International Journal of Gerontology Special Issue (2019) S29–S32
https://doi.org/10.6890/IJGE.201910/SP.0004

International Journal of Gerontology

journal homepage: http://www.sgecm.org.tw/ijge/

Special Issue

# The Effects of Polypharmacy on Bone Mineral Density in Middle-Aged and Elderly Men

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ARTICLE INFO

Accepted 6 July 2019

*Keywords:*
bone mineral density,
CYP450,
polypharmacy,
vitamin D

SUMMARY

*Background:* Osteoporosis is a loss of bone density among aging adults that can cause fractures and disability. Drug-induced osteoporosis is a noteworthy health problem, but many physicians are unaware that many commonly prescribed medications contribute to significant bone loss and fractures. This study investigated the cumulative effects of concurrent polydrug use (≥ 5 medications) on bone mineral density (BMD) with inhibited and induced cytochrome P450 (CYP450) enzyme activity.
*Methods:* This study enrolled 207 middle-aged and elderly male subjects who underwent two dual-energy X-ray absorptiometry (DXA) scans to measure lumbar vertebrae BMD between 2012 and 2018 and analyzed their prescribed medicines metabolized via the CYP450 system.
*Results:* The inhibitory group (n = 66) included patients prescribed more drugs that inhibit CYP450 than those that induce CYP450, the inductive group (n = 72) included patients prescribed more medications that induce CYP450 than those that inhibit CYP450, and the reference group (n = 69) included patients administered with the equal number of prescription drugs that inhibit and induce CYP450 or used neither. The results indicated a significant increase in the risk of BMD loss in the inductive group compared to the reference group (OR = 3.63, 95% CI = 1.43–5.84) (p = 0.013).
*Conclusions:* The prescription of drugs that induce CYP450 decreases the BMD in middle-aged and elderly males. A possible mechanism is that more CYP450 inducers in number would accelerate the metabolic rate of vitamin D and will eventually affect the function of parathyroid hormone in bone remodeling.



## 1. Introduction

Osteoporosis is a skeletal disorder characterized by low bone mass and micro-architectural degeneration of the skeleton resulting in bone fragility and the susceptibility of fractures.[1,2] Primary osteoporosis is the major cause of morbidity and mortality, predominantly in post-menopausal women and older men.[3] However, secondary osteoporosis could be existent in pre-menopausal women or middle-aged men, which is defined as a low bone mass with construction changes leading to fragile fractures in the company of an underlying disease or medication.[4] Moreover, up to 30% of post-menopausal women and 50 to 80% of men may also have potential factors contributing to osteoporosis after assessing the causes of the disease. Some medicines have been shown to cause bone loss and increase the risk of fractures. For example, glucocorticoid-induced osteoporosis is one of the most common types of secondary osteoporosis. In this respect, bone health concerns should be deliberated before prescribing medications. It is essential to identify the risk of medication-induced osteoporosis because the treatment may differ.[5]

Previous studies have shown that adverse side effects increase when patients simultaneously use more than five types of drugs because they may be affected by different metabolism pathways. One of the most common drug metabolism pathways is through cytochrome P450 (CYP450). CYP450 is a catalyst for the metabolism of many medications. Some drugs could induce the production of CYP450;[6,7] however, others may interrupt the pathway. Hence, combining drugs can have unpredictable and unwanted consequences. Drugs metabolized via the cytochrome P450 system act as enzyme substrates, inducers, or inhibitors and have viewed an important determinant in the occurrence of several drug-drug interactions.[8] For example, synthetic azoles, such as the antibacterial ketoconazole and the proton pump inhibitor omeprazole, have been shown to inhibit CYP3A4 and CYP24 in vitro, but so far no studies have explored the effects of these drugs on human vitamin D status.[9] Advances in realizing the mechanisms of CYP3A4-mediated drug metabolism and an increasing understanding of the role of vitamin D in CYP3A4 expression may lead to a systematic evaluation of potential interactions among drugs that are metabolized by CYP3A4 or other cytochrome subgroups. On the other hand, previous studies have shown that drugs which induce CYP450 may accelerate the metabolism of vitamin D, leading to vitamin D deficiency which decreases the amount of calcium and phosphorus ions in the blood, thus causing the loosening or weakening of the bone matrix.[10] However, the

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long-term effects of mixed use of CYP450 inducer and inhibitor on bone density have not been explored. Consequently, we tried to investigate the correlation between the number of drugs that inhibit or induce CYP450 in middle-aged or older subjects with polypharmacy and the change in bone mineral density (BMD).

## 2. Materials and methods

### *2.1. Study design and subjects*

We conducted a retrospective chart review of male patients ≥ 50 years of age prescribed polypharmacy (≥ 5 medications) and ever underwent at least two dual-energy X-ray absorptiometry (DXA) (Hologic, QDR 4500; Hologic Inc., Bedford, Massachusetts, USA) to measure lumbar vertebrae BMD for health examination surveys from 1 December 2012 to 31 November 2018 at a regional teaching hospital (National Yang-Ming University Hospital). The study protocol was approved by the National Yang-Ming University Hospital Institutional Review Board Committee (YMUH2018A023), in accordance with the ethical principles of the Declaration of Helsinki.

Patients were screened according to the eligibility criteria outlined below. In order to obtain an unbiased selection of patients as possible, patients were randomly selected. Men were considered eligible for inclusion if they were aged 50 years or older. Men were not eligible if they received anti-osteoporosis treatment, steroids or thyroid medication. Total numbers of drugs prescribed were collected. The data were further analyzed for drug metabolism as substrate, inhibitor or inducer for CYP450.[11] Finally, all subjects were allocated to three groups in accordance with the categories of prescription medicine: the inhibitory group included patients who took more drugs that inhibit CYP450 than those that induce CYP450, the inductive group included patients who took more drugs that induce CYP450 than those that inhibit CYP450, and the reference group included patients who took the same number of drugs that inhibit and induce CYP450 or used neither.

### *2.2. Data collection*

BMD was measured and BMD T-score calculated as part of health examination. It is the standard clinical procedure that each measurement is taken on the same dual-energy X-ray absorptiometry machine. The mean change in BMD from baseline to the second follow-up was calculated for all patients. In addition, 25-hydroxyvitamin D (25(OH)D) levels were also evaluated.

### *2.3. Statistical analyses*

All demographic and clinical characteristics were summarized using descriptive analyses. Categorical variables were summarized using the number, percentage and 95% CI. Statistical analyses were performed using IBM SPSS statistics software version 24 (IBM SPSS Statistics for Windows, Version 24.0, Armonk, NY: IBM Corp.) to assess changes in BMD and 25(OH)D levels from baseline to follow-up for patients receiving the different number of inhibitors and inducers for CYP450. Continuous variables with a normal distribution were analyzed by univariate ANOVA and adjusted analysis of covariance (ANCOVA) for adjusting associated factors. Comparisons between different groups were analyzed by chi-squared tests with data expressed in percentage terms. Linear correlation analysis was also carried out using the Pearson correlation followed by stepwise multiple logistic regression analysis. For all comparisons, statistical significance was defined as a p-value of $< 0.05$.

## 3. Results

Finally, we enrolled 207 men who met the inclusion criteria. The average age at the time of the last DXA scans was $60.6 \pm 8.5$ (52.7–69.1) years. The average duration between the two DXA scans was $2.6 \pm 1.2$ (1.1–3.9) years. The average lumbar vertebrae BMD in the first DXA scan was $1.27 \pm 0.26$ (0.80–2.46) g/cm$^2$ and the average BMD in the last scan was $1.21 \pm 0.26$ (0.61–2.02) g/cm$^2$. 112 (54%) of the subjects experienced losses in BMD while 95 (46%) experienced increases in BMD. BMD and 25(OH)D levels were significantly lower in the inductive group than in the inhibitory group ($p < 0.05$; Table 1).

The results indicated no significant difference between the BMD increases in the inhibitory group and the reference group (OR = 1.79, 95% CI = 0.84–6.60) ($p = 0.102$); however, there was a significant increase in the risk of BMD loss in the inductive group compared to the reference group (OR = 3.63, 95% CI = 1.43–5.84) ($p = 0.013$) (Figure 1).

## 4. Discussion

The study disclosed more CYP450 inducers of prescribed drugs in number would decrease BMD, but more CYP450 inhibitors may not improve BMD. CYP450 belongs to the family of hemoproteins and is present in bacteria, fungi, insects, fish, mammals, primates, and plants. The physiological functions of CYP450 aim to catalyze the monooxygenation of many compounds within the body to create oxidized metabolites with beneficial or harmful effects on the body.[7] The detoxification effects of some drugs are caused by hydroxylation which dissolves hydrophobic drugs,[12,13] and polydrug interactions would be the result of an alteration of CYP450 metabolism.[14–16] In other words, CYP450 enzymes can be inhibited or induced by medications, leading to clinically noteworthy drug-drug interactions that can cause unexpected therapeutic failures or adverse reactions. Additionally, the discrepancy in drug response among persons of different ethnic origins also can be caused by genetic variations in other drug-metabolizing enzymes, drug transporters, and receptors.[17]

The three major steps of vitamin D metabolism, 25-hydroxylation, 1$\alpha$-hydroxylation, and 24-hydroxylation are all performed by CYP450 mixed functional oxidase (such as CYP2R1) located in the endoplasmic reticulum or mitochondria (e.g., CYP27A1, CYP27B1, and CYP24A1). However, other enzymes including the drug metabolizing enzyme CYP3A4 have 25-hydroxylase activity and may function under different clinical conditions.[9] To our knowledge, this is the first study to prove taking more inducers of CYP450 enzymes in prescribed drugs probably decreases the BMD in males, which would not be improved by more inhibitors of CYP450. The reason may be that these drugs increase the metabolism rate of vitamin D in the liver, similar to previous studies that found that long-term use of phenytoin and phenobarbital cause a drop in blood calcium and blood 25(OH)D levels and increase alkaline phosphatase concentration in the liver and bones.[18] Nevertheless, some CYP450 inhibitors, such as proton pump inhibitors, would induce hypoacidity and decrease calcium solubility, leading to decreased intestinal calcium absorption, and counteract BMD improvement. In subjects prescribed CYP450 inducers, which are capable of activating the nuclear receptor pregnane X receptor (PXR), insufficient vitamin D with a decrease in calcium level would substantially stimulate parathyroid gland secretions, which expect to utilize calcium from the bones to maintain the calcium level (Figure 2).[19–21] PXR is closely related to vitamin D receptors and recognizes and activates vitamin D response elements, suggesting that PXR ligands can affect genes under the transcriptional control of vitamin D receptors.[21] It has been sug-

**Table 1**
Comparative analysis of demographics and characteristics of patients prescribed polypharmacy

| Variables | Reference group (n = 69) | Inhibitory group (n = 66) | Inductive group (n = 72) | Group comparisons |
|---|---|---|---|---|
| Age, y | 60.8 ± 8.3 | 58.8 ± 7.9 | 62.5 ± 8.5 | NS |
| Cigarette use, % | 32.3 | 34.7 | 29.8 | NS |
| Alcohol use, % | 23.4 | 26.8 | 22.7 | NS |
| DXA scans duration, y | 2.6 ± 1.2 | 2.9 ± 1.4 | 2.4 ± 1.2 | NS |
| Number of inhibitors | 1.1 ± 0.1 | 2.9 ± 1.1 | 0.7 ± 0.2* | p = 0.001 |
| Number of inducers | 1.1 ± 0.1 | 0.5 ± 0.1 | 1.2 ± 0.5* | p = 0.013 |
| Baseline BMD, g/cm$^2$ | 1.23 ± 0.21 | 1.18 ± 0.18 | 1.45 ± 0.37* | p = 0.021 |
| Follow-up BMD, g/cm$^2$ | 1.19 ± 0.29 | 1.24 ± 0.24 | 1.19 ± 0.18 | NS |
| Baseline 25(OH)D, ng/mL | 22.76 ± 6.54 | 23.21 ± 7.30 | 23.06 ± 8.23 | NS |
| Follow-up 25(OH)D, ng/mL | 23.18 ± 8.09 | 23.89 ± 8.85 | 21.36 ± 6.77* | p = 0.037 |
| High-frequency prescription drugs | NA | Cimetidine<br>Cyclosporine<br>Ranitidine<br>Fluconazole<br>Omeprazole<br>Itraconazole<br>Verapamil<br>Ketoconazole<br>Amiodarone<br>Tranylcypromine<br>Gemfibrozil<br>Haloperidol<br>Fluvoxamine<br>Paroxetine<br>Sertraline<br>Quinidine<br>Fluoxetine<br>Nefazodone | Rifampin<br>Phenobarbital<br>Phenytoin<br>Oxcarbazepine<br>Carbamazepine | NA |

**Notes:** Values are presented as mean ± SD. ANOVA was used for analysis. * $p < 0.05$, compared to inhibitory group.
**Abbreviations:** BMD, bone mineral density; DXA, dual-energy X-ray absorptiometry; NA, not applicable; NS, not significant; 25(OH)D, 25-hydroxyvitamin D.

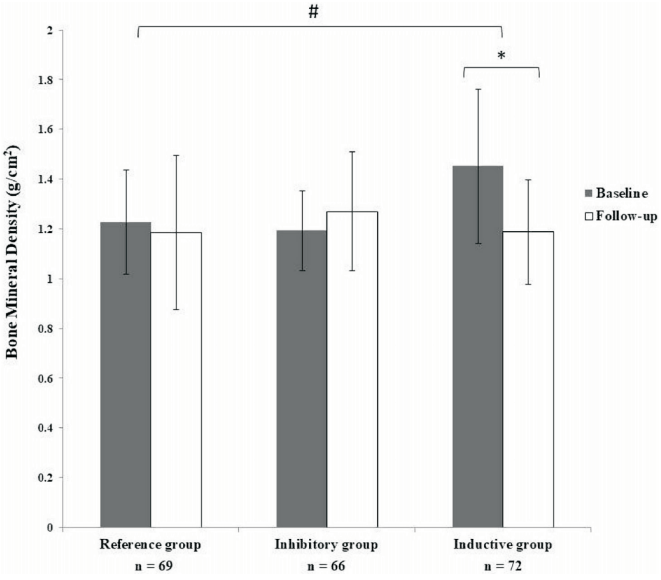


**Figure 1.** Changes in bone mineral density. Values are means ± SD. * Statistically significant difference between baseline and follow-up (1.45 ± 0.81 versus 1.19 ± 0.62 g/cm$^2$; p = 0.028); # statistical significance of bone mineral density reduction in inductive group compared to reference group (p = 0.013).

gested that activation of PXR induces CYP24A1 in the liver and intestine, and enhances the metabolic clearance of 25OHD and $1\alpha,25(OH)_2D_3$, which is a cause of drug-induced osteomalacia.[22] The drugs analyzed in this study were mainly metabolized by CYP3A4, which is also greatly enhanced by the activation of PXR. 25OHD and $1\alpha,25(OH)_2D_3$ are also substrates for CYP3A4, producing a stereochemistry that is different from the primary product induced by CYP24A1. Long-term treatment with certain PXR ligand drugs can up-regulate the expression of CYP3A4, enhance the 4-hydroxylation of 25OHD, and ultimately reduce the circulating level of 25OHD.[21,22]

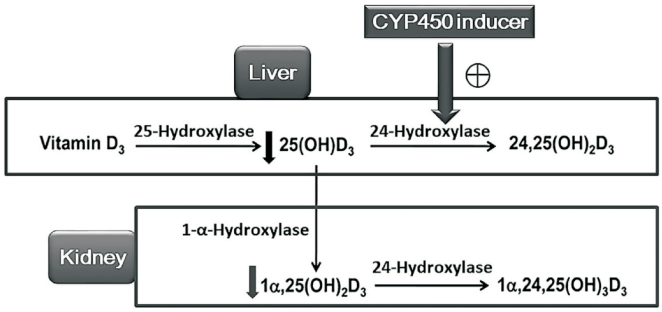


**Figure 2.** Proposed mechanism that CYP450 inducers accelerate $25(OH)D_3$ metabolism in the liver and then reduce the production of active form, $1\alpha,25(OH)_2D_3$, in the kidney.

Limitations of this retrospective study include the lack of available data on a dietary supplement, such as vitamin D, and the impact of personal chronic diseases. In addition, we do not provide the correlation between 25(OH)D and calcium levels regulated by parathyroid hormone. Furthermore, women were not enrolled in the investigation because it is suggested that sex hormone changes may unpredictably interfere on BMD in peri-menopausal and post-menopausal females.

In conclusion, we found that patients prescribed more CYP450 inducers in number have a higher risk of bone loss, which may be due to the reduction of vitamin D levels. Therefore, bone density may need to be evaluated periodically in long-term polydrug users.

## Conflicts of interest

The authors declare that they have no conflict of interest.

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