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学 位 論 文 要 旨

ABSTRACT

In this study, a theoretical model of mechanical bone adaptation which was applicable to normal bone remodeling, abnormal bone remodeling with metabolic disease and healing of bone traumata had been developed. Moreover, theoretical models of adaptive bone remodeling with new concept were proposed. One was a model considering fluid flow effect inside bone, and another was a model using the cellular automata to represent autonomic and dynamic activity of the bone cells. These theoretical models were compared in viewpoint of their advantages and disadvantages, then limitations and potentialities were considered.

INTRODUCTION

The mechanical adaptive bone remodeling is a phenomenon in which bone changes the morphology itself adapting mechanical environment. It is a very important factor in medical treatments of orthopaedic surgery such as fracture fixation, grafting reconstruction or prosthesis replacement. Theoretical studies of the adaptive bone remodeling are useful for the treatments expecting bone recovery after the operation. Although a large number of the theoretical studies have been carried out before, almost all of them have been limited to the normal bone remodeling. In order to apply the theory to clinical problems with bone healing or disease, it is required to improve on the adaptive remodeling theory to be applicable to abnormal remodeling situations. In this study, a theoretical model of mechanical bone adaptation which was applicable to normal bone remodeling, abnormal bone remodeling with metabolic disease and healing of bone traumata were developed.

The adaptive bone remodeling theory has some limitations. For example, it can not describe time depending non-linearity and complexity of bone formation. One of key point in developing a new adaptive remodeling theory is how the bone cell activity and its related factors are introduced into the theory. In the latter half of this study, theoretical models of adaptive bone remodeling considered the bone cell activity and their environment were proposed, and their capability was discussed.

GENERALIZED THEORY OF STRESS-INDUCED BONE FORMATION

In the bone remodeling process, old bone tissues are resorbed by osteoclasts and new bone tissues are created by osteoblasts. Bone structure is maintained by balance between the basal bone resorption and deposition in the normal remodeling. In generalized theory of stress-induced bone formation proposed here, it was assumed that the balance between basal bone deposition and absorption was changed depending on metabolic condition. Relationship between separated bone apposition and resorption with stress stimulus are shown as dotted curve in figure 1. r^+ and r^- are substantial bone apposition and resorption ratio per day. Total bone apposition and resorption ratios are given by summing up r^+ and r^-. It is assumed that the substantial apposition ratio is constant (r_0^+) when the stress stimulus is low and increases proportionally as the stress stimulus is higher. The substantial resorption ratio is assumed vice-versa. The bone healing with active bone formation is expressed by a state in which basal bone apposition ratio (r_0^+) is larger than basal bone resorption ratio (r_0^-) in the theoretical model. On the other hand, the osteoporosis situation with inactive bone formation or active bone resorption is expressed by assumption of larger basal bone resorption ratio.

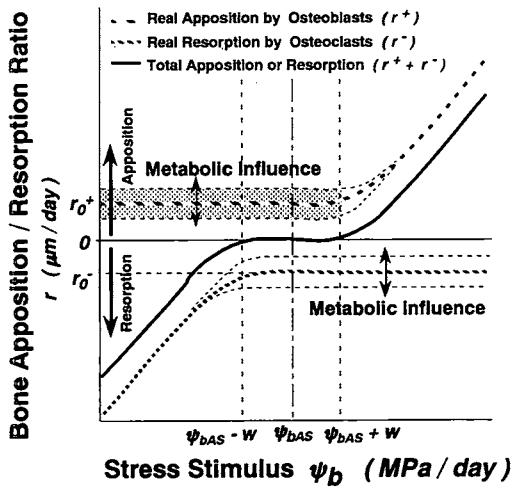


Figure 1 Relation between bone appositon or resorption ratio and stress stimulus in proposed theory.

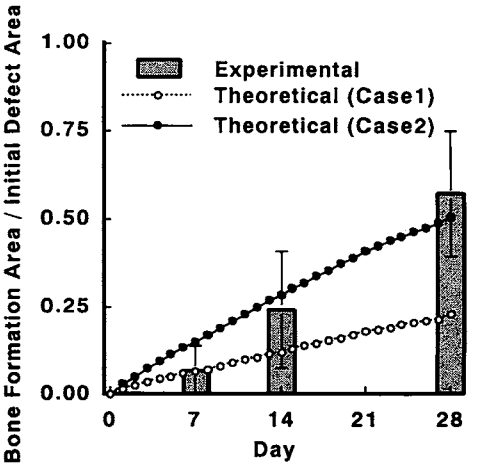
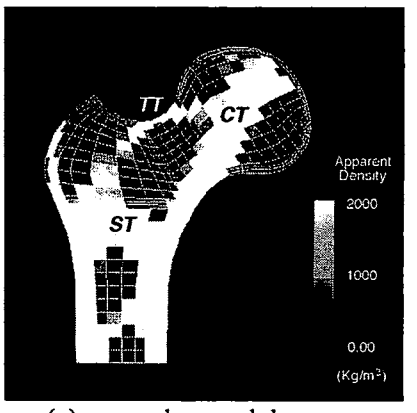


Figure 2 Time history of bone formation quantities on the computer simulation and the experiment.

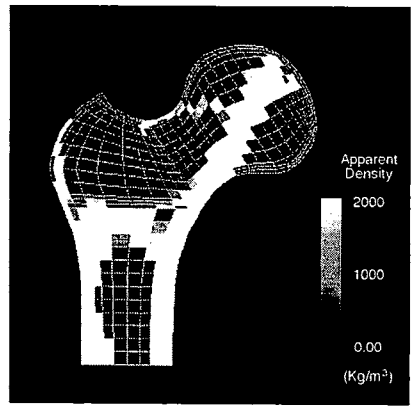
Experiments of stress-induced bone formation were carried out in order to ensure effectiveness of the theoretical model. In the experiments, intermittent load (1 hour/day) was applied to the rabbit's tibia for four weeks in which a circular defect was made at the center. Bone formation at the circular bone defect was evaluated histologically. The proposed theory was applied to the simulation of the experiment. Computer simulation of the defect shape change was carried out for comparing the simulation and the experimental results. The defect shape obtained by the simulation corresponded with the experiment. Quantities of the bone formation in the computer simulation also consist with the experiment as shown in figure 2 (Case 2). On the other hand, the bone formation was underestimated when the bone remodeling theory was used directly (Case 1). It was demon-



(a) normal remodelng case.

strated that the proposed theory could represent bone formation including bone repair by adjusting balance between the basal bone apposition and resorption ratios.

Furthermore, the proposed theory was applied to a bone remodeling problem of the human upper femur in osteoporotic condition. r_0^+ and r_0^- were given as the same value in the simulation corresponded to normal remodeling. For simulation of the osteoporotic condition, r_0^- was given as larger than r_0^+. Distributions of the bone apparent density after convergence are shown in figure 3 for normal remodeling (a) and osteoprotic remodeling (b). Singh classified clinically the osteoporosis grade for the human upper femur. Bone density distribution obtained by the simulation shows good agreement with arrangement of the trabecular bundles denoted in the Singh's classification. It was confirmed that the proposed theoretical model was effective to simulate not only bone repair but also the osteoporosis.



(b) osteoporosis case.

Figure 3 Distribution of bone apparent density obtained by bone remodeling or osteoporosis simulation.

ADVANCED THEORY OF STRESS-INDUCED BONE REMODELING

A theoretical model of adaptive bone remodeling considering fluid flow effect inside bone was proposed. Since bone fluid flow influenced transportation of bone growth factor and mechanical environment around bone cells, it was assumed that quantity of bone formation depended on fluid flow condition. The biphasic theory for porous material includes liquid was used to analyze pressure and velocity of bone fluid flow. Example problems of bone remodeling in a simplified vertebral column and a human upper femur were solved by the theory to examine its effectiveness. Figure 4 shows the distributions of apparent bone density obtained by the fluid flow based method after convergence. In contrast to the stress based method, extreme bone resorption was restrained even at low stress region in the remodeling simulation based on fluid flow. Continuous bone density distribution obtained by the proposed method seems to be more natural than the result of stress based method.

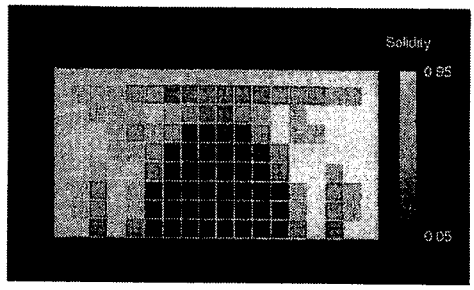


Figure 4 Bone density distributions of a simplified vertebra (upper half).

To represent autonomic and dynamic activity of the bone cells in bone remodeling, a theoretical model using the cellular automata was proposed. The cellular automaton is an artificial system constructed by many cells which a state of a cell changes automatically due to conditions of surrounding cells under a certain transition rule. In this model, automaton cells corresponding to osteoblasts, bone tissue or lacunae (empty space) automatically changed their condition in the remodeling process. Figure 5 shows examples of the cell transition rule. Finite-elements are subdivided into the automaton cells, and transition rules on each element determined due to the stress

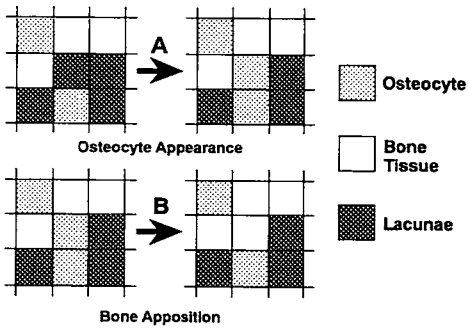


Figure 5 Examples of transition rule applications.

level in the computer simulation. It was applied to a bone remodeling problem of the upper femur, and the bone topology obtained by the method was similar to the real femoral head (figure 6).

CONCLUSION

It is confirmed that the generalized theory proposed first is applicable to wide area that includ adaptive bone remodeling, repairing and diseases in practical use. Although the later two theories using the biphasic model and the cellular automaton were rough and primitive to be compared with the first theory, the idea included essential points of adaptive bone remodeling. It is considered that the theoretical models have the potential for expansion in future studies.

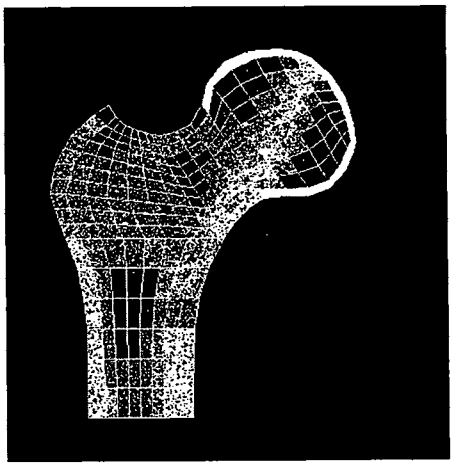


Figure 6 Distributions of the bone tissue cells in the adaptive bone remodeling of the human proximal femur

学位論文審査結果の要旨

今年３月以降，約半年間にわたる予備審査期間を経て提出された論文に対し，慎重審査を行い，また申請者の学力も試験し，かつ８月11日に口頭発表と最終審査委員会を開催し，協議の結果以下の通り判定した。

骨がその環境変化に伴う力学的刺激に対応して組織や形態を変化させる現象は良く知られている。しかしそのような変化を支配しているメカニズムについては明確ではない。本論文はまず骨形成に及ぼす力学的刺激の影響を，家兎脛骨を用いた刺激実験により明らかにしている。特に骨形成は圧縮のみならず引張り刺激に対しても生ずることや，刺激の持続時間に大きく影響されることを確認している。次にこのような現象を骨に作用している応力レベルを基準にしたBeaupré理論を拡張する形で説明している。しかしBeaupréらのこれまで提示されている理論は，骨に骨折等による欠損を伴わない，いわゆる正常時での再構築現象に対応したものであるが，本論文では，骨のいかなる状況に対しても適応できる再構築理論の一般化を考えている。その理論は骨再構築が，骨芽細胞による骨形成と破骨細胞による骨吸収の線形和として与えられるとするものであり，このような理論の有効性を有限要素法を用いた大腿骨近位部の骨再構築シミュレーション計算により明らかにしている。さらに骨芽細胞や破骨細胞の挙動をセル・オートマトンモデルを適用して検証している。

以上の成果は医学における臨床分野はもちろん，力学的適応構造物を求めるという工学的立場においてもきわめて有用であり，新しい知見を見い出していることから，申請者の能力を含め審査委員会は本論文が博士論文として十分価値あるものと判断した。