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Sensing technologies for monitoring of bone-health: A review

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ABSTRACT

Osteoporosis is still a serious concern in most countries and it is increasing with the aging population. Early detection of bone loss is important to successfully manage the disease. Monitoring the bone turnover markers can be helpful in early detection, diagnosis and monitoring bone disorders and deciding on medication and treatment. Different gold standard techniques are available for accurate and reliable measurement of bone remodeling and bone mineral density which indicate the health of bones. However, they are expensive, time-consuming and need expertise. In order to overcome these concerns, newer methods are being developed and it is greatly desirable to design and fabricate bone biosensors which are low-cost, portable and easy to use. This paper gives an overview of the available biochemical markers of bone turnover and focuses on the recent advancements in bone biosensing technologies for monitoring bone biochemical markers as well as the biomechanical assessment of bone.

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1. Introduction

Osteoporosis is a disease that reduces the strength and density of bones and makes them more porous and brittle. Usually there are no symptoms of the disease before the first fracture happens. Osteoporosis is increasingly growing among the elderly and has conspicuous impacts on individuals as well as health economics [1–5]. All over the world, one out of three women and one out of five men over the age of fifty will encounter osteoporotic fractures in their life [6].

Bone metabolism is a dynamic remodeling procedure, including the resorption of old bone and the formation of new bone. The activity of osteoclasts, osteoblasts and osteocytes significantly affects the resorption, formation and maintenance of bones, respectively [7–9]. Bone resorption and bone formation are normally kept in a good balance and this balance is controled and modulated through the activity of the steroid hormones and local mediators such as cytokines [10]. Osteoporosis usually occurs when bone loss outruns the formation of new bone [11].

Bone strength can be dependent on different biomechanical factors such as force, displacement and energy absorption and is affected by bone size, shape and properties of bone tissue. Biomechanical assessment of these factors verify the biomechanical properties of bone, such as strength, toughness, stifness, fatigue and creep properties. Biomechanical assays can be employed at various loading conditions such as shear, tention and binding, and different techniques can be used to assess biomechanical performance of bone [12,13].

The diagnosis of osteoporosis is normally made using a measurement of bone mineral density (BMD). Currently, dual-energy X-ray absorptiometry (DEXA) is the gold standard to assess the BMD and bone remodeling procedure. However, BMD studies have undeniable limitations. The technology is costly and requires at least 2–3 years to observe bone loss. Thus, an instantaneous measurement of bone metabolism is essential [14–16].

Biochemical markers of bone turnover can provide a real-time evaluation of the bone remodeling process and can be used in the management and monitoring of bone diseases such as osteoporosis [17].

In this paper, an overview of the available biomarkers of bone turnover will be introduced and existing biosensors for the monitoring of bone strength, as well as the bone mechanism, will be discussed.

2. Biochemical markers of bone turnover

Bone markers, generated during various stages of remodeling, indicate any variations in bone remodeling. Biochemical markers of bone turnover (BMBT) are fragments of bone-tissue enzymes or proteins, usually measured in blood or urine, and indicate the bone metabolism [18–20]. BMBT are usually classified into two main categories: biochemical markers of bone formation and biochemical markers of bone resorption.

2.1. Biochemical markers of bone formation

2.1.1. Alkaline phosphatase (AP)

Alkaline Phosphatases (APs) are enzymes in the cell membranes of osteoblasts. The total AP consists of different isoforms, produced from several tissues: liver, bone, intestine and kidney [21–23]. Bone-specific AP (BAP) is produced by osteoblasts during the bone formation process and therefore is a significant biomarker of bone formation action. Clinically, measurement of BAP is increasingly preferred due to the high specificity [24–26]. BAP levels in men stay comparatively stable throughout their life, whereas BAP levels in women rise around menopause [27]. BAP measurement assays are prevalent, widely accessible and commonly used in clinical assessment of osteoporosis treatments [28–30].

2.1.2. Osteocalcin (OC)

Osteocalcin (OC) is a comparatively small non-collagenous protein comprising of vitamin K and glutamic acid residues, produced by osteoblasts and odontoblasts [31–33]. The lowest OC levels in men are observed in the mid years and increase afterwards in life. The levels of OC in women follow the same pattern to BAP levels with a notable growth in the premenopausal time [27,34]. OC is counted as a particular biomarker of osteoblast activity [35,36]. After being released from osteoblasts, the largest part of the newly produced OC integrates to the bone matrix. A small fragment is released into the circulation where it can be measured by immunoassays [37,38].

2.1.3. Propeptides of type I procollagen (PICP & PINP)

The peptides of procollagen type I are extracted from type I collagen. Type I collagen forms 90% of the organic matrix of bone and is produced as a procollagen molecule. This molecule includes amino-terminal as well as carboxy-terminal peptides (PICP and PINP). These peptides are divided and released into the circulation and therefore can be considered as markers of bone formation. Fig. 1 depicts the schematic representation of type I procollagen propeptides.

2.1.4. Biochemical markers of bone resorption

Excluding tartrate-resistant acid phosphatase, most of the bone resorption markers are produced from bone collagen, as shown in Fig. 2. Recently, the non-collagenous markers of bone resorption such as bone sialoprotein and osteoclast-derived have been studied as well [10].

2.1.5. Hydroxyproline

Hydroxyproline (OHP) is an amino acid produced from the post-translational hydroxylation of proline. It forms 13–14% of the total amino acid content of collagen and is also found in some other tissues such as skin and cartilage [40]. The majority of bone OHP is fragmented to free amino acids that are processed by the kidney and then oxidized by the liver, therefore only 10–15 % releases into the urine. About 90% of OHPs are in the form of peptides, a small

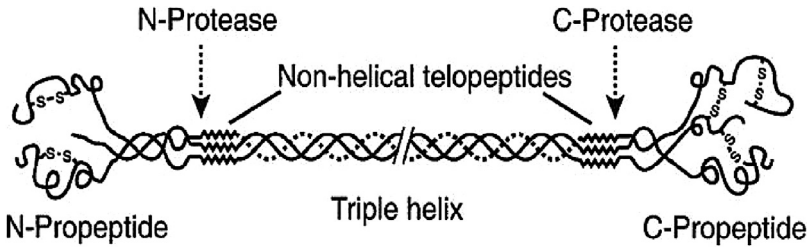

Fig. 1. Schematic representation of type I procollagen Propeptides [10].