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BONE QUALITY SEMINARS: BONE FRACTURE HEALING AND STRENGTHENING

# Biomechanics and tissue engineering

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**Abstract** Development of artificial scaffold for musculo-skeletal applications, especially in load-bearing situations, requires the consideration of biomechanical aspects for its integrity and its function. However, the biomechanical loading could also be used to favour tissue formation through mechano-transduction phenomena. Design of scaffold could take advantages of this intrinsic mechanical loading.

**Keywords** Bone · Mechano-transduction · Orthopaedics · Scaffold · Stress

## Introduction

Every tissue of our body is affected by mechanical stress. This stress is transmitted to the cells in the tissues generating a biological reaction. At the level of the tissues, the structural support of our body relies mainly on the musculo-skeletal system. Biomechanics is then an important parameter to consider in tissue engineering and is capital if musculo-skeletal tissues are targeted. As illustration of the biomechanical principles in tissue engineering, we will focus on bone tissue engineering as both the aspects of biomechanics on the tissues and on the cells are important, the tissues giving the mechanical supports and the cells adapt the tissue for its mechanical function. The initial mechanical aspects are essential to the outcome of a functional tissue engineering approach, so are aspects of interface micromotion, bone ingrowths inside the scaffold and finally the mechanical integrity of the scaffold during its degradation. A proposed view is presented herein on how biomechanical aspects can be synthesized and in particular, a distinction is made between the mechanical and the mechano-transductional aspects in bone tissue engineering: the former could be related to osteoconduction, while the latter may be correlated to the osteoinductive properties of the scaffold. This distinction allows biomechanicians to follow a strategy in the development of a scaffold having not only mechanical targets but also incorporating some mechano-transduction principles.

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## Mechanical stress is present in every tissue of our body

Gravity, muscular contraction and fluid flow can all generate mechanical stress in the different constituents of our body, making mechanical stimulation a universal phenomenon to be considered in the physiology of any tissues. Especially for the musculo-skeletal system, its tissues support important loads and have then a structural role to play in the mechanical stability of our body. This is one reason why musculo-skeletal system is the most studied from a biomechanical point of view. In this manuscript, we will focus on bone tissue engineering aspect; nevertheless, the concepts developed are similar for other tissues having also a load-bearing function.

The influence of the loading on the evolution of the tissues' mechanical properties has been intensively described. In bone, this evolution process, called remodelling, was shown to be adequately described by correlating bone density evolution with mechanical stimulation, e.g. [1]. This knowledge has been used in the development of orthopaedic implants [2] and is still central for the improvement of implant outcome such

as for orthopaedic implant used as drug delivery system [3]. Biomechanical description of conventional implant has then demonstrated its usefulness and this kind of description would then probably find an ideal field of applications in the development of scaffold for tissue engineering.

At the level of the cells, the influence of mechanics is described under the denomination "mechano-biology" or equivalently "mechano-transduction", e.g. [4]. Mechano-transduction is the process by which the mechanical signal is transduced into a chemical reaction by the cells. Most of the cells demonstrate some sensitivity to mechanical stimulation. Obviously, as a clear correlation exists between the mechanical stimulus and the bone density, bone cells are very responsive to mechanical stimulation. For example, the effect of different regimes of fluid flow on bone cells has been studied and demonstrated that mechanical stimulation plays an important role [5]. In addition to effects obtained via fluid-mediated stimulation, stretching the surface on which the cells are attached can also induce bone cell differentiation [6]. This mechanical stimulus has been shown to be integrin mediated [7]. These examples highlight the two possible mechanisms—fluid flow and/or stretching of the cells through extracellular matrix deformation—by which cells may be mechanically stimulated. Unlike orthopaedic implant, development of scaffold for tissue engineering applications should then also consider mechano-transduction aspect in its development as the scaffold is designed to be colonized by cells which will be mechanically stimulated. It could be advantageous for the tissue ingrowths in the scaffold to optimize the mechanical load transmitted to the cells via the scaffold deformation.

The need for biomechanical studies is clearly justified when we consider, for instance, that the absence of mechanical loading could affect the osteoconduction of well-accepted biomaterials such as calcium phosphate granules [8]. Indeed, bone tissue engineering constructs promote more bone repair when dynamic loading is applied [9]. Biomechanical aspects in tissue engineering therefore become as important as biomaterial considerations.

From a general point of view, two aspects have been considered with biomechanical studies in bone tissue engineering: structural biomechanics and mechano-transduction. The former is related to the osteoconductive properties of the scaffold while the later concerns its potential osteoinductive properties.

## Biomechanical considerations in the development of scaffold for tissue engineering application

A scaffold developed for load-bearing situations must obviously sustain the stress it will be exposed to. Moreover, if the scaffold is supposed to be mechanically functional immediately after its implantation, the term functional tissue engineering has been coined for this kind of application [10]. In the design of a scaffold, the biomechanics is then central to insure its structural integrity.

In a first step, the tissue mechanical properties should indeed be well defined. For bone, this also includes morphological aspects such as bone permeability which directly affect interstitial fluid flow [11], bone anisotropy which is considered either as transverse isotropic or orthotropic [12] and hierarchical tissue organization which is described through a multi-scale approach [13].

The material properties of the tissues are but one part of the mechanical aspects to be taken into account. It is obvious that the particular loading condition also needs to be evaluated. Indeed, the loading condition is linked to the clinical application targeted. Applications for bone reconstruction often require scaffolds with a specific set of mechanical properties, which may vary greatly from one case to another. Revision procedures in total hip arthroplasty, tibial or femoral osteotomy and maxillo-facial situations are the most demanding in terms of scaffold biomechanics. In other applications, the load could be distributed between the scaffold and the implant or the external fixator. The required volume of the bone substitute varies between different applications; the largest defects usually arise following massive tumour resections. Important volumes may also be needed in osteotomy. In the case of tibial osteotomy for example, a biomechanical analysis was performed to define mechanical targets for scaffold development [14]. These targets were partially reached by developing a composite scaffold made of polylactic acid reinforced with micrometre calcium phosphate particles [15]. Many different scaffolds have been developed for bone tissue engineering but only a few have taken into consideration the mechanical aspect as a main design target. Usually, mechanical aspects are described only at the end of the development by quantifying the scaffold mechanical properties.

The aspects of scaffold incorporation were also mentioned in the definition of functional tissue engineering [10]. As for orthopaedic implant, the micromotions at the interface of the scaffold and the bone certainly play an important role in the scaffold incorporation. Excessive micromotion at the interface may mechanically impair the osteointegration of the scaffold [16]. Indeed, for aspects of scaffold integration, Brunski et al. proposed that biomechanics is more important than biomaterial properties per se [17].

Unlike metallic orthopaedic implants, which have an elastic modulus several orders of magnitude higher than bone, the amplitude of the micromotion at the interface of the scaffold and the bone is correlated to the scaffold mechanical properties as well as to its size [14]. Depending on the values of the micromotions, bone resorption can be induced [18] and a fibrous tissue may be produced around

the scaffold [19]. Biomechanical analyses could also be used to anticipate the tissue differentiation based on the knowledge of the micromotion values [20–22].

The major difference in the biomechanical analysis of conventional orthopaedic implants versus bone scaffolds is that the mechanical properties of the scaffold will change over time as its degradation occurs. The cornerstone of biodegradable bone scaffolds is that the decreased mechanical properties of the scaffold during its degradation will be compensated by the increased mechanical properties of the new bone formation inside the scaffold [23]. It would then be important to anticipate the degradation process with respect to the scaffold mechanical properties. We may imagine following similar theoretical developments as those proposed with bone remodelling driven by biomechanical parameters [1, 24], but applying this approach to scaffold remodelling. In this case, the scaffold remodelling will mean bone ingrowths in the scaffold and scaffold degradation. Experimental data on scaffold degradation will then be necessary. Indeed, most synthetic biodegradable polymers degrade by passive hydrolysis. They undergo bulk degradation, which leads to a sudden drop in mechanical properties without a change in the overall dimensions of the polymer. It will then be difficult to evaluate its biomechanical properties solely based on imaging data. Moreover, depending on the scaffold composition, its degradation time can range from weeks to years [23]. Obviously, only in vivo studies would be able to feed the parameters of a model for scaffold remodelling. Specific in vivo studies on the degradation aspect of bone scaffolds are almost non-existent and this point will certainly need to be further described in the future.

To tackle the mechanical aspects for bone tissue engineering, computer methods have been extensively used. One of the major questions which were addressed in these studies concerns the mechanical integrity of the scaffold used in loaded situations. For example, Brazel and Taylor extended a technique used to predict fatigue failure in metal and composites and applied it for bone graft material [25]. The results showed that graft materials with much lower mechanical properties than cortical bone could sustain the physiological loads due to a reduction of local stress concentration. Computational analysis could also be used to evaluate the mechanical properties of custom-made scaffolds and verify that targeted values are obtained [26].

## Mechano-transduction considerations in the development of scaffold for tissue engineering application

While it is clear that the mechanical aspects are essential for the clinical success of a bone scaffold, bone ingrowths in the scaffold is necessary, a factor that does not come into play for metallic implants. The "remodelling" of the scaffold should finally lead to a complete healing of the treated bone. Bone ingrowths are driven by cells from the host. It is therefore evident that the effect of biomechanical stimuli on cells due to the scaffold deformation has to be taken into account. As mentioned by Sikavitsas et al., apart from the biochemical strategy which mostly relies on the addition of growth factors and the selection of ideal osteoconductive and biodegradable materials for the scaffold, mechano-transduction could be used to control the proliferation and differentiation of bone cells [27]. This point has also been observed by Klein-Nulend et al. who stated that "in bone tissue engineering, it is essential to understand how mechanical conditions affect the formation of bone matrix components by the cells at a local level in order to generate tissues which will be functionally appropriate" [28].

As for mechano-transduction studies, it has been proposed that fluid flow and its corresponding transport-induced process are important mechanical aspects to be considered in the development of bone scaffolds [11]. Despite all these results, most of the gathered mechano-transduction knowledge has been used only for the development of bioreactors to optimize in vitro tissue formation in scaffolds [29]. Rotating bioreactors have been designed to increase mass transfer by inducing dynamic flow conditions in culture [30]. Fluid shear stress generated in a flow perfusion bioreactor was used as an osteoinductive factor on mesenchymal stromal cells [31]. Other mechanical stimulations, such as strain induced by a scaffold subjected to a four-point bending, induced the osteogenic differentiation of mesenchymal stromal cells [32]. These bioreactor studies also brought new insight in our understanding of the mechano-transduction phenomena and could ultimately translate in scaffold design with mechanical properties allowing "osteoinductive fluid flow" in the scaffold.

Biomechanical numerical studies are more and more used in the development of scaffold, capitalizing on the knowledge accumulated in orthopaedic implant. Using this tool, one of the most rational targets for a scaffold development would probably be to mimic the native bone strain. Following this idea, μCT measurement and finite element method could be used to develop a scaffold for which the strain histograms for scaffold and native trabecular bone under the same loading conditions must be similar. Osteogenic loading conditions for bone tissue engineering should then be obtained [33]. By combining finite element methods with computational fluids dynamics, it could be possible to optimize the level of compression and strain rate applied on a scaffold to favour osteogenesis [34]. Computational models also allowed describing the

large difference in cell wall shear stress induced by fluid flow either between different scaffolds or even in the same scaffold presenting an inhomogeneous pore diameters distribution [35]. Another approach proposed by Prendergast consists in applying a mechano-regulation algorithm which drives the tissue differentiation by taking into account the mechanical properties of scaffold for an osteochondral defect [36].

In addition to mechano-transduction aspects, other factors such as nutrient transport, cell adhesion and migration or cell-scaffold mechanical interactions can be considered in different computational modelling [37].

## Biomechanical signal use to drive a tissue formation in a scaffold

The example given in this manuscript on incorporating biomechanical knowledge for bone tissue engineering could be adapted to other tissues. In fine, the ideal situation would, through mechanical considerations, confer bioactivity (osteoinductivity for bone) to a synthetic scaffold in order to reduce the dependency of this material on growth factors or drugs. If the developed scaffold can induce by itself tissue ingrowths due to the incorporation of mechano-transduction concepts in its development, an off-the-shelf product could be obtained. This would obviously allow avoiding the burden of the regulatory affairs related to bioreactors or biological products [38] as well as facilitating the translation of the developed scaffold into clinical practice.

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