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Interrelationship between bone substitution materials and skeletal muscle tissue

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SUMMARY

Bone density and quantity are primary conditions for the insertion and stability of dental implants. In cases of a lack of adequate maxillary or mandibulary bone, bone augmentation will be necessary. The use of synthetic bioactive bone substitution materials is of increasing importance as alternatives to autogenously bone grafts.

It is well known that bone can influence muscle function and muscle function can influence bone structures. Muscles have a considerable potential of adaptation and muscle tissue surrounding an inserted implant or bone surrogate can integrate changes in mechanical load of the muscle and hereupon induce signaling cascades with protein synthesis and arrangement of the cytoskeleton.

The Musculus latissimus dorsi is very often used for the analyses of the in vivo biocompatibility of newly designed biomaterials. Beside macroscopically and histologically examination, biocompatibility can be assessed by analyses of the biomaterial influence of gene expression.

This review discusses changes in the fiber type distribution, myosin heavy chain isoform composition, histological appearance and vascularization of the skeletal muscle after implantation of bone substitution materials. Especially, the effects of bone surrogates should be described at the molecular-biological and cellular level.

1. Introduction

After blood, bone is the most commonly transplanted tissue. Worldwide, 2.2 million grafting procedures are performed annually to repair bone defects in orthopaedics, neurosurgery, and dentistry (Giannoudis et al., 2005). The increasing number of grafting procedures and the disadvantages of current autograft and allograft treatments drive the quest for alternative methods to treat bone defects. The use of synthetic bioactive bone substitution materials is of increasing importance as an alternative to autogenous bone grafts.

Biomaterials can be applied for tissue engineering; the tissue response to these materials has been evaluated. Therefore, it is important to analyze how the newly formed tissue integrates with the synthetic scaffold and to what extent the implanted scaffold causes a foreign body reaction. Furthermore, the biocompatibility of a scaffold or matrix for a tissue engineering product refers to the ability to perform as a substrate that will support the appropriate cellular activity, including the facilitation of molecular and mechanical signaling systems, in order to optimize tissue regeneration, without eliciting any undesirable local or systemic responses in the eventual host (Williams, 2008). The tissue response to biomaterials depends on a variety of factors, including the physical–chemical properties of the implant, reactivity (bioactive or inert), surface texture, biodegradability/bioresorbability, as well as the duration and site of implantation (Pieper et al., 2000; Burugapalli and Pandit, 2007; Kunert-Keil et al., 2013). It is well known that bone can influence muscle function and muscle function can influence bone structures. The stomatognathic system is a functional unit characterized by several structures: skeletal components (maxilla and mandible), dental arches, soft tissues (salivary glands, nervous and vascular supplies), temporomandibular joint and masticatory muscles (Fig. 1) (Schumacher, 1991; Gedrange and Loster, 2008). These structures act in harmony to perform different functional tasks (speaking, chewing, and swallowing).

Muscles and bones interact mechanically and functionally with each other, not only in the craniofacial area, but throughout the entire body. Wolff's (1995) law describes that both the external shape and internal structure of the bone depend on the stress placed

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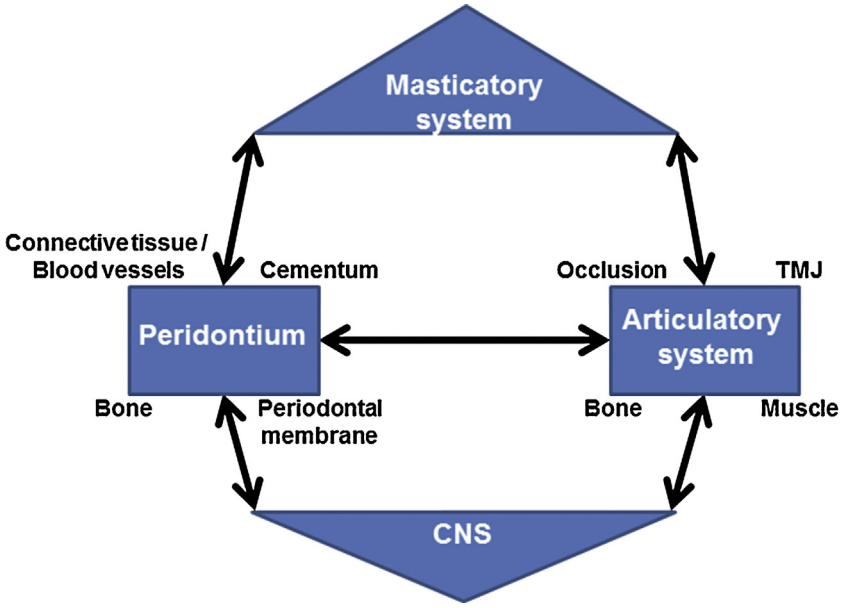

Fig. 1. Schematic illustration of the stomatognatic system. TMJ = temporomandibular joint, CNS = central nervous system.

on the bone by the musculature. This means that an increase in muscle mass results in stretching of collagen fibers and periosteum at the interface with subsequent stimulation of local bone growth. From clinical observation, it is known that patients with weak masticatory muscles usually have a long face with a small posterior face height and a large lower face height (Sassouni, 1969). Furthermore, it has been shown that osteoporosis is dependent, among other things, on decreased muscle mass and impaired muscle function (Kaji, 2014).

Muscles are known to have a considerable potential of morphological and neural adaptation (Fluck, 2003; Coffey and Hawley, 2007). Neural adaptations occur rapidly and are followed by hypertrophic adaptations. Muscular tissue can transfer changes in mechanical load to the muscle and hereupon induce signaling cascades with protein synthesis and subsequently a re-arrangement of the cytoskeleton (Booth and Gollnick, 1983; Kjaer, 2004). Changes can occur at the level of (i) structure, e.g., changes in fiber size; (ii) myosin heavy chain isoform; (iii) metabolism, e.g. activity of oxidative enzymes; (iv) capillarity and/or (v) function, e.g. force production, speed of contraction/relaxation as well as resistance to fatigue (Folland and Williams, 2007). The major morphological and neural adaptations include (1) an increase in muscle cross-sectional area and in the proportion of noncontractile tissue such as collagen (muscle hypertrophy) (Folland and Williams, 2007) as well as (2) improvements in motor unit activation, firing frequency, and synchrony of high-threshold motor units (Egan and Zierath, 2013). Even though muscle fiber type distribution is genetically determined during development, muscle adaptations are reflected by changes in contractile protein and function, so called adaptive transformation (Adams et al., 1993; Widrick et al., 2002). Otherwise, human skeletal muscle is predominantly composed of mature muscle fibers (multinucleated, post-mitotic), which have no regeneration capability. Furthermore, a small percentage of quiescent myogenic progenitor cells, capable of muscle regeneration were found in mature skeletal muscle (Alameddine et al., 1989).

This review discusses changes in the fiber type distribution, myosin heavy chain isoform composition, histological appearance and vascularization of the skeletal muscle after implantation of bone substitution materials. Especially, the effects of bone surrogates are to be described at the molecular-biological and cellular levels.

2. Tissue response—Histological examinations

Host reactions following implantation of biomaterials include injury, blood–material interactions, provisional matrix formation, acute and/or chronic inflammation, granulation tissue development, foreign body reaction, and fibrosis/fibrous capsule development (Anderson, 2000, 2001; Gretzer et al., 2006; Luttikhuizen et al., 2006).

Vascularization is an essential factor for tissue engineered constructs as it determines the extent of blood supply, which determines oxygen, nutrient and waste product exchange within the host tissue infiltrating the scaffold. Angiogenesis (neo-vascularization) associated with implanted biomaterials is dependent on at least three factors: the bioactive nature of the scaffold, the extent of porosity, pore interconnectivity, and the metabolic activity of the infiltrating host tissue (Burugapalli and Pandit, 2007). Besides, an increase in macrophage population/activity has been reported to increase vascularization (Censi et al., 2011).

Skeletal muscle cells are able to interact with bone substitution materials. It has recently been shown, that myoblastic cell lines, such as mouse myoblasts C2C12 and embryonic rat myocardium cells H9c2, can proliferate and differentiate on nanofibrous poly(3)hydroxybutyrate (PHB) scaffolds, as well as PHB films (Ricotti et al., 2011, 2012). The reaction of the skeletal muscle tissue to intramuscular insertion of polymeric PHB implants was expressed in a transient post-traumatic inflammation and the formation of a fibrous capsule. Macrophages and foreign-body giant cells with a high activity of acid phosphatase as well as no acute vascular reaction were also detectable (Shishatskaya et al., 2004). After intramuscular injection of resorbable PHB microparticles, a slight inflammatory reaction and pronounced progressive macrophage infiltration were found, but without any formation of a fibrous capsule around the microparticles, neither necrosis nor other adverse morphological changes (Shishatskaya et al., 2007). Mai et al. (2006) could show that PHB and hydroxylapatite (HA) implants were surrounded by a very thin fibrous capsule,