

# 学位論文の要旨

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学位論文名 Discordance Between Prevalent Vertebral Fracture and Vertebral Strength Estimated by the Finite Element Method Based on Quantitative Computed Tomography in Patients With Type 2 Diabetes Mellitus

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## 論文内容の要旨

### **INTRODUCTION**

Meta-analyses have demonstrated that patients with type 2 diabetes mellitus (T2DM) are at increased risk of hip fracture compared with non-T2DM subjects. However, assessing the bone fragility in patients with T2DM by bone mineral density (BMD) is difficult because BMD at any site is not significantly associated with the presence of vertebral fractures (VFs). Bone strength is a composite of both BMD and bone quality, and these findings suggest that the patients with T2DM might have a poor bone quality that is not apparent in the BMD measurements.

The finite element method (FEM) is a computational analytical tool for a complex system such as the stress analysis of a structure. The quantitative computed tomography-based FEM (QCT-based FEM) was superior to BMD for assessing the bone strength of vertebrae because QCT-based FEM can estimate the integrated bone strength which consists of BMD and bone structure (one of a component of bone quality). To clarify whether the bone strength of T2DM patients can be estimated by QCT-based FEM, we investigated the relationship between the presence of VFs and the bone strength index calculated by QCT-based FEM in T2DM patients.

## **MATERIALS AND METHODS**

A total of 146 Japanese patients with T2DM were enrolled [54 postmenopausal women (age range 47-84 years) and 92 men (age range 51-88 years)]. All of these patients underwent BMD measurements using a QDR-4500 system (Hologic, Waltham, MA) for the diagnosis of osteoporosis and multi-detector computed tomography (MDCT) scans (the Aquilion 64, Toshiba Medical Systems Corporation, Otawara, Japan) to exclude secondary diabetes. Conventional thoracic and lumbar radiographs using lateral and anterior-posterior projections were obtained. A VF was diagnosed according to a reduction of  $\geq 20\%$  as defined by the Genant visual criteria.

The FEM procedure in this study was performed according to the protocol of the previous study for nondiabetic subjects to compare with the results from this population. QCT data were embedded into an image that was diverted from MDCT scan. A 3-dimensional FEM of the vertebral body was constructed with 2-mm tetrahedral elements and 2-mm triangular plates from the CT image using Mechanical Finder software (Mitsubishi Space Software, Tokyo, Japan). The ash density of each voxel was assigned using the linear regression equation created from the values of the calibration phantom. Young's modulus and the yield stress of each element were calculated from the equations proposed for nondiabetic subjects according to a previous study.

Complete restraint to all nodes of the lower end of the vertebral model was applied as boundary conditions for the simulation of VF. The bone strength was calculated every 50 N under the condition of uniaxial and uniformly distributed compression to the upper site of the vertebrae. The vertebral yield and VFs were determined by the occurrence of the yield and failure in at least one element. The fracture load was defined as the vertebral strength index.

The statistical analyses were conducted using StatView (Abacus Concepts, Inc., Berkeley, CA, USA). Multiple logistic regression analysis was performed after adjusting for the confounding variables. *P*-values of less than 0.05 were considered to be significant.

This study was approved by the Ethics Committee of Shimane University and review board of our institution the Shimane University Institutional Committee on Ethics and written informed consent was obtained from all subjects.

## **RESULTS AND DISCUSSION**

In total, 20 women (37.0%) and 39 men (42.4%) had VFs. Six women (11.1%) and 12 men (13.0%) had grade 2 or 3 VFs and multiple prevalent VFs. Logistic regression analysis that

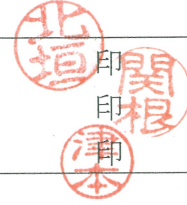
adjusted for age, spine BMD, BMI, HbA1c, and duration of T2DM did not reveal a significant relationship between any of the severities of the VFs defined by the grade or number and the vertebral strength index.

The estimation of the skeletal strength of the vertebrae by QCT-based FEM is well established in non-diabetic subjects. However, FEM using a patient's own material properties has not been achieved because the determination of the material properties requires invasive procedures such as a bending strength test. According to a published protocol, the values obtained from nondiabetic subjects were used as the bone material properties of T2DM patients in this study because no specific values are available for patients with T2DM. Taken together, substituting these values may lead to false results. In addition, this finding indirectly suggests that patients with T2DM have deteriorated bone material properties compared with nondiabetic subjects, which may underlie the bone fragility in T2DM.

## **CONCLUSION**

The presence of VFs in T2DM patients was not significantly associated with the vertebral strength index calculated by QCT-based FEM based on an established standard protocol when the parameters derived from nondiabetic subjects were applied to the bone material properties of diabetic patients. This finding suggests that the bone material properties of T2DM individuals could be deteriorated compared to nondiabetic subjects.

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## 論文審査の結果の要旨

2型糖尿病患者では、非糖尿病患者と比較して有意に大腿骨近位部骨折の相対危険度が増加しているが、骨密度は増加している。骨強度は骨密度と骨質で決定されることから2型糖尿病では骨質の低下があると推測されるが、これを示す報告はない。申請者は2型糖尿病患者の椎体骨折と骨強度指標との関連を調査した。146名の日本人の2型糖尿病患者、閉経後女性54名、92名の男性を対象とし、X線写真で椎体骨折を診断、CT画像を基に骨強度指標を測定した。本研究では椎体の3次元有限要素モデルを専用ソフトウェアで構築した。先行研究に従い、非糖尿病患者に対して使用された計算式を用いた。2型糖尿病患者のうち女性20名と男性39名に椎体骨折を認めた。全患者の椎体強度指数は、年齢と有意な負の相関を示し、また骨密度と有意な正の相関を示した。しかし、骨折群と非骨折群の間には、年齢、椎体骨密度、BMI、HbA1cおよび2型糖尿病罹病期間の影響を排除しても、椎体強度指数に有意差は無かった。非糖尿病患者を対象として先行研究において得られた有意差が、十分なサンプル数の2型糖尿病群で得られなかったことから、統計検出力ではなく、前提条件として同一と仮定した骨の材質特性値が非糖尿病と2型糖尿病では異なることを示している。本研究は2型糖尿病患者の骨材質特性が、非糖尿病患者よりも劣化している可能性を示している。これは糖尿病患者の予後を左右する骨折の危険性を推測するには新しい概念が必要であることを示す知見であり、学位授与に値すると判断した。

## 最終試験又は学力の確認の結果の要旨

申請者は146名の2型糖尿病患者のCTデータから3次元有限要素モデルを用いた解析と種々のデータを分析し、2型糖尿病患者の骨折が骨密度ではなく、骨質に起因することを示した。質疑には的確に返答でき、周辺知識も豊富であることから学位授与に値すると判断した。

(主査 北垣 一)

申請者は、2型糖尿病患者における椎体の有限要素法により骨質の解析、並びに骨折と骨形成・骨吸収マーカーなどとの関連を検討した。本研究は、2型糖尿病患者の骨脆弱性の評価法が確立できることを示唆するもので、学位授与に相応しいと判定した。

(副査 関根浄治)

申請者は、有限要素法によるコンピューターシミュレーションの結果および椎体骨折に関するリスクとなりうる諸要因のデータを解析して、2型糖尿病の骨折が骨密度ではなく、骨質の変化に起因することを精緻な仮説検証の結果として得た。関連知識も豊富で学位授与に値すると判断した。

(副査 津本周作)

(備考) 要旨は、それぞれ400字程度とする。