# Bioceramics & Bone Grafts

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# Why Would We Need to Replace Bone?

- Trauma
- Disease
- Congenital defects
- Wearing Out (Age / Over use)

# Trauma

- Guns & Cars

- Osteoporosis affects 33% women and 8% of men
- 20% of women who fracture a hip are dead within 1 yr.
- Less women die from breast cancer.
- Women reach their peak bone mass by around age 25 to 30, men by age 30 to 35

ORIGINAL ARTICLE

# Low bone mineral density is two to three times more prevalent in non-athletic premenopausal women than in elite athletes: a comprehensive controlled study

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**Objective:** To compare bone mineral density (BMD), investigate factors associated with BMD, and examine the prevalence of low BMD in athletes and non-athletic controls.
**Methods:** The study included a questionnaire (part I), measurement of BMD (part II), and a clinical interview (part III). All Norwegian female athletes on national teams (n = 938) and an aged matched random sample of non-athletic controls (n = 900) were invited to participate. The questionnaire was completed by 88% of athletes and 70% of controls. A random sample of these athletes (n = 300) and controls (n = 300) was invited to participate in parts II and III. All parts were completed by 186 athletes (62%) and 145 controls (48%).
**Results:** Mean (standard deviation) total body (TB) BMD was higher ($p<0.001$) in athletes (1.21 (0.09) g/cm$^2$) than in controls (1.18 (0.08) g/cm$^2$), and higher ($p<0.001$) in high impact (HI) sports athletes than in medium impact (MI) and low impact (LI) sports athletes. In athletes, body weight and impact loading sports were positively associated, and percent body fat and eating disorders were negatively associated with TB BMD. Body weight and weight bearing activities were positively associated and menstrual dysfunction was negatively associated with TB BMD in controls. A higher percentage of controls (28.3%) than athletes (10.7%) had low BMD ($p<0.001$).
**Conclusion:** Female elite athletes have 3–20% higher BMD than non-athletic controls and HI sports athletes have 3–22% higher BMD compared with MI and LI sports athletes. Low BMD is two to three times more common in non-athletic premenopausal women than in elite athletes.

In recent years, the use of exercise to maintain bone health throughout life and ultimately prevent osteoporosis related fractures has received substantial research attention.[1 2]

We defined an elite athlete as one who qualified for the national team at the junior or senior level, or who was a member of a recruiting squad for that team. The athletes

# What is a bone graft

- Word ‘graft’ conjures image of transplant tissue, not true but is the terminology used.
- Any implanted material that alone or in combination promotes a healing response by osteogenic, osteoconductive or osteoinductive activity….

# Definitions

- Osteogenic: contains living cells capable of differentiation into bone
- Osteoconductive: promotes bone apposition onto its surface, functioning as receptive scaffold
- Osteoinductive: provides biological stimulus that induces native or transplanted cells to differentiate into osteoblasts

# Types

- Autograft
  - Aspirated Marrow/Processed Cells
  - Cancellous Bone
  - Non vascularised Cortical Bone
  - Vascularised Bone

- Allograft
  - Anatomy
    - Cortical, cancellous, osteochondral
  - Processing
    - Fresh, frozen, freeze dried, demineralised
  - Sterilisation
    - Sterilely Processed, irradiation, EtO
  - Form
    - Powder, particulate, gel, paste, chips, strips, massive

# Great so why make artificial grafts

- Synthetic
  - Osteoconductive Blocks/Granules
  - Osteoconductive cements
  - Osteoinductive proteins
  - Composites

# Graft Incorporation

- Depends on material, implant site, disease state.

- Following Implantation
  1. Haematoma
  2. Inflammation/MSC/ FV tissue
  3. Blood vessel invasion
  4. OC resorp
  5. Bone formation at graft surface

- Inflammation stage release of growth factors
- Collagen formation simultaneous with collagen degradation
- Mechanical Environment
- Tissue Quality…e.g. scar tissue, heart disease, immunocompromised, smokers

# Autografts

- Vasularised
  - Best Incorporation
  - 90% osteocyte survival
- Cancellous
  - Most cells die but MSC are the most ischemia tolerant, remodelled rapidly
- Cortical
  - Necrotic/not osteogenic/mechanically strong
- Bone Marrow
  - Osteogenic limited quantity/ concentrate or in vitro culture

# Allografts

- Rejection:
  - Class I & II histocompatibilty complex antigens
  - Animal studies suggest there is significant response.  In humans HLA antibodies are detected but results good.
  - Sensitisation against other grafts

- Union by periosteal new bone formation
- 1-2mm bone formed on surface
- Mainly osteoconductive BUT

Demineralised graft osteoinductive.

# Synthetic Materials

- Often used in combination with allograft
- Generally all osteoconductive
- May have inflammatory response, no immune response
- Concerns surrround particulate generation cf wear debris

# BMP

- Realisation that demineralised matrix induced bone formation led to discovery of BMPs
- BMP2/4/7
- Many animal trials report one induction but larger animals show need for near toxic doses to replicate rodent results.

# Remodelling

- Vascularised allograft is remodelled in response to mechanical loading
- Non loaded allograft resorbed, loaded remodelled.
- Resorbable osteoconductive materials eg HA cement is resorbed in loaded regions.

# Graft Materials

- Ceramics
  - Resorbable
  - Non Resorbable
- Polymers
  - PMMA
  - Degradable

# What do you know about HA

- Formula
- Constituents
- Bone Bonds to it, (so does skin)
- Osteoconductive
- White
- Least soluble CaP at pH7
- Same as bone mineral?

# Bone Mineral

- Is apatitic but so are lots of minerals, apatite is a crystal structure, not a material.
- Contains Mg, $CO_3$, Na, K, F, Si, $HPO_4$, and traces of all you eat, Sr, Pb, etc
- It is nanocrytalline (10-100nm)
- SSA related to particle size, bone mineral 100-200$m^2$ $g^{-1}$.

- SSA affects kinetic solubility
- Synthetic HA can be precipitated as small crystals but to turn that into a material requires sintering…..(>1000C). Particle growth/ 1-10 microns, I.e. 100 times bigger, I.e. 1,000,000 times the volume
- Not resorbable

# Various routes to HA manufacture

- Sintering powder
- Sintering animal bone
- Hydrothermal processing of $CaCO_3$

# Processed Into

- Blocks, granules with and without holes in
- Also used as a composite with other materials

# Other CaPs

- Tricalcium Phosphate
- More soluble than HA, processed by sintering
- Alpha and beta forms

# Low temperature formation

- Smaller particle size
- Drug incorporation/Cell? incorporation
- In situ setting
- HT unstable phases can be used, most notably brushite, $CaHPO_4.2H_2O$
- Mouldable
- Minimally Invasive Application

# Cements

- Apart from TTCP:DCPD and TCP:MCPD acid base reactions also amorphous cements.  I.e. metastable crystalline material crystallises in presence of water
- Reacting v concentrated solutions and freeze drying products or reacting in absence of water

# Coral

- Also soluble like TCP, no apparent advantage over TCP, but partial conversion to HA means that HA is resorbable

# PoP

- Used since 1892, very soluble….too soluble?

# Polymers

- PLA/PGA
  - Mainly for drug delivery
  - Various Experimental

- None of these are weight bearing…..does a resorbable material need to be weight bearing?

# References


- Clin Orth Rel Res
- 1996, 324, p55
- 2002, 395, p 11
- 2000, 371, p 10

# Bioceramics

# What is a ceramic?

- **DICTIONARY DEFINITION**
- **ce·ram·ic** (s-rmk) *n.*
- Any of various hard, brittle, heat-resistant and corrosion-resistant materials made by shaping and then firing a nonmetallic mineral, such as clay, at a high temperature.
- An object, such as earthenware, porcelain, or tile, made of ceramic.
- **ceramics.** *(used with a sing. verb)*The art or technique of making objects of ceramic, especially from fired clay.

# What about sand/cement/plaster/glass?

- Inorganic, non metallic compounds
- E.g. carbon, silicon, silica, glass, porcelain, chalk etc etc.

# 4 Categories of tissue response

- Toxic, tissue dies-> may be desirable
- Non-toxic and nearly inactive, fibrous tissue formation
- Non-toxic and active, interfacial bond
- Non-toxic, soluble, replaced by tissue, type depends on rate.

# Main forms

- Polycrystalline dense form
- Macroporous polycrystalline dense blocks
- Coatings
- Granules
- Cements

# Ceramics in Use in vivo

- Hydroxyapatite ($Ca_{10}(PO_4)_6(OH)_2$)
- Calcium Carbonate (Coral)
- Calcium Sulphate (Plaster of Paris)
- Tricalcium Phosphate
- Zirconia
- Alumina
- Bioglass
- Carbon

# Processing Routes

- Laboratory synthesised ceramics for medical use are usually precipitated, even if it is a mineral, in order to purify the material.
- Precipitation is a very difficult process to control, especially since it is usually a batch process.

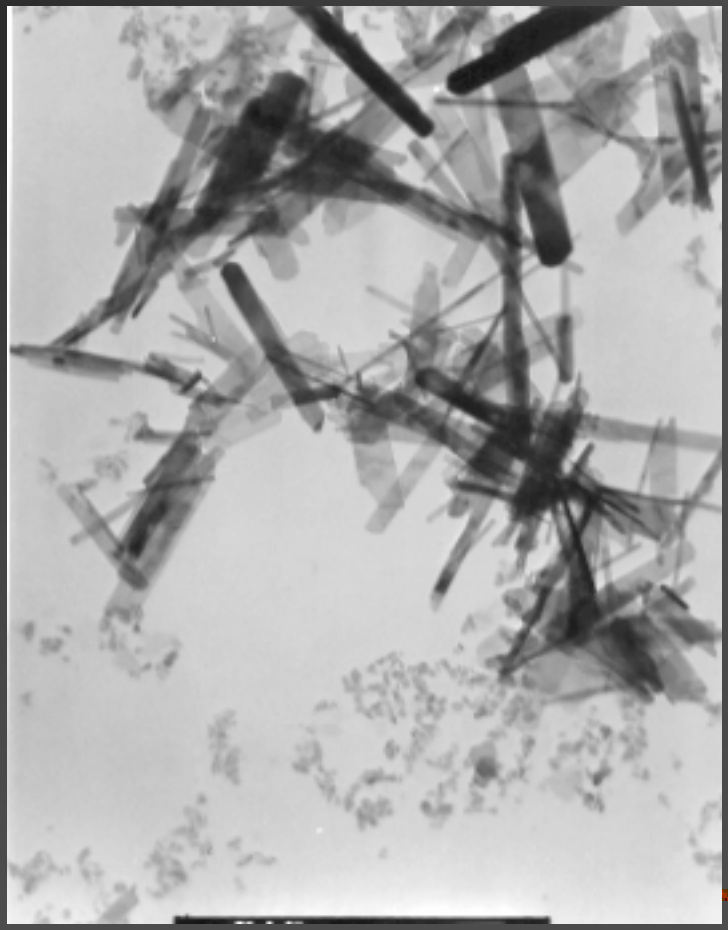
# Precipitate Characteristics

- Primary particle size, (TEM)/BET
- Primary particle shape, (affects packing)
- Agglomerate size, (Particle Size Analysis)
- Agglomerate Strength (affects packing)
- Phase purity (XRD only accurate to ~5%)
- Solute Impurities

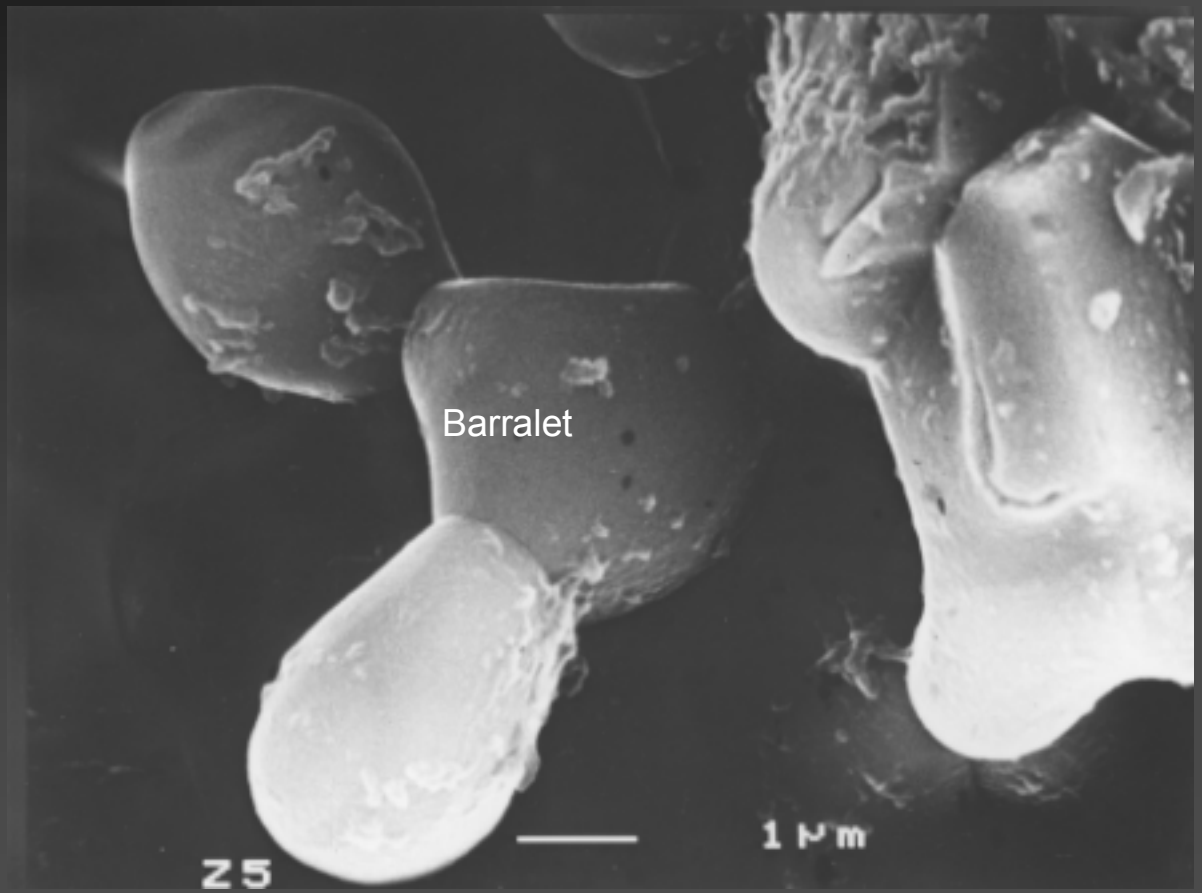
# Powders usually sintered or plasma sprayed

- Sintering
  - high temperature densification process
    - Step1, compaction into desired shape.
    - Step2, heat below $T_m$ or decomposition temp.
      - densification occurs by vacancy diffusion
      - continues up to 100% theoretical density, get shrinkage
      - crystals grow into “grains” x10-100 increase in linear dimension=> $10^3$-$10^6$ increase in volume
    - Step 3, cool

# Typical Precipitate



# Typical Ceramic



# Plasma Spraying

- Very hard to control.
- Huge temperature gradient means a variety of phases can be deposited.
- Poor characterisation a feature of biomaterials in general.

# Natural Bioceramics

- Coral.
- Nacre, still ‘experimental’ phase despite being used by the Mayans ~1-2,000yrs ago as tooth replacement.
- Animal Bone, calcined to remove organic component:- concerns over transgenic infection and lack of reproducibility mean it is seldom used.

# Calcium Phosphates

- Interest in these ceramics is based upon the fact that these compounds are found in all vertebrates as bone or tooth mineral.

# Calcium Phosphates

| Ca/P | Formula | Name | Abbreviation |
|---|---|---|---|
| 2.0 | $Ca_4O(PO_4)_2$ | Tetracalcium phosphate (Hilgenstockite) | TeCP (TTCP) |
| 1.67 | $Ca_{10}(PO_4)_6(OH)_2$ | Hydroxyapatite | HAp |
| | $Ca_{10-x}H_{2x}(PO_4)_6(OH)_2$ | Amorphous calcium phosphate | ACP |
| 1.50 | $Ca_3(PO_4)_2$ | Tricalcium phosphate (α, β, γ) | TCP |
| 1.33 | $Ca_8H_2(PO_4)_6{\cdot}5H_2O$ | Octacalcium phosphate | OCP |
| 1.0 | $CaHPO_4{\cdot}2H_2O$ | Dicalcium phosphate dihydrate (Brushite) | DCPD |
| 1.0 | $CaHPO_4$ | Dicalcium phosphate (Monetite) | DCP |
| 1.0 | $Ca_2P_2O_7$ | Calcium pyrophosphate (α, β, γ) | CPP |
| 1.0 | $Ca_2P_2O_7{\cdot}2H_2O$ | Calcium pyrophosphate dihydrate | CPPD |
| 0.7 | $Ca_7(P_5O_{16})_2$ | Heptacalcium phosphate (Trömelite) | HCP |
| 0.67 | $Ca_4H_2P_6O_{20}$ | Tetracalcium dihydrogen phosphate | TDHP |
| 0.5 | $Ca(H_2PO_4)_2{\cdot}H_2O$ | Monocalcium phosphate monohydrate | MCPM |
| 0.5 | $Ca(PO_3)_2$ | Calcium metaphosphate (α, β, γ) | CMP |

# Apatites

- Least soluble of the calcium phosphates
- Have general formula:
  - $M_{10}(ZO_4)_6X_2$
    - where M= Ca, Sr, Ba, Cd, Pb, Mg, Na, K, H

      Z= P, $CO_3$, V, S, Si, Ge, Cr, B

      X = OH, $CO_3$, O, $BO_2$, F, Cl

# Bone Mineral

- Predominantly a substituted calcium hydroxyapatite
  - $Ca_{10}(PO_4)_6(OH)_2$
- Also contains a variety of other ions such as carbonate, magnesium, fluoride, chloride
- Extremely small, ~20nm embedded in collagen matrix.

- It forms a bond to bone
- It is only slightly soluble.
- Therefore it is a permanent implant so cannot be used in load bearing applications.

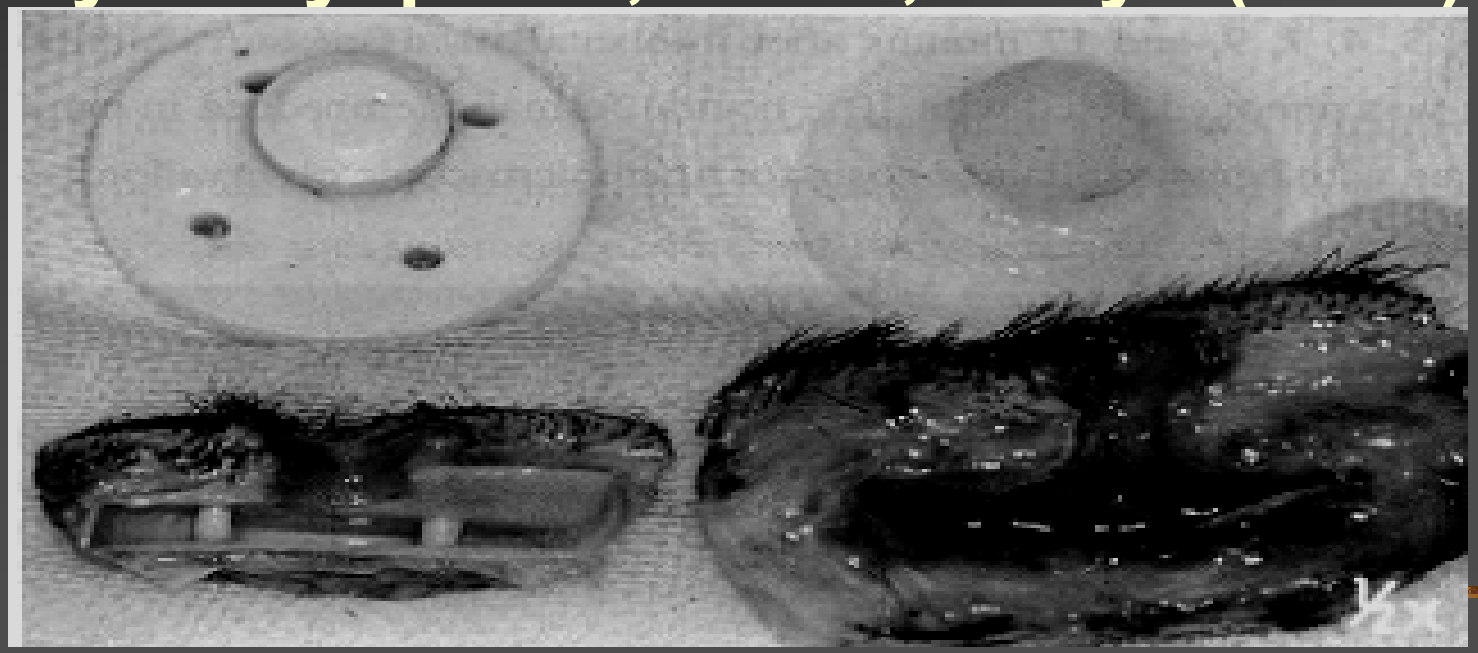
- Its ability to bond to bone is exploited in its most widespread use as a plasma sprayed coating on joint stems.
- The bond prevents wear debris from becoming lodged near the joint stem.

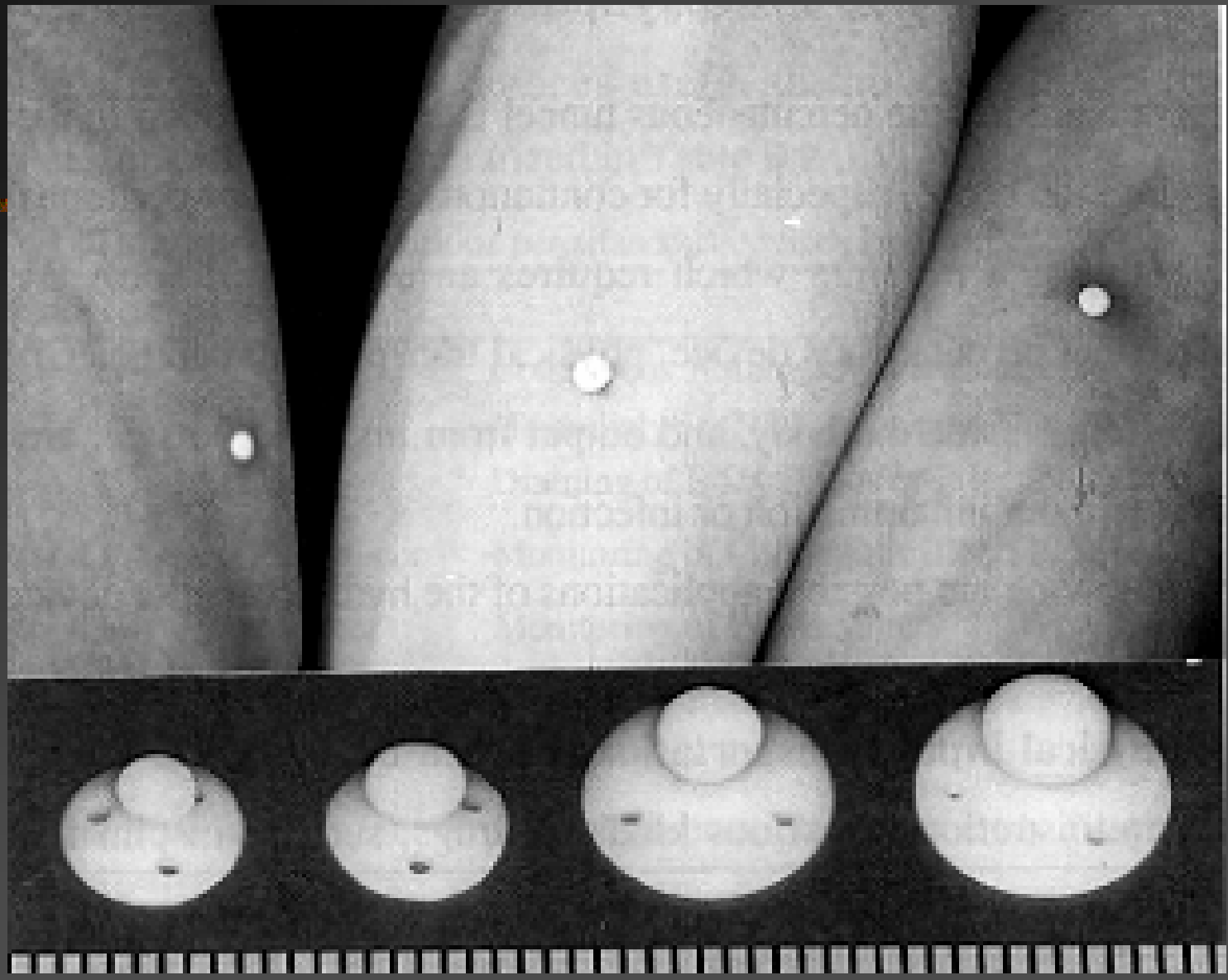
# Main Applications of Bioceramics

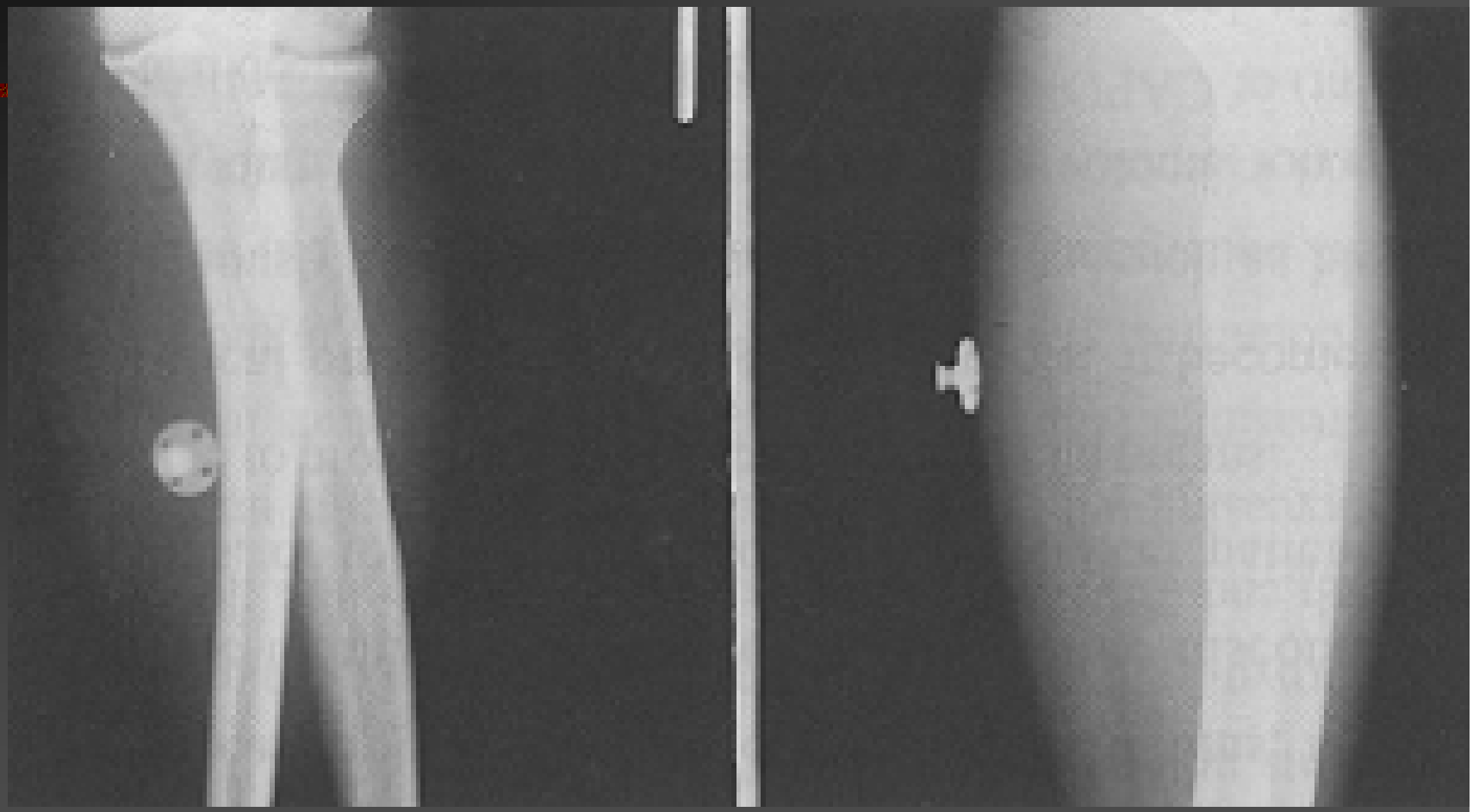
- Orthopaedic
  - Bone Graft, e.g. following tumour resection
    Alveolar Ridge Augmentation
  - Hip/knee articulating surfaces
  - Stem coatings
- Prosthetic teeth
- Artificial Ligaments
- Heart Valve Coatings

# Various Experimental

- E.g. Percutaneous, images from **H. Aoki Science and Medical Applications of Hydroxyapatite, JAAS, Tokyo (1991).**







# Main Draw Backs

- Brittle
- Cannot be shaped during surgery
- Shrink during processing.

# Current Status / Future

- Because of stringent regulatory hurdles: animal testing, clinical trials, a new material takes around 15 to 20 years to hit the market
- Trend is towards resorbable materials which eliminate the need for a secondary procedure and mouldable materials which can be applied by minimally invasive methods.

- novel configurations or combinations of existing, licensed materials.
- E.g.  Interpore, No.1 best selling porous HA.
  - Made by hydrothermally converting coral to HA, non resorbable
  - Partial conversion gives apatite surface (bone attachment) and soluble core.
  - Made a new product Interpore R

# Apatite Cements

- Reaction between tetracalcium phosphate and dicalcium phosphate in presence of water to give insoluble apatite.
- Minimally invasive
- Resorbable, (small crystal size)
- About as strong as wet Plaster of Paris.

- Bioceramics are also added to soluble/degradable polymers to give stiffness and improve tissue / implant interface.  If resorption rates do not mach get particulate formation.
- Also can be used to act as buffers, e.g. $CaCO_3$ lowers pH of polylactic acid during hydrolysis.

# Gone Full Circle

- Bioceramics are now a commodity, most are ex-patent.  There is no need for another way to make the same thing…

# Low Temperature Bone Graft Printing/Metal Ion Induced Angiogenesis

- Currently Embargoed, please see Advanced Materials journal soon for article.