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研究成果報告書

研究課題名
加齢による副腎由来ホルモンの不均衡に着目した骨粗鬆症の病態解明と早期診断法の開発

Age-related Adrenal Hormone Imbalances in Osteoporosis:
Pathophysiology and Early Diagnostic Development

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## Abstract

**Background and Objectives**

Osteoporosis affects over 15 million people in Japan. About half of fragility fractures occur in patients with normal bone mineral density, which has been referred to as "50% wall" in conventional densitometry. Because bone strength depends not only on bone mass but also on bone quality, methods for early detection of bone quality deterioration are needed.

The adrenal gland produces aldosterone, cortisol, and adrenal androgens from its three cortical layers. While cortisol is a well-known cause of "glucocorticoid-induced osteoporosis," our studies with patient with hormone-prooducing adrenal tumors revealed that excess aldosterone or catecholamines predisposes to fragility fractures through bone quality deterioration. Moreover, Mendelian randomization showed protective effects of adrenal androgens. These findings led us to propose the concept of "adrenal-bone crosstalk," where hormonal imbalance as a result of age-related adrenal changes contributes to the development of osteoporosis. The objectives of this study are to test the above hypothesis and develop early diagnostic strategies.

**Methods and Major Findings**

We pursued two objectives: (1) integrated understanding of age-related adrenal changes and hormonal imbalance, and (2) elucidation of osteoporosis mechanisms via adrenal hormones. We identified steroid-producing nodules with a two-layer structure as precursors of cortisol-producing adenomas, therby proposing a multistep tumorigenesis model (**eBioMedicine** 103: 105087, 2024). Single-cell multiomics revealed heterogeneous cortisol production within aldosterone-producing tumors, which is linked to vertebral fracture risk (**Proc. Natl. Acad. Sci. USA** 122: e2421489122, 2025). Single-cell analysis of normal adrenal tissues from young and elderly showed age-related disruption of cortical zonation, inflammation, with a shift toward cortisol biosynthesis (**Mol. Metab.** 84: 101954, 2024). We also developed a comprehensive steroidomics analysis system using LC/MS/MS, enabling detection of subtle steroid imbalances, which have been undetected by conventional single-hormone assays (**J. Lipid Res.** 65: 100492, 2024). Patient analysis revealed that imbalance of multiple steroid metabolites increases osteoporosis risk (**eBioMedicine** 95: 104733, 2023). Even "non-functioning" adrenal incidentalomas exhibited mild steroid imbalance associated with diabetes, suggesting systemic effects of subclinical dysfunction (**J. Endocr. Soc.** 8: bvae140, 2024).

**Significance and Future Perspectives**

By translating pathological insights obtained from adrenal tumors to normal aging, a series of our works have elucidated how adrenal hormone imbalance accelerates bone quality deterioration. It provides a pathway for early diagnosis of osteoporosis beyond densitometry, potentially overcoming the so-called "50% wall" and reducing fracture burden and healthcare costs. Building on the "adrenal-bone crosstalk" concept and comprehensive steroidomics, we aim to establish practical diagnostic system using large prospective cohorts and develop adrenal-based health assessment system, and advance personalized preventive medicine.