieved in one or more operative treatments. Marti et al. have studied the operative treatment of subtrochanteric nonunion with a condylar blade plate using compression osteosynthesis. Their results are similar: 23 of 24 cases (96%) healed.
Figure 3.
Radiographs of the proximal femur before (A) and after (B) intertrochanteric corrective osteotomy for femoral neck nonunion.
Biological principle

Possible bone grafting materials are autogenous grafts, allografts, xenografts and alloplastic grafts: autogenous bone graft = fresh cancellous or corticospongy bone from the patient themselves
allograft bone = deep frozen donated human bone
xenografted bone = deproteinized, defatted bone from non-primates
alloplastic graft = synthetic materials serving as a scaffold.

The effect of bone substitutions can be classified in osteoconductive, osteoinductive and osteogenic properties. The osteoconductive effect is when the material acts as a scaffold for bone ingrowth from the host tissues. The material stimulating the host tissues to form bone is the osteoinductive effect. Finally, an osteogenic effect is when the material itself has the potential to form bone.

The best bone substitute is the autogenous bone graft. It contains all the properties of bone. However, the amount of bone available for grafting is limited and there is the risk of donor site morbidity. Allografts are freely available, but carry the risk of graft rejection and transmission of pathogenic organisms. Xenografts have excellent osteoconductive properties. Unless the xenograft is freeze-dried (lyophilized), there is an immunoresponse from the host, which can lead to rejection. Other osteoconductive biomaterials include: calcium sulfate, calcium phosphate ceramics, such as hydroxyapatite (HA) and tricalciumphosphate (TCP), and coral and bioactive glasses. Calcium sulfate (plaster of Paris) undergoes a chemical reaction and forms a variable crystalline structure. It resorbs rapidly. The rate of resorption of ceramics is dependent on the structure. Ceramics are brittle and not particularly resistant to compressive stress, so it should be applied only in metaphyseal and not in diaphyseal fractures or nonunions. In a prospective randomized trial the use of HA/TCP in operative scoliosis correction gives a similar result to an autogenous bone graft. Bio-active bone cement paste (Norian SRS) is used in calcaneus, proximal tibia and distal radius fractures. Distal radius fractures treated by reduction, cast and bone cement showed better results than reduction and cast alone. Coral (calcium carbonate) has excellent mechanical properties. There is high compressive strength, but it is brittle and has low tensile strength and a porous structure. Large defect cannot be bridged. In delayed fracture healing and nonunion a more osteoinductive material is needed. A collagen mineral composite graft consisting of bovine collagen, HA and bone marrow aspirate is comparable to autogenous bone graft in long bone fractures with a defect stabilized by internal or external fixation. No differences in time to union or functional outcome were found. One of the current strategies in the use of osteoinductive materials and growth factors is the use of a one single recombinant osteoinductive factor delivered in much higher doses than during normal fracture repair. The other strategy consists of naturally derived bone extracts.
with multiple osteoinductive factors and perhaps unintentionally undesirable factors. The fundamental question remains. Are the added osteoinductive factors necessary and can they initiate the complete cascade of bone induction process? Also a more staged release of factors in time or multiple dosages would perhaps be more appropriate. A lot of experimental work is being done on bone morphogenetic proteins and other growth factors. Their clinical use is promising, but further investigations are needed to determine if a single factor initiation of the cascade is possible or if multiple factors are needed. Further fine tuning of the delivery of rhBMP to the site where bone formation is needed might be possible through gene therapy. Ex vivo gene transfer in animal experiments is promising and human clinical application can be expected.

Bone marrow contains the osteogenic precursor cells, which can be used for osteogenic purposes in a graft together with an osteoconductive material. The osteogenic capacity is dependent of the capacity to select and expand the osteocompetent cells, bone marrow stromal fibroblasts. There are no clinical trials on this type of fracture treatment yet. A free vascularized fibular transplant and autografting is a challenging, difficult operative solution to the problem of nonunions in previously irradiated bone. The results are promising, and can in some cases prevent amputation.

There might be a single systemic factor that can induce bone. In patients with brain injury as well as a fracture, fractures tend to heal faster and produce more callus. Patients with a spinal cord lesion develop more heterotopic bone. No causal molecule has been identified yet. Perhaps prostaglandins are the agents.

A difference can be made in the stimulation of bone healing by the use of physical methods such as mechanical stimulation, electrical stimulation and low-intensity ultrasound stimulation. In the area of mechanical stimulation, Kenwright et al. showed that in response to dynamic loads, through adaptation, the bone optimizes its architecture. Electrical stimulation techniques including: implanted-electrodes, capacitive-coupled, non-invasive pulsed electromagnetic fields (PEMFs), and combined magnetic fields (CMF) change the negatively charged bone in nonunion. Many animal and human experiments have established the positive effect of electrical stimulation on bone healing. No randomized, placebo-controlled study on the effect of electricity on fresh fractures has yet been published. In the only trial for established nonunions using electrical stimulation without concomitant conservative or surgical treatment, in the placebo group (no electrical stimulation and no other treatment) healing rate was 0% (0/11) versus 60% (6/10) in the actively treated group (electrical stimulation and no other treatment). Comparison of electrostimulation and low intensity ultrasound in rat fibular osteotomy show a similar stimulation of bone healing of both noninvasive therapies.
Low-intensity pulsed ultrasound (1.5 MHz; 30mW/cm²) has demonstrated a positive effect on the bone healing process through high-frequency, acoustic pressure waves that cause low-level micro-mechanical pressure on the bone tissue. Animal studies, using ultrasound stimulation for bone healing, have shown an increase of callus tissue and an acceleration of bone healing, with one report showing early healing confirmed by scintigraphic analysis. Callus maturation is enhanced and bone mineral content increased by low-intensity ultrasound in animal and human studies using distraction osteogenesis. It has been suggested that the stimulation mechanism of low-intensity ultrasound is based on electrical potentials (piezo-electricity) and not thermal effects. More obvious is the direct mechanical stimulus, which changes cell metabolism. The influence of ultrasound on secondary messenger activity in rat chondrocyte cultures using fluorescent markers has been demonstrated. Low intensity ultrasound (0.5 W/cm²) induced a real time increase in intracellular calcium. Human osteoblastic and endothelial cells cultures increase the secretion of platelet-derived growth factor, one of the promoters of fracture healing. Accelerated bone healing by low-intensity ultrasound could be mediated by increased production of prostaglandin E₂. Therapeutic ultrasound at an intensity of 0.1 W/cm² stimulates in vitro collagen and noncollagenous protein synthesis, whereas higher intensities (1.0-2.0 W/cm²) inhibit the protein synthesis in a mouse calvarial bone organ culture system. The expression of genes involved in the stages of fracture repair could be increased by low-intensity ultrasound. Chondrocyte cultures exposed to ultrasound were studied in vitro and showed increased aggrecan mRNA levels and proteoglycan synthesis, suggesting direct ultrasound stimulation of aggrecan expression. Stimulation of aggrecan gene expression by low intensity ultrasound was demonstrated in both animal and in vitro experiments. Osteogenic cells stimulated in vitro by ultrasound showed biphasic anabolic response, leading to bone matrix formation. The production of prostaglandin E₂, which has been shown to stimulate new bone formation, might be stimulated by low-intensity ultrasound. Bone defect and trabecular bone regeneration are affected by ultrasound in vitro. An in vivo study using rats has shown that low intensity ultrasound did not stimulate longitudinal growth of the femur, thus excluding adverse effects on physeal growth. An increased vascularization in animal experiments with ultrasound was seen by Rawool. Prospective, randomized, placebo-controlled and double-blind studies in humans have demonstrated a 40% acceleration of time to clinical and radiological healing in both fresh tibial diaphysis fractures and distal radial metaphysis fractures with the latter study also reporting significantly less loss of reduction of fracture reposition. Stratification of the data of these two studies by smoking habit showed that the negative effects of nicotine on bone healing were minimized by low-intensity ultrasound. The bone healing in scaphoid fractures was enhanced by low-intensity ultrasound in 30% in a prospective randomized
trial using CT scan imaging. However, Emami et al. could not find a difference between ultrasound and placebo treatment in a small randomized trial with intramedullary nailed tibial fractures. Patients with a delayed healing of tibial fracture had lower serum levels of alkaline phosphatase compared to patients with a normal healing. Emami et al. concluded that this might indicate more bone resorption without effect on bone formation by low-intensity ultrasound. In case reports and uncontrolled trials the positive effect of low-intensity ultrasound is further demonstrated in stress fractures, Charcot neurarthropathies and nonunions. A large prospective, prescription use registry report shows an overall success rate for delayed union of 91% and for nonunions 86%. In a rat nonunion model low-intensity pulsed ultrasound promotes healing of the nonunion in 50%. The cost effectiveness analysis of low-intensity ultrasound in the prevention treatment of delayed union of tibial fractures show a cost savings over $13,000 per case in the USA.

1.4 Aims of the thesis

Nonunion treatment is, despite improvement of surgical techniques and a better understanding of the biology and pathophysiology of fracture healing, a challenging undertaking. The aim of this thesis is to examine the results of surgical treatment of some non-infected nonunions and the effect of low-intensity pulsed ultrasound on bone healing. Scaphoid fractures have a higher incidence of nonunion and avascular necrosis than other fractures. The development of a scaphoid nonunion might be the result of untreated instability in association with avascularity of the proximal pole. The surgical treatment of a scaphoid nonunion confronts the surgeon with all three principles of nonunion treatment: create stability, compress the ununited bone, and add viable bone tissue through an autogenous bone graft. Osteosynthesis and bone grafting are the standard treatment for scaphoid nonunions. Is there one operative technique for scaphoid nonunions which gives superior results? Controversy still exists on the natural course of scaphoid nonunions. Will osteoarthritis develop with or without treatment? The results of a large series of patients with a symptomatic scaphoid nonunion are analyzed in Chapter 2.

The operative techniques using plate and screws in clavicular nonunions are well established with predictable good results regarding bone healing. The impression is that any numbness with or without pain in the arm (defined as brachalgia) associated with clavicular nonunion is underestimated. What is the occurrence of brachialgia in our series? A comparison is made between standard AO osteosynthesis and the specially developed wave-plate osteosynthesis to assess the effect on brachialgia in Chapter 3.

The effect of low-intensity ultrasound, one of the new promising non-operative techniques, on bone healing in nonunions is examined in Chapter 4. The data of patients with different types and localizations of nonunions is available for analysis. The study of identical nonunions
(localization and type) in a randomized way would need a large study population. Furthermore, it seems unethical to randomize between surgical (osteosynthesis and autologous bone graft) and nonsurgical therapy. Does low-intensity pulsed ultrasound have any effect on established nonunions? If there is an effect, is the healing rate greater than the expected spontaneous healing in nonunions?

Some basic aspects of low-intensity ultrasound on bone healing are still unknown. The effect of low-intensity ultrasound on endochondral ossification in vitro in metatarsal rudiments of the mouse is studied in Chapter 5. This in vitro model represents two phases of embryonic bone development and mimics events occurring in bone healing. Namely, cartilage ossification and bony collar formation, which can be measured microscopically. Does ultrasound have an effect on calcifying cartilage and the total length of the rudiments? Are the rudiments growing and healthy?

To establish the effect of low-intensity ultrasound on human bone a prospective randomized trial is needed. The osteotomy of the lower leg for mild varus or valgus deformity was chosen for the study because of its uniform operative technique and follow-up treatment. A double blinded, randomized trial in 90 patients with 153 osteotomies was carried out, to determine the additional effect of ultrasound on bone healing (Chapter 6). The results of bone healing, with or without ultrasound stimulation, in metaphyseal region (primary bone healing) and in diaphyseal defect bone healing are discussed. Is the study population large enough to draw definite conclusions? Is there a statistically significant effect of ultrasound on bone healing in osteotomies? Can 20 weeks ultrasound treatment prevent the development of a nonunion?

Finally, in Chapters 7 and 8, general discussion and a summary are presented.

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