

Ultrasound stimulation of bone healing

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Outline

Bone

- architecture, composition

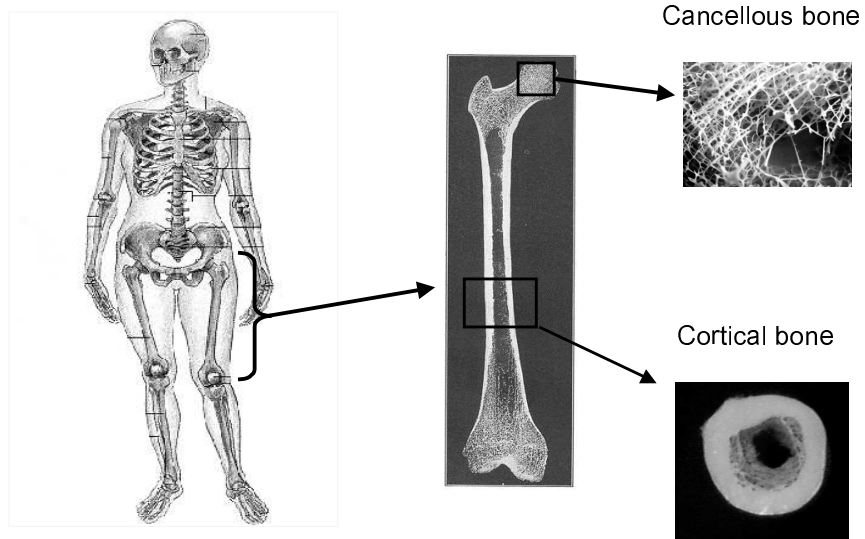
Diagnostic ultrasound for bone status assessment

- Devices
- Clinical results

Therapeutic ultrasound & bone healing : a review

- History
- Clinical results
- Evidence of the effect of LIPUS on animal and biological effects on bone cells
- Mechanisms of action of the ultrasound

Architecture of bone



Bone : multi-scale medium

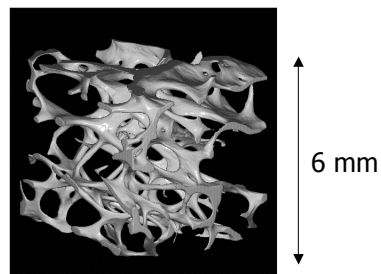
Trabecular bone

High porosity : 70-95%

Typical trabecular thickness : 50-150 μm

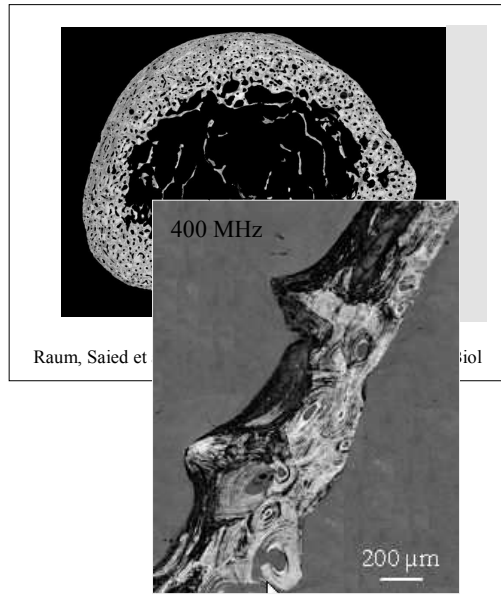
Pores size: 0.2-1.5 mm

Synchrotron micro-tomography



Bone : multi-scale medium

Cortical bone



Bone : multi-scale medium

Cortical bone

1 to 5 mm thick envelope of the skeleton

Heterogeneity & anitropy (osteon)

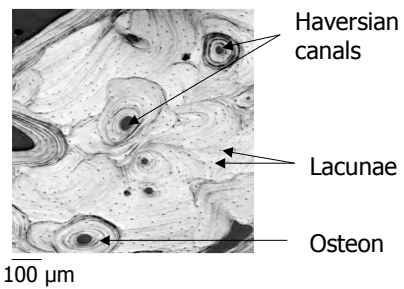
Low porosity: 5-10%

Two levels of porosity (oriented):

canals $\text{\O} \sim 50 \mu\text{m}$

lacunae $\text{\O} \sim$ a few μm

Acoustic microscopy 400 MHz

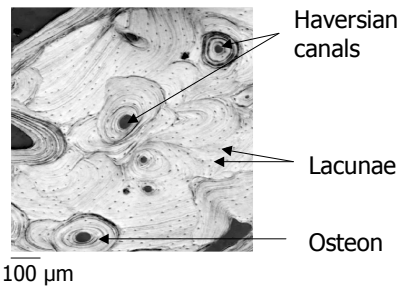


Bone : multiphase medium

Composition

- organic (collagen)
- inorganic (mineral and calcium)
- bone marrow, blood vessels

Acoustic microscopy 400 MHz



Bone as a living organ

Modeling

addition or removal of bone on external surfaces, leading to a change in architecture.

Remodeling

removal and replacement of bone in the same place, usually internally and in general not leading to a change in architecture.

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Diagnostic ultrasound

In vivo assessment of fracture risk or bone strength

- bone fragility in adults and children caused by osteoporosis, inherited or secondary bone disorders
- bone growth

X-ray absorptiometry

- Gold standard for diagnostic of bone status
- Bone mineral density (major determinant of bone strength)

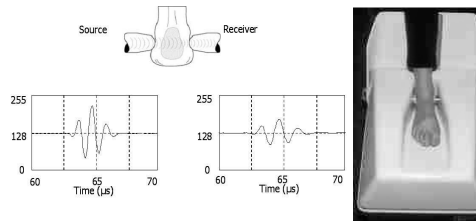
Quantitative ultrasound (QUS)

- Alternative approach to X-ray bone densitometry testing (osteoporosis)
- Based on the assumption that QUS are sensitive to skeletal factors of bone fragility (mass, macro and microstructure, material properties)

Ultrasonic techniques and parameters

Trabecular transverse transmission

- Slope of frequency dependent attenuation (BUA)
- « Apparent » speed of sound (SOS)
- Calcaneus (heel)
- 500 kHz

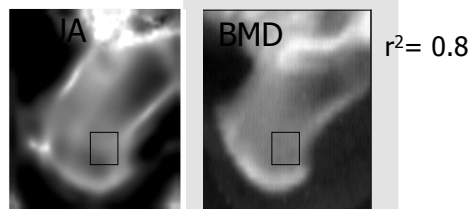


QUS imaging



Laugier, Fournier et al. Osteoporosis Int 1997

QUS parameters correlates strongly with bone mineral density

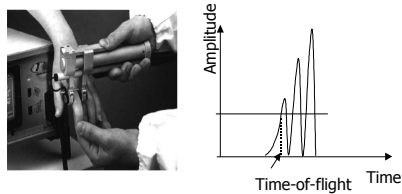


Chappard et al. Osteoporosis Int 1997

Ultrasonic techniques and parameters

Cortical transverse transmission

- « Apparent » speed of sound (SOS)
- Finger phalanges
- 1.25 MHz



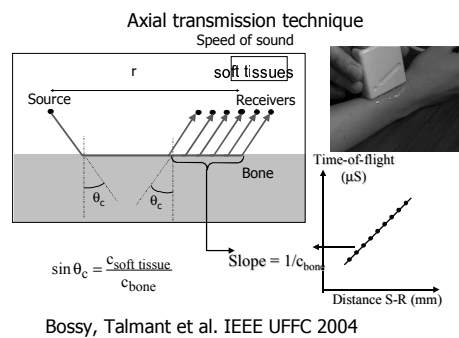
Ultrasonic techniques and parameters

Cortical transverse transmission

- « Apparent » speed of sound (SOS)
- Finger phalanges
- 1.25 MHz

Cortical axial transmission

- Speed of sound (SOS)
- Radius, tibia
- 250 kHz to 2 MHz



Clinical results

Several prospective studies using trabecular transverse transmission

EPIDOS studies (Hans *et al.* Lancet 1996)

- 5662 elderly women
- Ultrasonographic measurements of the os calcis predict the risk of hip fracture in elderly women as well as X-Rays absorptiometry of the hip does.

Trabecular transverse transmission

Discrimination of osteoporotic from control

Prediction of fracture risk (*in vivo*)

What are we measuring ?

Most of our knowledge about what we are measuring is empirical

Interaction mechanism ?

- attenuation = absorption+scattering

Solution to the direct and inverse problem

cancellous bone

- Poroelasticity (Williams, Hosokawa & Otani, Fella, ..)
- Multilayer model (Hughes, Wear)
- Scattering (Wear, Padilla, ...)
- Multiple scattering in porous media (Luppe)

cortical bone

- Surface wave (Bossy), guided waves (Moilanen)

Work in progress

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Bone fracture

Fractures are unfortunate but inevitable (bones that would never failed would be too heavy)

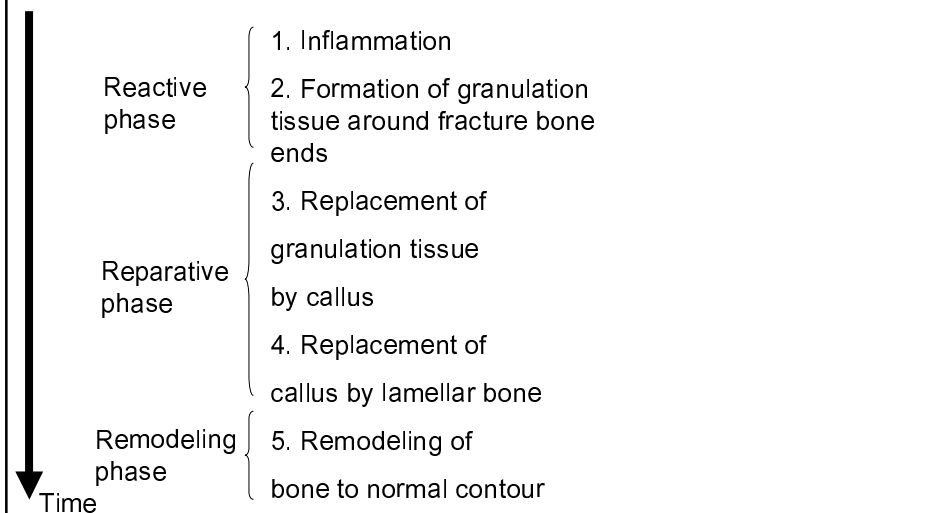
Fracture has two major causes :

- fatigue : bone becomes damaged, often so much as to lead to fracture, after being loaded many times to a load that would not break in a single loading
- traumatic loading : great enhancement of normal loading (and generally in an abnormal direction)

Once bone becomes fractures, it is like the liver : it is one of the few organs that is able to regenerate and restore structure to its pre-injured state.

Elements of bone healing

Bone healing involves a complicated set of cellular events that are mediated by numerous local and systemic factors



Delayed union and nonunion fractures

Severe fractures, especially of long bones, such as the tibia, are particularly susceptible to bone union problems :

- *delayed union* : if the healing process is slower than expected,
- *nonunion* : if the healing process stops.

An estimated 5.6 million fractures occur in the United States annually, and the healing of 5 to 10% of them is reportedly delayed or impaired [Einhorn, 1995].

Treatment of fractures

The aim of treating fractures is to create an environment favourable to healing.

Understanding these processes has led to substantial developments in the techniques and treatment outcomes.

During the American Civil War, an open tibial fracture almost always resulted in amputation.

Treatment of fractures


Surgical management

Sling immobilization
Cast immobilization
External fixation
Intramedullary fixation

Enhancement of natural biological healing phenomena by

Electromagnetic field
Electrical stimulation
Mechanical stimulation
Biological treatments
Extracorporeal Shock Waves ...
.... **Ultrasound**

Origins of ultrasound as an intervention in fracture healing

- 
- 1952 First study by Corradi & Cossolino of radial fractures on rabbits : CW ultrasound stimulates the formation of bone callus.
- 1953 First 'clinical' study on 8 patients : CW ultrasound produces an increase in periosteal callus.
- 1983** Dyson & Young demonstrated acceleration of fracture healing in rats, with 500 mW/cm² (SAPT), pulsed 2 ms on, 8 ms off for 5 minutes/days, at 1.5 or 3 MHz. Treatment was most effective during the inflammatory and early proliferative phases of healing (before hard callus formation).
- Xavier & Duarte reported healing of nonunions in humans and acceleration of bone healing in rabbits using 30 mW/cm² (SATA), 1.6 MHz, 200 μs pulse width, PRF 1 kHz, 15 minutes/day

“Optimization” of ultrasound parameters

1994 Wang *et al.* (J Orthop Res) reported that 0.5 or 1.5 MHz can accelerate fracture repair in a model of femoral shaft fracture in the rat.

1998 Jingushi *et al.* found in a femoral fracture model in rats that a pulse width of 200 μ s was more osteo-inductive than 100 or 400 μ s, and that PRF of 1 kHz was more osteo-inductive than 2 kHz.

The clinical device : Exogen

World-wide monopoly

- Exogen is an ultrasound bone healing system marketed by Smith & Nephew corporation.
- It seems to be the only technology marketed worldwide that uses low intensity ultrasound to influence the fracture healing process.



Characteristics

burst width of 200 μ s (\pm 10%) containing 1.5-MHZ (\pm 5%) sine waves, with a repetition rate of 1 kHz (\pm 10%) and a spatial average temporal intensity of 30 mW/cm² (\pm 30%).

Treatment

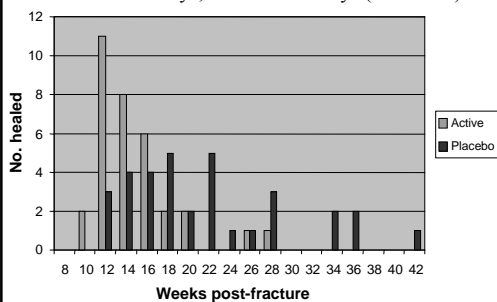
20-minute sessions at home, for several months

Clinical studies : State of the art

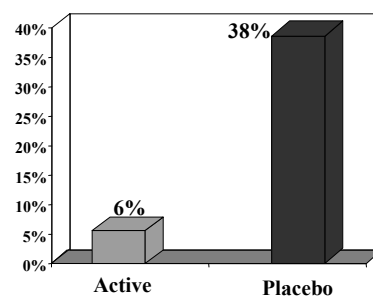
Tibial Diaphysis Fractures – Cortical Bone Cast immobilisation

- Prospective, Randomised, Double-Blind, Placebo-Controlled, Multi-Centre
- active: 33, placebo: 34

38% Faster Time to Healed Fracture
Active - 96 days; Placebo 154 days (P<0.0001)



84% Reduction in Incidence of Delayed Unions (not healed after 150d)

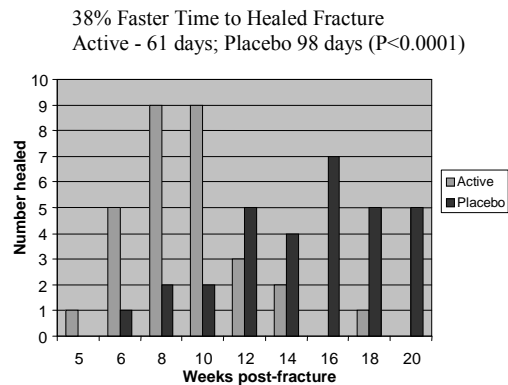


Results suggest that ultrasound not only accelerates healing, but also helps to ensure healing

Heckman et al. J Bone Joint Surg Am 1994

Distal Radius Metaphysis Fractures Cancellous Bone

- Prospective, Randomised, Double-Blind, Placebo-Controlled, Multi-Centre
- active: 30, placebo: 31



Kristiansen et al. *J Bone Joint Surg Am* 1997.

Tibial Diaphysis Fractures – Cortical Bone Intramedullary nailing

- Prospective, Randomised, Double-Blind, Placebo-Controlled
- active: 15, placebo: 17

No significant difference between active and control in healing time in fresh tibial fractures treated with a reamed and statically locked intramedullary nail

Emami et al. *J Orthop Trauma* 1999

Treatment of nonunions

No scientific study available

One study by Nolte et al.

- 29 cases of nonunions (tibia, femur, radius/ulna ...)
- patients served as their own control : their prior failed treatments (conservative and/or operative) are the basis for evaluating the effect of the ultrasound treatment
- No additional treatment procedure during the period of ultrasound treatment

=> 25 of the 29 healed in a an average treatment time of 22 weeks

BUT

- great variety of bones => different biologic capacities of healing
- great variety of fractures types => different time to healing
- wide variances of surgical techniques => different responses

Nolte, J Trauma, 2001

Therapeutic indications based on FDA approvals

The U.S. Food and Drug Administration (FDA) authorized the use of the device for the first time in 1994, for the following indications:

- acceleration of the healing of fresh fractures of the distal radius with posterior displacement (Colles' fractures);
- acceleration of the healing of fresh closed or grade I open fractures of the tibia, provided such fractures are immobilized with a cast after closed reduction, if appropriate.

For the indication of accelerating the healing of certain fractures, Exogen is therefore used as an adjunct to conventional treatment.

In 2000, the FDA added the indication of fracture nonunion to its authorization. For this indication, Exogen is used either to treat patients after other modalities have failed to unite the fracture, or to avoid further surgery.

The prevention of nonunion in certain higher-risk patient populations is also promoted as another indication.

Conclusion on clinical results

The effect of low-intensity ultrasonography on fracture healing is controversial, and current management of fractures does not generally involve the use of ultrasound therapy.

TABLE 2

Efficacy evidence	
INDICATION	EFFICACY EVIDENCE
Acceleration of healing	Effective for fractures treated without surgical intervention, according to a meta-analysis of three randomized studies with a small total number of patients, which considerably weakens the evidence.
Prevention of nonunion	No evidence of clinical efficacy.
Treatment of nonunion	Effective, according to case series. No randomized studies.
Other indications	No evidence of clinical efficacy.

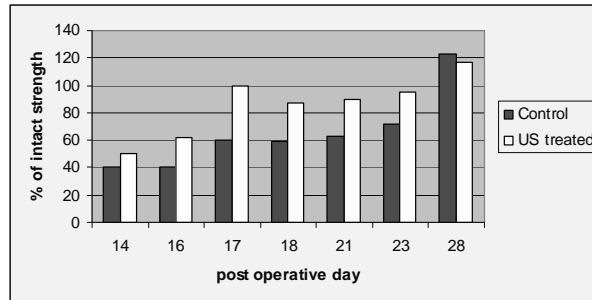
From Busse et al. *Cmaj* 2002

It seems that a consensus is reached for tibial fracture nonunion, because the prognosis is so grim that it seems reasonable to consider the use of low-intensity ultrasound after failure of at least one surgical intervention and after the healing process has ceased for several months.

Evidence of the effect of LIPUS on animal and biological effects on bone cells

Animals studies

Rat osteotomy



- From day 17, all fractures were as strong as intact bone in the treated group
 - The control group attained intact value only by day 28
- => Acceleration of time to healing by a factor 1.7

Pilla et al. *J Orthop Trauma* 1990

Animals studies

Ovariectomized rodent (osteoporosis)

Low-intensity pulsed US did not influence the bone changes due to ovariectomy, suggesting that the US dose introduced may not be a beneficial treatment for osteoporosis.

Warden et al *Ultrasound Med Biol* 2001

Animals studies

- earlier expression of genes implied with cartilage formation
- increase in callus formation
- increase bone mineral density at the fracture site
- increase in mechanical strength of the treated bones
- increase the degree of vascularity
- ...

- no effect on intact bones

In vitro studies

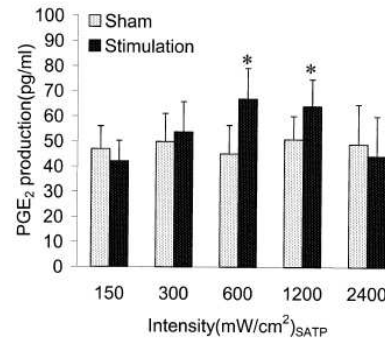
Culture of osteoblast

Table 1. Change of cell population 24 h after osteoblasts were treated with different intensities of US

Intensity, mW/cm ² (I _{SATP})	Cell density (cells/mm ²)	
	Sham, mean (SD)*	Stimulation, mean (SD)*
150	162.93 (11.41)	159.64 (17.88)
300	188.24 (9.80)	193.70 (19.06)
600	186.82 (7.28)	203.37 (8.11) [†]
1200	201.3 (12.26)	215.59 (15.55)
2400	213.62 (28.87)	211.04 (32.02)

* Sham = osteoblasts were sham treated; stimulation = osteoblasts were treated with ultrasound;

[†] p < 0.05 (n = 10) when compared with sham group.



prostaglandin E2 (PGE2)

Li et al. *Ultrasound Med Biol* 2002

In vitro studies

Culture of mice bone tissue

- bone volume and calcified cartilage percentage were significantly higher in the ultrasound-stimulated bones compared to untreated controls.
 - the number of the cells was not changed by the ultrasound treatment.
- => These results suggest that the stimulatory effect of low-intensity ultrasound on endochondral ossification is likely due to stimulation of **bone cell differentiation** and **calcified matrix production**, but not to changed cell proliferation.

Korstjens et al. *J Orthop Res* 2004

In vitro studies

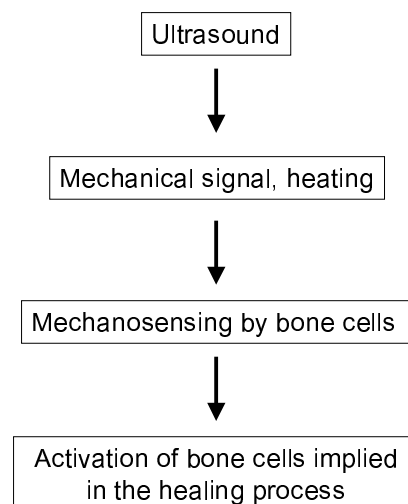
The observed effects :

- increase of calcium uptake
- increase of expression of genes implied in the healing process
- increase of collagen production
-

indicate a potential osteogenetic effect of ultrasound

However, the effect of ultrasound on the process of osteogenesis during fracture repair has not been adequately established

Interaction of ultrasound and bone tissues Mechanotransduction



Mechanisms of ultrasound action in bone tissues

Thermal effects : in cell culture experiments, temperature measurement increase < 1°C

- suggest non thermal effects

Radiation pressure : mechanical stimulation of bone

- activation of bone metabolism.

Streaming

- stimulation of bone cells via mechanical (shear stresses on cell membranes) and/or electrokinetic effects

Cavitation

- micro streaming
- alteration of membrane permeability

Micro-movements
Pilla
J Orthop Sci 2002
Hadjigryrou
Clin Orthop Relat Res
1998

Conclusion

In vitro & in vivo

- osteogenetic effect of ultrasound on bone healing demonstrated both on animals and on bone cells
- underlying mechanisms are still misunderstood

Clinical results

- clinical evidence that ultrasound stimulation accelerate fracture healing
- treatment of nonunion (according to case series)

Potential applications

- Distraction
- Bio-reactor
- Bone repair after surgery
- Bio-integration of implants