THE EFFECT OF BONE QUALITY ON OSTEOCLASTIC BONE RESORPTION

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An Abstract of a Thesis Submitted to the Graduate

Faculty of Rensselaer Polytechnic Institute

in Partial Fulfillment of the

Requirements for the Degree of

DOCTOR OF PHILOSOPHY

Major Subject: BIOMEDICAL ENGINEERING

The original of the complete thesis is on file
in the Rensselaer Polytechnic Institute Library

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May 2010
(For Graduation May 2010)

ABSTRACT

It is well documented that fracture risk increases with age and decreasing bone density. In particular, osteoporotic fractures pose a hefty burden to the health system. Specifically, osteoporosis associated costs are anticipated to reach $25 *billion* dollars in the United States by 2025. Unfortunately, Dual energy X-ray absorptiometry (DEXA) and bone mineral density do not fully predict a patient's fracture risk, despite being the golden standard of the field.

Previous studies have examined the effect of bone quality on fracture risk. However, the majority of the work has only investigated the effect of bone quality on the material properties of bone. It is likely that changes in bone quality may also affect osteoclastic bone resorption. As a person ages, bones remodel to maintain calcium homeostasis and repair microdamage. Remodeling alters the distribution of new (osteonal) and old (interstitial) bone. With this alteration comes a change in the distribution of two key proteins - osteocalcin and osteopontin. In addition, all proteins - both collagen and non-collagenous proteins - undergo different post translational modifications.

To address the above issues, the goal of this doctoral research is to examine the role of bone quality in osteoclastic bone resorption. Specifically, the effects of microstructure (including the cement line), tissue age (such as interstitial vs. osteonal), post translational modifications (glycation and phosphorylation), availability of mesenchymal stem cells, and protein content were investigated through both *in vitro* and *in vivo* resorption studies.

In vitro bone resorption studies demonstrate that bone quality affects and directs osteoclastic bone resorption. First, the microstructure of the bone influences osteoclastic resorption. In particular, the cement line acts as a barrier to osteoclastic bone resorption. Non-collagenous proteins, especially osteopontin, modulate this effect. The post-translational modification state of the proteins within bone also affects bone resorption: an increase in post-translational modifications, including phosphorylation and glycation of bone proteins, results in a decrease bone at-

tachment, and subsequently, resorption. Osteoclasts also preferentially resorb older interstitial bone, which contain remnants of cement line.

When osteoclast precursors are cultured with human mesenchymal stem cells, a decrease of the mesenchymal stem cells - akin to the decrease in stem cell number seen with aging - results in increased differentiated osteoclasts. This effect is contact-mediated, and mimics the *in vivo* environment where osteoclast precursors and mesenchymal stem cells are likely to be in contact.

In conclusion, this dissertation presents several aspects of bone quality and their adverse effect on osteoclastic bone resorption.