PEEK / β-TCP / TiO_2: a smart biocompatible composite with osteoconductive properties

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Polyetheretherketone (**PEEK**) is a well-known aromatic, rigid semi-crystalline thermoplastic used more than 30 years ago as an alternative to metal alloys in some orthopaedic devices (ex : spinal fusion cages, fixation of bone fractures, …)

PEEK shows:

- Excellent mechanical properties
- Bone-like stiffness
- Good biocompatibility

PEEK is considered to be relatively inert in a biological context.

More particularly, **PEEK** exhibits poor osteoconductive properties which severely limits its application in the field of hard tissues.

To overcome this lack of efficacy, a

"bioactive PEEK-based composite"

was developed as a mixture of 2 ceramic powders within a PEEK matrix .

The ceramics are the following :

- [Beta]–tricalcium phosphate(β-TCP)(14% w/v) and
- Titania (titanium dioxide-anatase)(TiO_2)(8% w/v)

Samples of the material are obtained by injection moulding using standard PEEK processing conditions.

Then sample surface is activated by a chemical treatment prior to gamma sterilization.

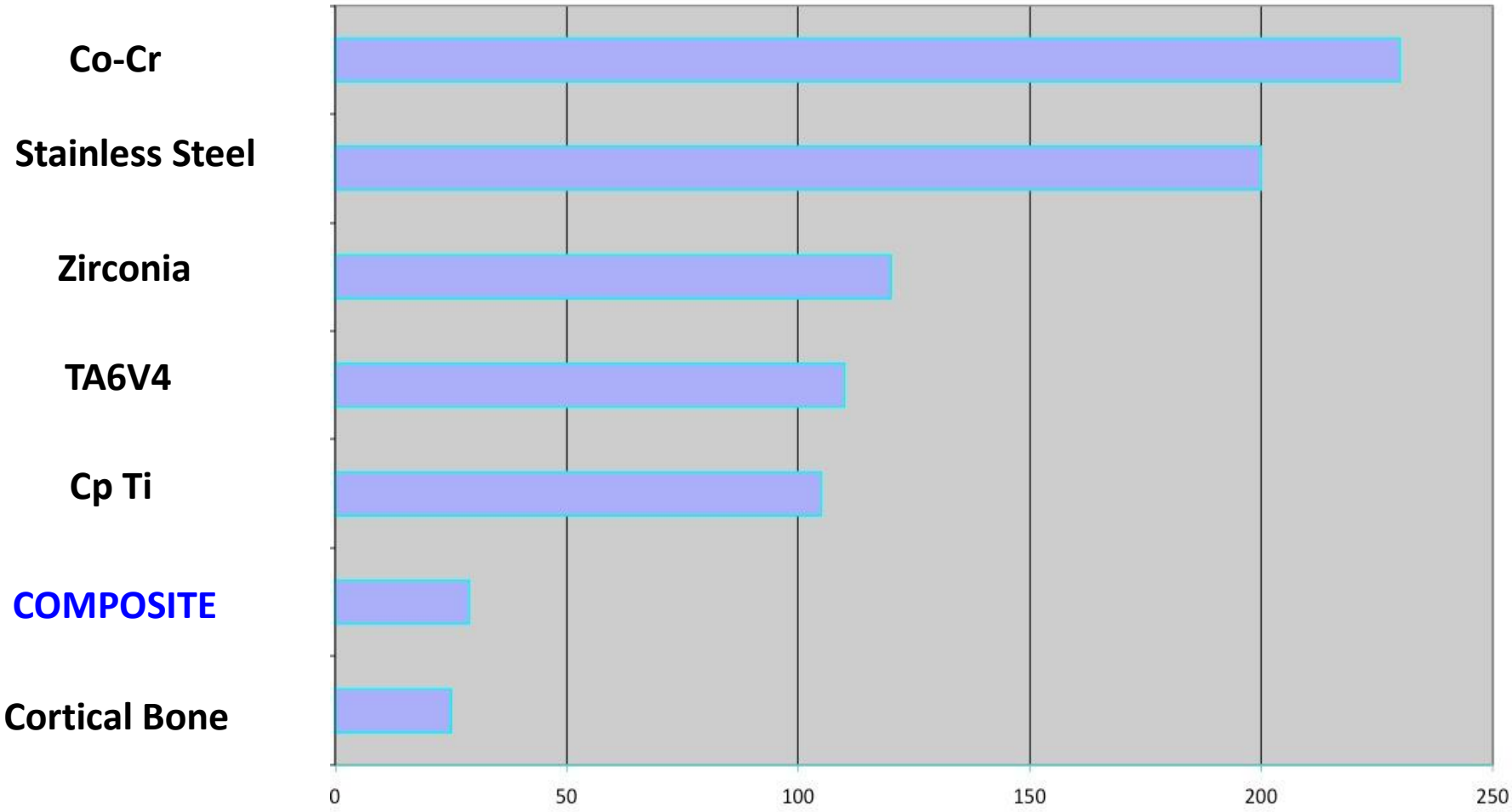
As we shall see no trade-off is observed in mechanical properties in exchange with bioactivity.

What about mechanical properties ?

This composite displays mechanical properties comparable to those of human cortical bone.

For example, its elastic modulus is similar to that of human cortical bone.

PEEK COMPOSITE: Elastic modulus



Test (ISO)	PEEK OPTIMA	PEEK composite
Impact (KJ/m²)	7.3	6.7
Flex Strength (MPa)	162.4	158.7
Flex Modulus (GPa)	3.96	4.69
Tensile Strength (MPa)	99.25	94.21

First part
In vitro studies

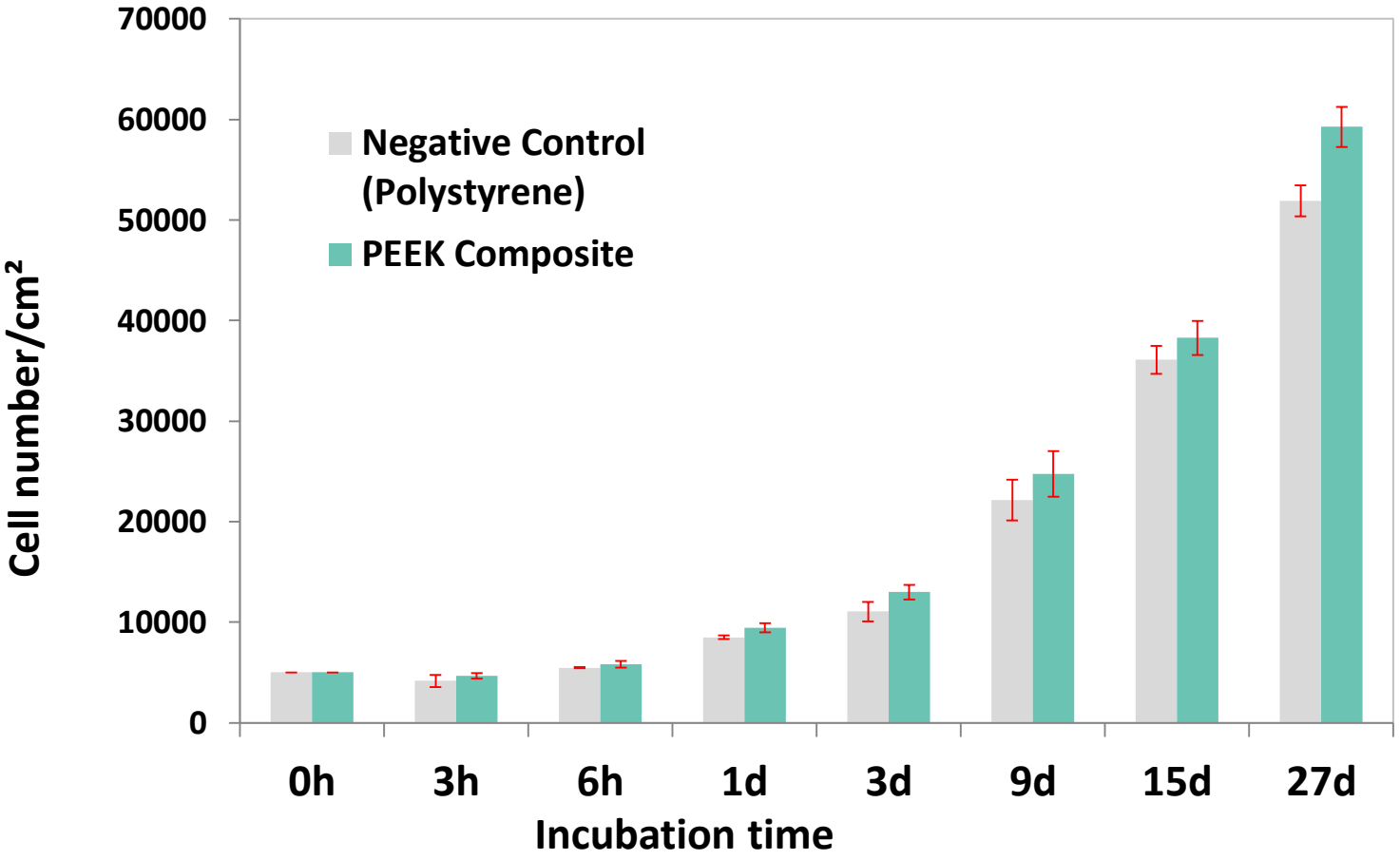
Cytocompatibility study: First study

- **Purpose of the study :** measure *in vitro* whether the osteoblast differentiation is maintained, inhibited or stimulated in direct contact with the test material.
- **Test system :** Human osteoblasts (HAB) arising from human alveolar bone.

> *HAB are mature cells expressing a specific osteoblastic phenotype defined by cell adhesion and growth, alkaline phosphatase activity, collagen type I synthesis.*

- **Protocol :**
  - Cell adhesion (3h, 6h) and proliferation (1 to 27 days)
  - Alkaline phosphatase (ALP) activity (3, 15 and 27 days)
  - SEM study

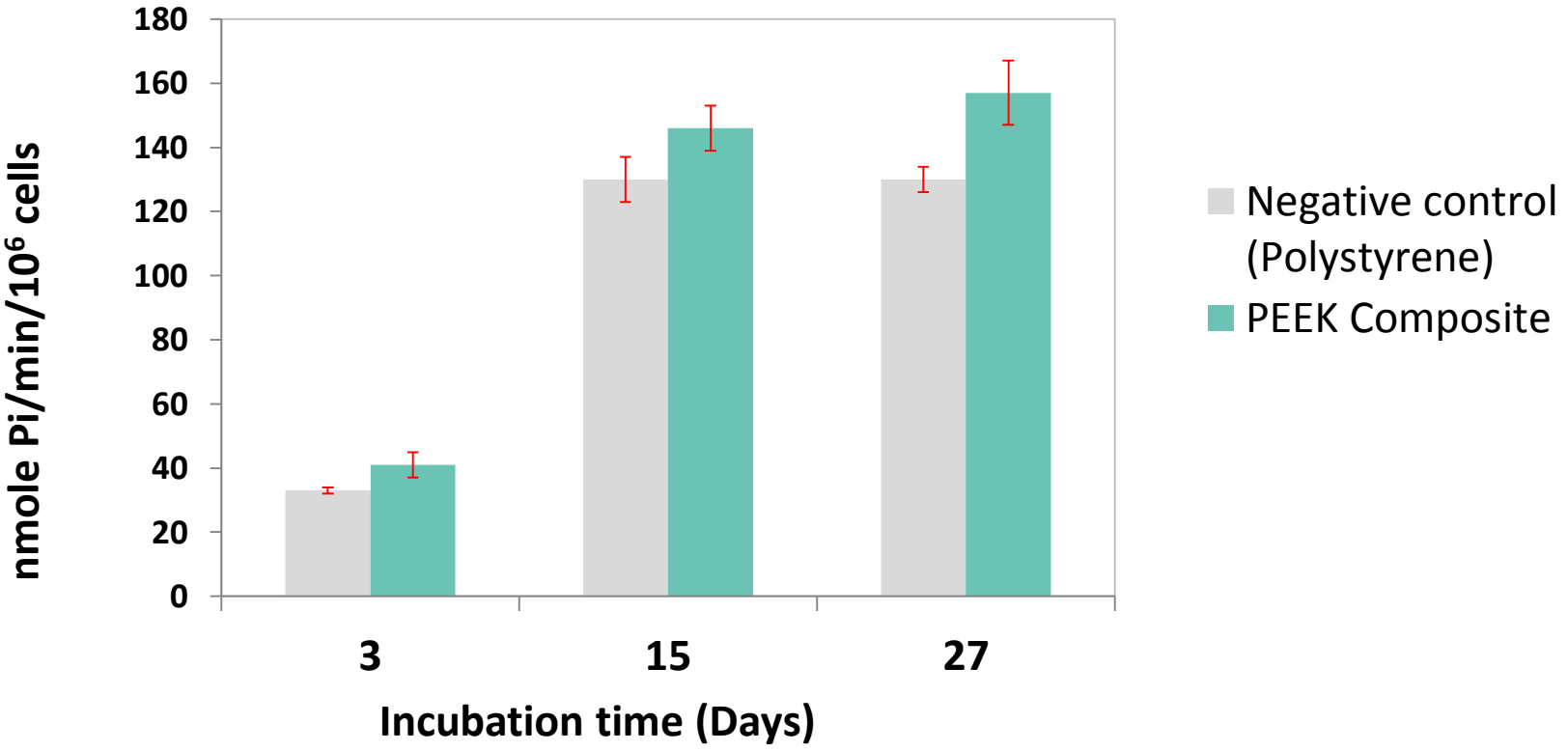
Cell proliferation (HAB)



A slight **increase** (+12 %, $P < 0.02$) in **cell adhesion** is observed with regards to negative control at 3 h.

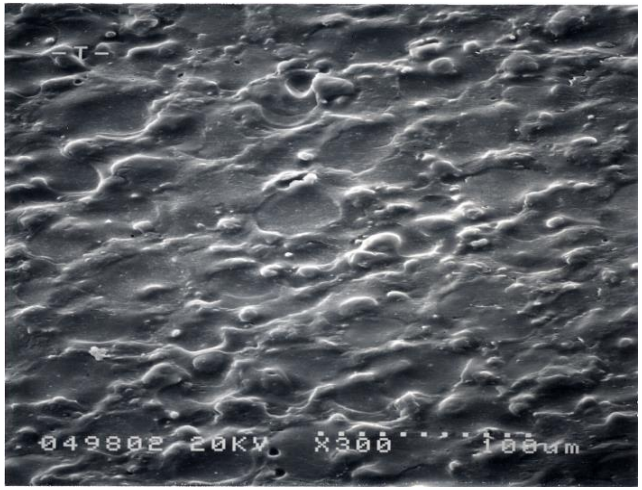
HAB proliferated better on the composite than on the negative control. At 27 days, cell density is 17 % ($P < 0.01$) higher than on the negative control.

Alkaline Phosphatase Activity (ALP)

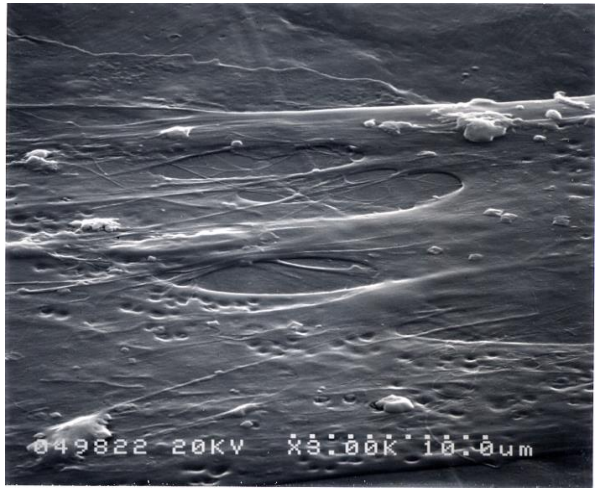


At 27 days a significant enhancement (+21 %, P< 0.01) of ALP activity, a specific enzyme of osteoblast differentiation, is observed.

Cell Adhesion by SEM

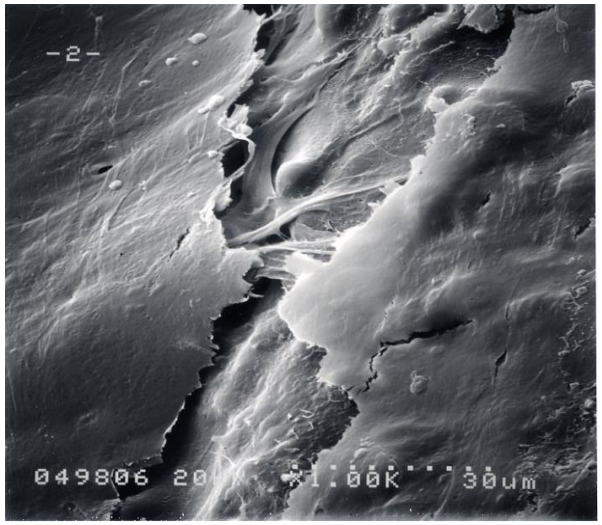


Surface State of PEEK / TCP / TiO_2



HAB at 3 days (x3,000)

HAB at 27 days (x300)



HAB at 27 days (x1,000)

To summarize,

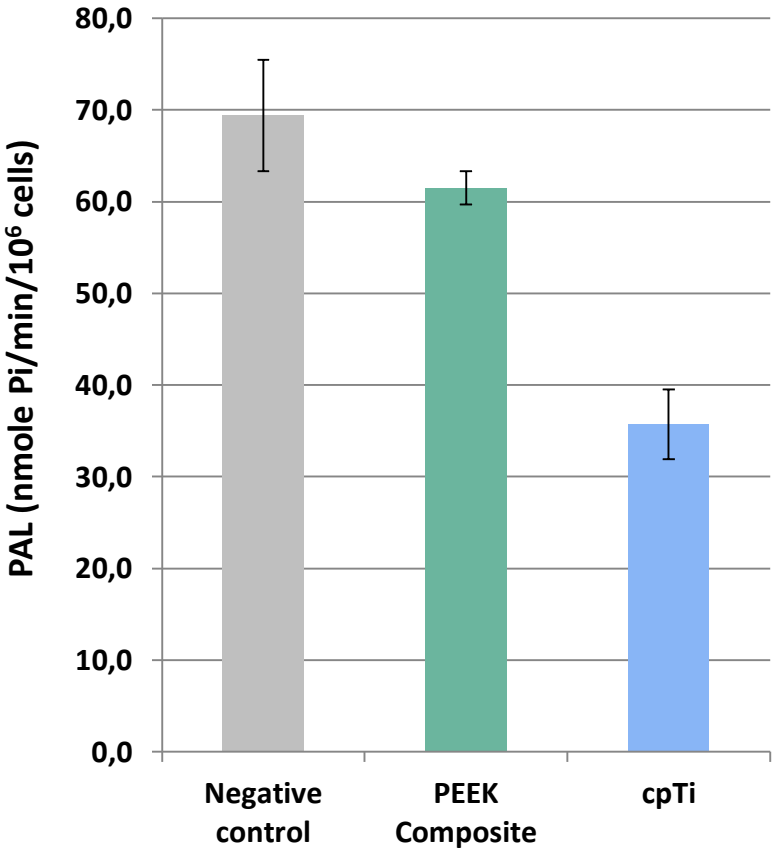
Human mature alveolar osteoblast adhesion, growth and phenotype expression (ALP) are slightly enhanced « in vitro » in direct contact with the composite suggesting a stimulation of osteoblast differentiation and an osteoconduction process « in vivo ».

Cytocompatibility study: Second study

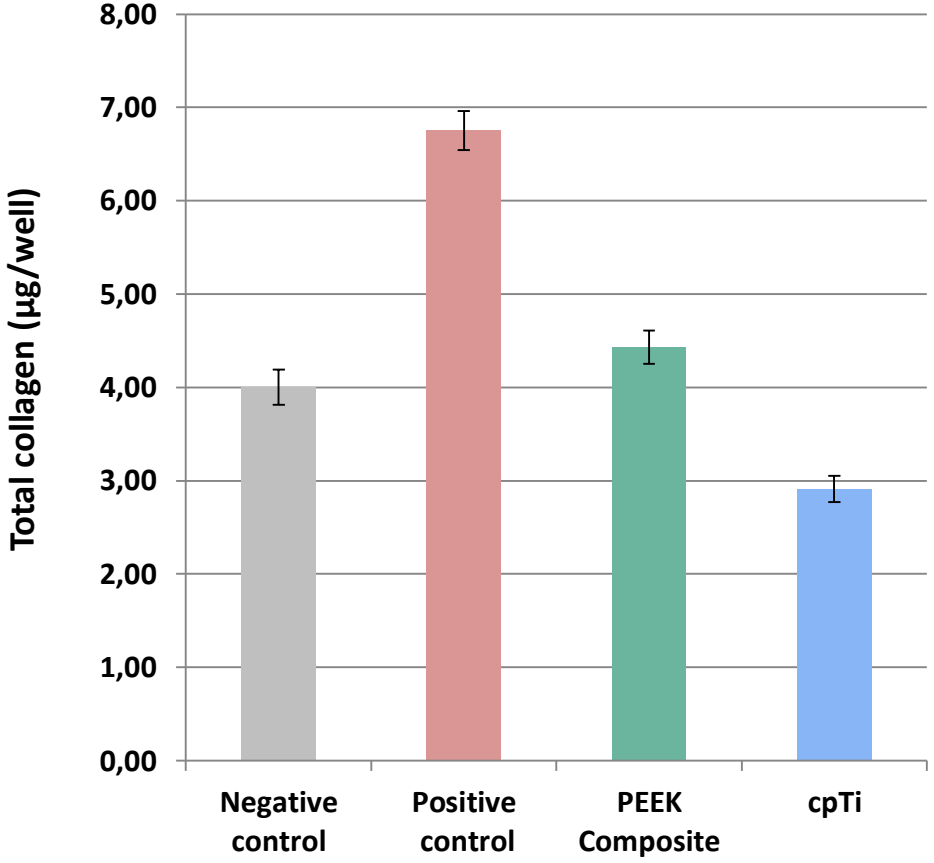
- **Purpose of the study :** evaluate *in vitro* whether osteogenic stem cell differentiation is stimulated, or inhibited, in direct contact with the test materials, cpTi (polished) or PEEK composite.
- **Test system :** Human mesenchymal stem cells from bone marrow (hBMS).

  hBMS are Bone Marrow Mesenchymal Stem cells which are the main contributors to bone healing through a differentiation process towards a mature osteoblast phenotype.
- **Protocol :**
  - Collagen synthesis (24 hours)
  - Alkaline Phosphatase activity (ALP) (24 hours)

Alkaline Phosphatase (ALP) Activity



Collagen synthesis



Human Bone Marrow Mesenchymal Stem cell (hBMS) differentiation is higher on PEEK composite than on cpTi. Alkaline Phosphatase Activity (ALP) is increased by 72 % ($P < 0.001$) and collagen synthesis (90 % of organic extracellular matrix) is increased by 52 % ($P < 0.01$).

To summarize,

Human bone marrow mesenchymal stem cells, seem to undergo a more effective differentiation process towards a mature osteoblast phenotype when cultured in direct contact with the PEEK composite than when cultured on Titanium.

This is highly favorable to bone healing and osteoconduction processes « in vivo ».

GENERAL CONCLUSION OF *IN VITRO* STUDIES

These *in vitro* studies suggest osteoconductive potential for this PEEK composite.

This is confirmed *in vivo* in the rabbit (bone implantation) and in the human (clinical application).

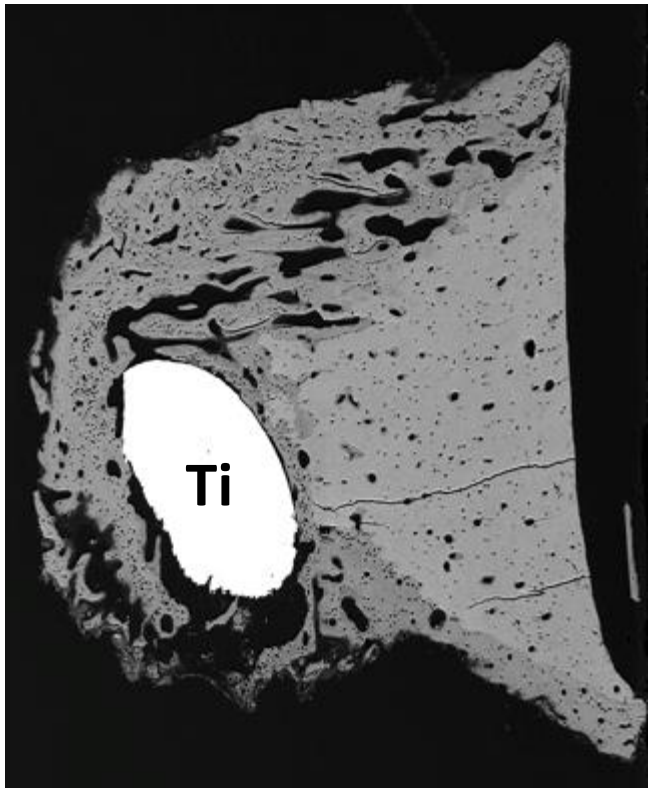
Second part
In vivo study in the Rabbit
(Bone implantation)

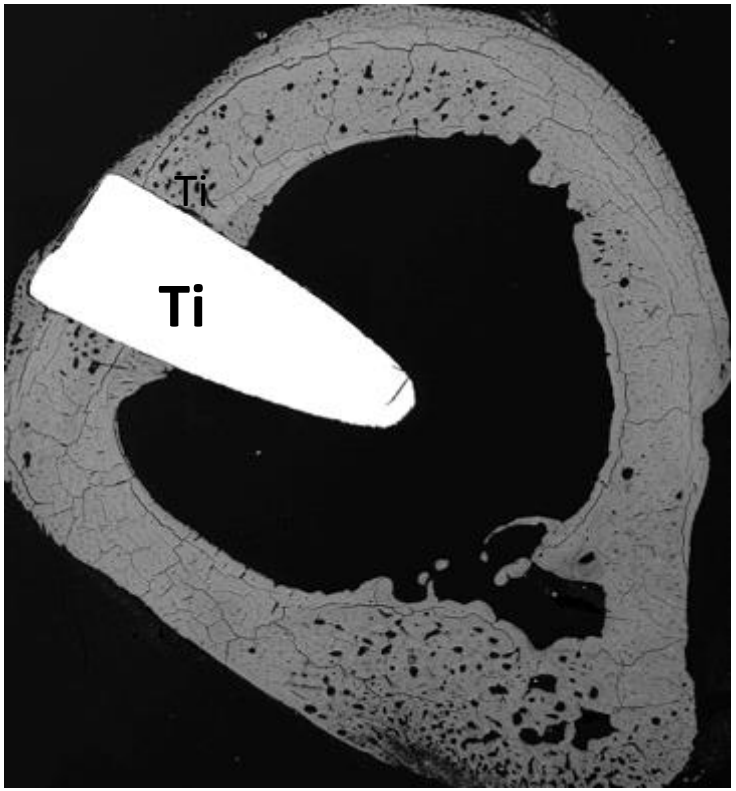
PROTOCOL

- Test materials : cpTi and PEEK composite (2 mm in diameter, 6 mm length).
- Test system : 15 New Zealand White Rabbits. 5 animals are sacrified at 4, 12 and 24 weeks.
- Press-fit insertion of test materials in drilled femoral diaphysis, perpendicular to the femur axis of rabbits.
- Preparation of the bone segments containing the implants for SEM analysis to characterize Bone to Implant Contact (BIC).
- Study performed at « Ecole Nationale Vétérinaire de Nantes ».

FEMORAL DIAPHYSIS IMPLANTATION (cpTi)

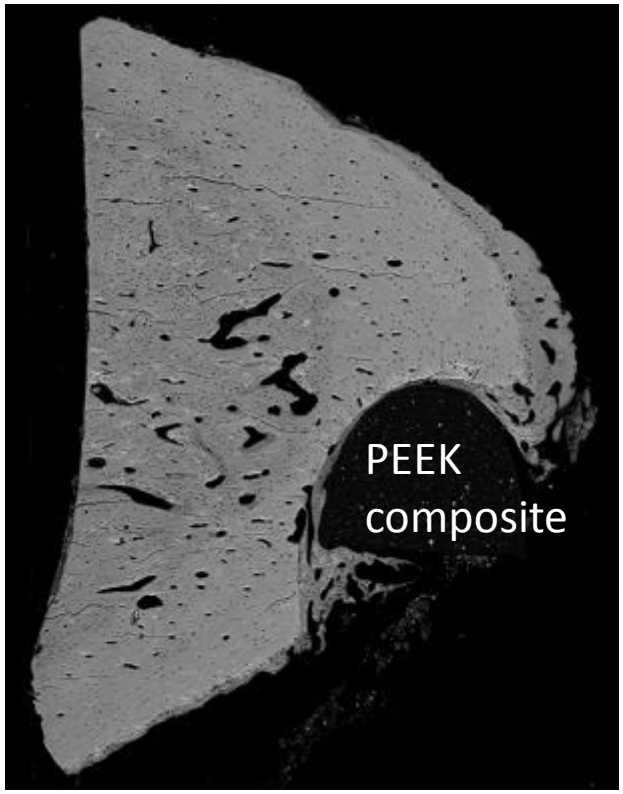
At 4 weeks, one can observe a new irregular bone layer in contact with the titanium implant. Histology (not shown) confirmed these results.

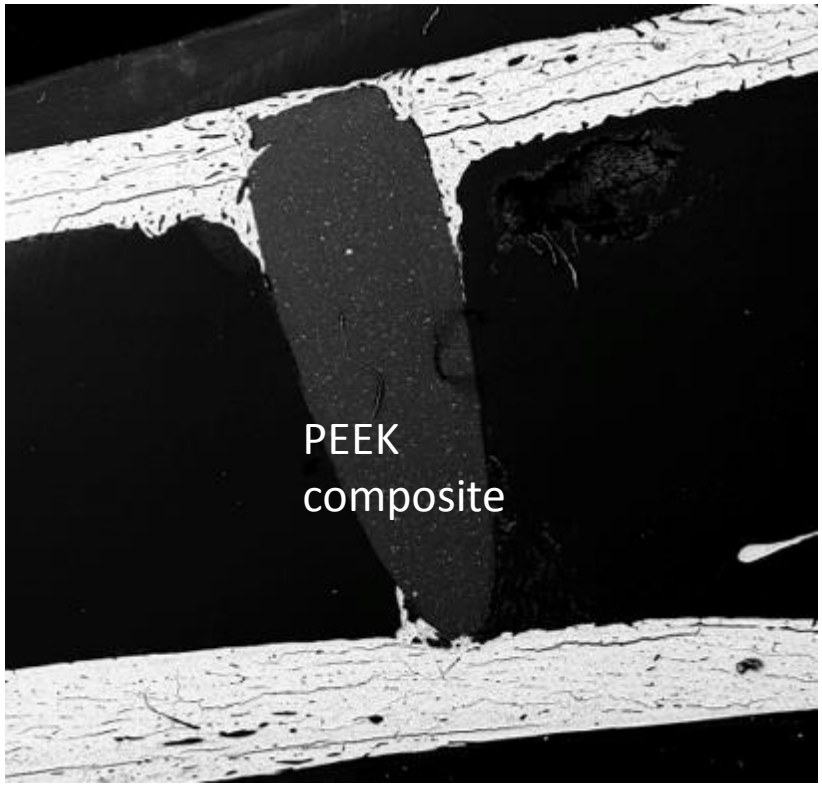




FEMORAL DIAPHYSIS IMPLANTATION (PEEK composite)

At 4 weeks, new bone tissue encircles the PEEK composite implant, filling the gap between the test material and the recipient bone (osteoconduction). Histology (not shown) confirmed these results. One can observe apposition by “invagination” of newly formed bone along the PEEK composite surface without any soft tissue interposition.





To summarize :

- comparable results are obtained for both PEEK composite and cpTi ;
- both PEEK composite and cpTi induced an increase in bone thickness in direct contact accompanied with apposition of woven bone (4w), thereafter lamellar bone along the implant surface (12w and 24 w).

However osteogenesis seems favorized in contact with PEEK composite.

These *in vivo* results confirm *in vitro* results and demonstrate the osteoconductive potential of PEEK composite.

Third part
Clinical aspects

CE marked Implants

2 types of implants :

- one-piece (monobloc) implants inserted by press-fit and designed depending on bone classification :
  - THETA → D1-D2
  - TAU →D3-D4
  - IOTA →any type of bone , and
- a two-pieces implant (PHI) inserted by press-fit and screwed by a quarter turn.

One-piece implants

THETA

TAU

IOTA

Two-pieces implant (PHY)

Healing cap

Abutment

BIOCOMPATIBILITY STUDY performed according to ISO 10993 (« Biological evaluation of medical devices – Part 1 : Evaluation and testing within a risk management process") showed that these implants meet the requirements of the standard.

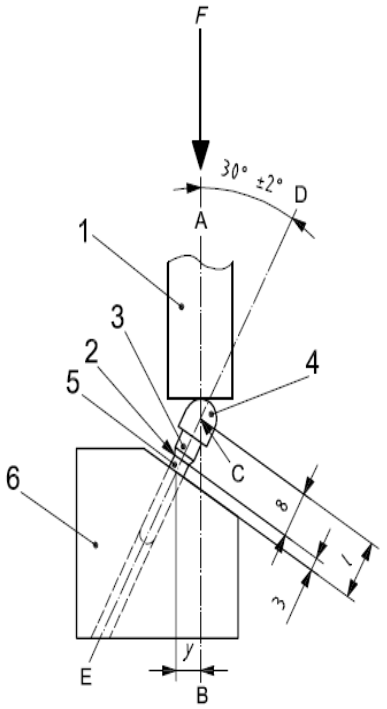
- Cytotoxicity (ISO 10993-5 : "Tests for *in vitro* cytotoxicity")
- Systemic acute toxicity in the mouse (ISO 10993-11 : "Tests for systemic toxicity")
- Intradermal irritation (ISO 10993-10 : "Tests for irritation and sensitization")
- Sensitization (ISO 10993-10 : "Tests for irritation and sensitization")
- Genotoxicity (ISO 10993-3 : "Tests for genotoxicity, carcinogenicity and reproductive toxicity") :
  - Ames test (OECD n° 471 : "Bacterial Reverse Mutation Test")
  - Chromosome aberrations using human lymphocytes (OECD n° 473 : "*In vitro* Mammalian Chromosome Aberration Test")
  - Sister chromatide exchanges using CHO cells (OECD n° 479 : "Genetic toxicology: In vitro Sister Chromatid Exchange Assay in Mammalian Cells")

Mechanical characterization

Implants were mechanically characterized by static and dynamic fatigue testing under « worst case » conditions,

This study was performed in compliance with ISO 14801 « Dentistry – Implants – Dynamic fatigue test for endosseous dental implants ».

Dimensions in millimetres



Key

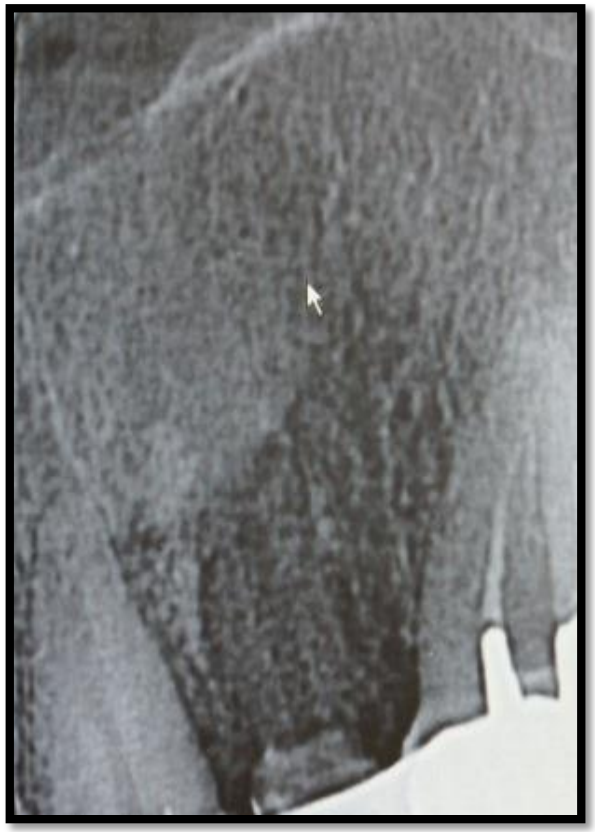
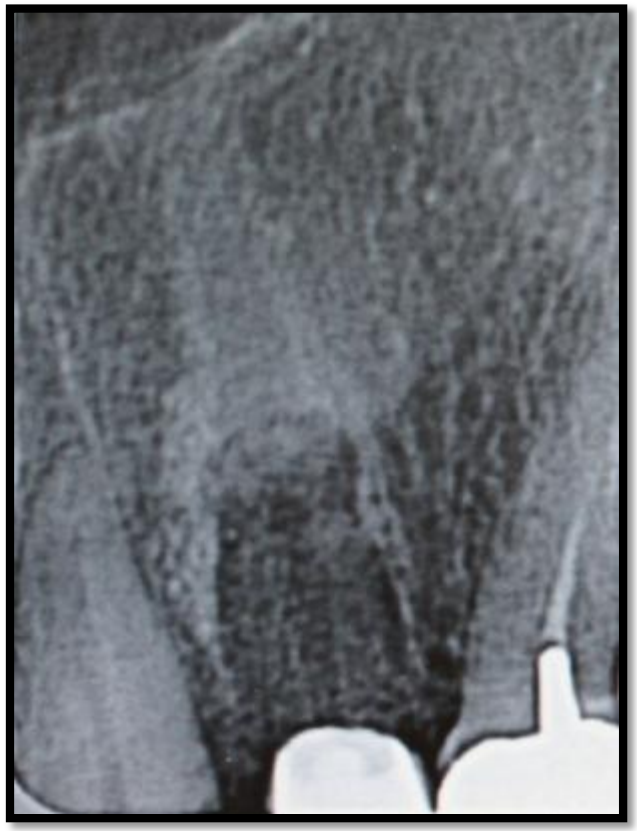
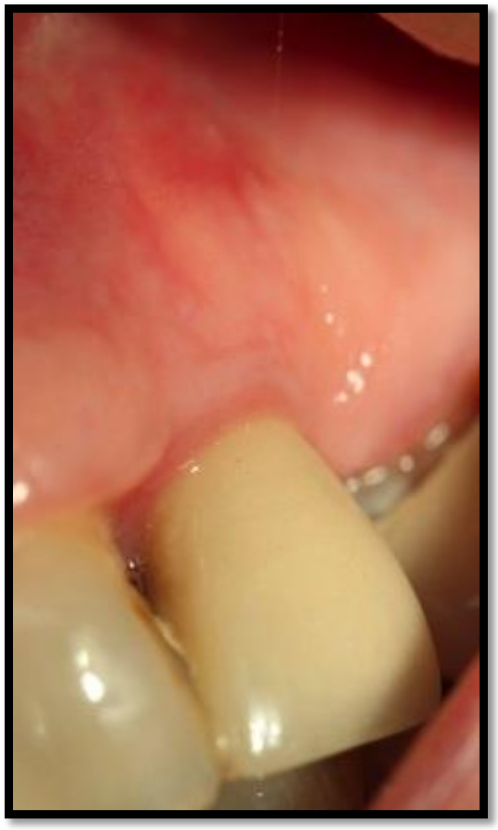
1 loading device [shall be allowed free movement transverse to loading direction (see 5.2.6)]
2 nominal bone level (see 5.3.2)
3 connecting part
4 hemispherical loading member
5 dental implant body
6 specimen holder

Figure 1 — Schematic of test set-up for systems with no pre-angled connecting parts

LNE (Laboratoire National d'Essai)
Report n° 91247-2014

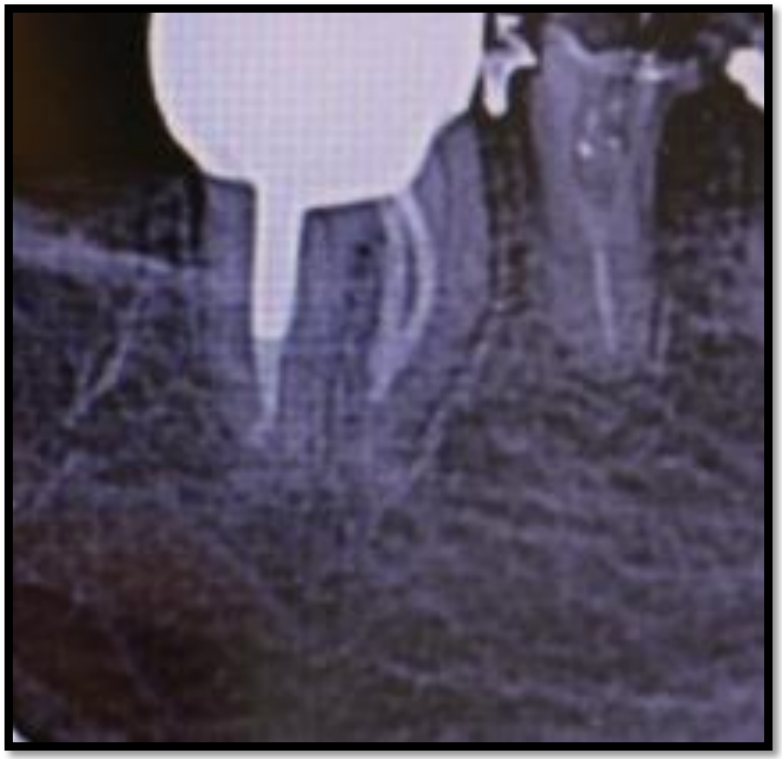
From ISO 14801

Three clinical cases

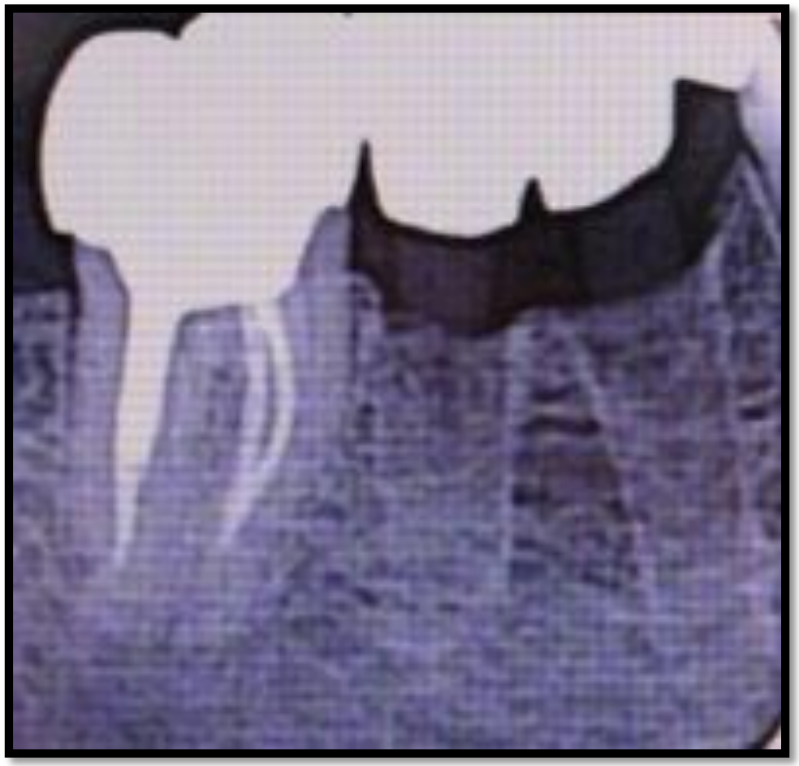




Case n°1 : **Because of implant radiolucency, clear visualization of surrounding tissues is obtained.**
Six month after the implantation one can observe cortical bone surrounding the whole surface of the implant.

Note the excellent biointegration and quality of peri-implant mucosa.

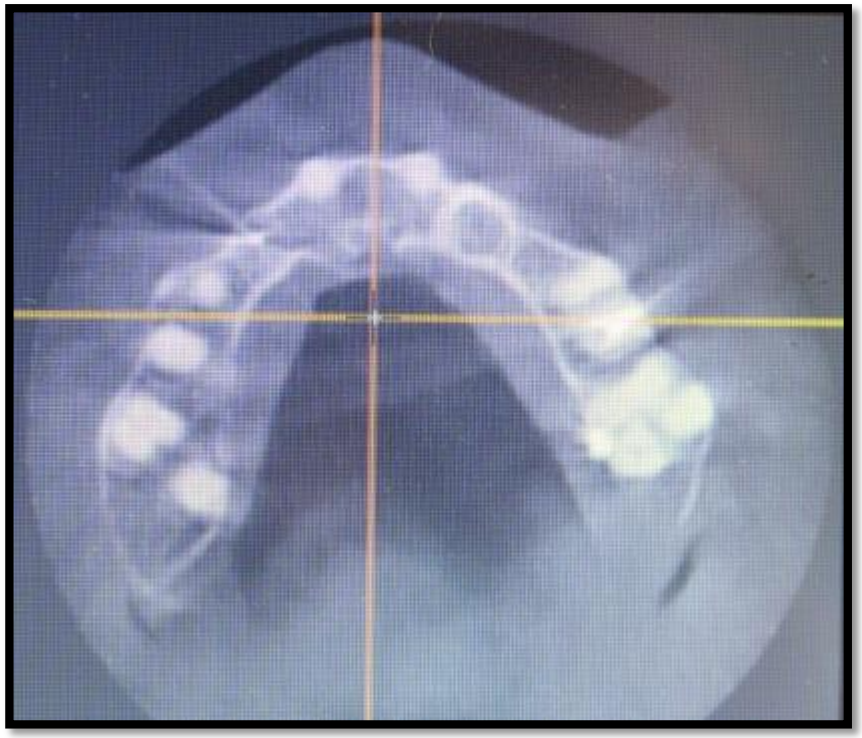


Before



6 month implantation

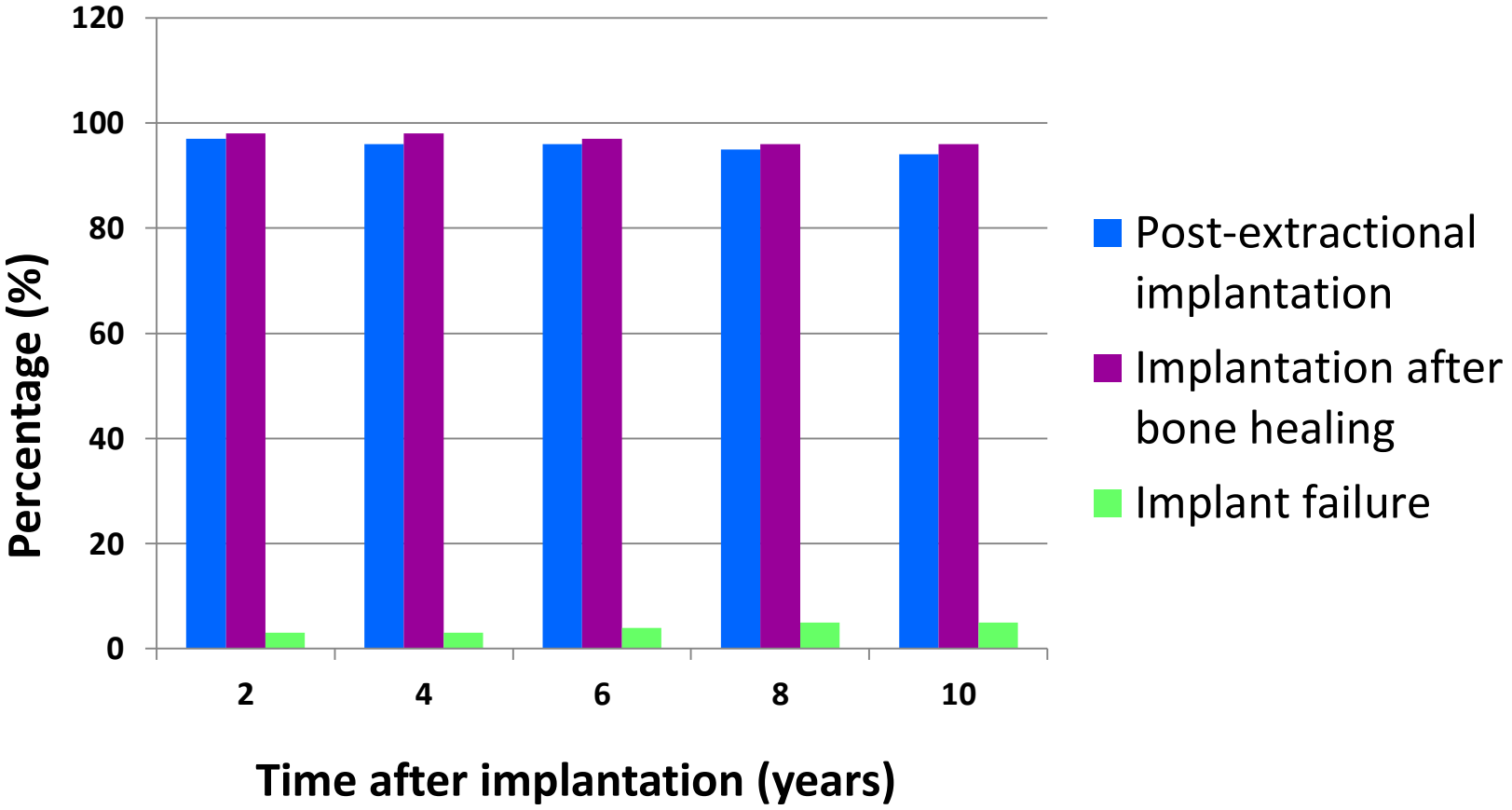
Case n° 2



3D vision of peri-implant bone

Case n° 3

A global retrospective clinical analysis



Ten-years retrospective follow-up study on 600 implants (PEI: 80% and HBI: 20%) showing the cumulated survival rate (%) for both post-extractional implantation (PEI), implantation after bone healing (HBI), and the percentage of implant failure (IF).

GENERAL CONCLUSION

Both *in vitro* and *in vivo* results presented here show obvious osteoconductive properties of PEEK composite.

These experimental results are confirmed by the successful development of a clinical application in the field of oral implantology.

Thank you for your kind listening