BMI reduction and vitamin D insufficiency mediated osteoporosis and fragility fractures in patients at nutritional risk: a cross-sectional study

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Abstract
It seemed to be common sense that malnutrition was associated with osteoporosis, but there were few studies with detailed data proving that. Additionally, the association between BMI and osteoporosis was still under discussion. In our study of 138 patients, we first confirmed the association between nutrition and osteoporosis with propensity score matching method reducing the confounding bias, then discovered that body mass index (BMI) and 25OHD level acted as two crucial factors of nutrition risk-mediated osteoporosis. Moreover, a new BMI classification was proposed in our article to do more help for nutrition management and anti-osteoporosis treatment for the old in China. Consequently, nutrition is important to bone health, with BMI and 25OHD level playing key roles.

Introduction
Nutritional risk (NR) and malnutrition could be the cause or aggravating factor of many diseases, and it is now very important in health care. The body mass index (BMI), for example, is an important index in evaluating patients' nutritional status [1]. And the Nutritional Risk Screening (NRS 2002) method is most widely used among all kinds of screening tools for nutritional assessment [2, 3]. Although many people believed that malnutrition caused osteoporosis, which is a metabolic disease of bone, there was rare evidence. In this article, we investigated the association between NR and osteoporosis, and further investigated the risk factors of nutrition for osteoporosis, to improve the understanding of nutrition and bone metabolism.

Methods
From July to November 2016, 138 patients were admitted to our hospital with different fractures and underwent surgical treatments. A cross-sectional study of NR group (NRS 2002 score ∈ [3, 5], 40 patients) and rational-nutrition group (NRS 2002 score < 3, 98 patients) was performed. To reduce the confounding bias, propensity score matching (PSM) was performed to balance the age, sex, trauma history and past history of these two groups [4]. The pre-operative and postoperative courses, such as bone mineral density (BMD), osteocalcin and serum vitamin D (25OHD), were compared to analyze the association between nutrition and osteoporosis. Then, 122 patients were divided into osteoporosis group (BMD ≤ −2.5, 38 patients) and osteopenia group (BMD ∈ (−1, −2.5), 84 patients). A logistic regression analysis was made to investigate more about the risk factors of nutrition in this cause-effect relationship. All of the detailed methods, including the inclusion, exclusion criteria, and PSM data, were in supplementary files.
Results

Part 1. NR induces osteoporosis and fragility fracture

The overall average age of the patients in NR and rational-nutrition groups was 69.6-year old (range 54–85). The basic characteristics of the patients in this part were summarized in Table 1. After PSM analysis mentioned above, there were 30 patients in NR group with NRS 2002 score ≥ 3, and 52 patients in rational-nutrition group with NRS 2002 score < 3. There were no significant differences of basic information between these two groups.

The patients in NR group had a much lower 25OHD level than that in rational-nutrition group (17.22 vs. 26.48 ng/ml, \( P = 0.0003 \)), as well as the level of osteocalcin (1.30 vs. 3.66 ng/ml, \( P = 0.0003 \)) (Table 1). As for BMD measured at hip, the patients in NR group had a significantly lower \( T \)-value than that in rational-group (−2.61 vs. −1.55, \( P = 0.0113 \)), while the BMD measured at lumbar vertebra showed the same trend (−2.59 vs. −1.64, \( P = 0.0387 \)) (Table 1). The incidence of fragility fracture in NR group was obviously higher than that in rational-nutrition group (80.00% vs. 46.15%, \( P = 0.0113 \)) (Table 1). As for postoperative complications, there were no significant differences between these two groups. However, the postoperative length of the hospital stay was significantly longer in NR group than that in rational-nutrition group (15.62 vs. 67.13 days, \( P = 0.0055 \)), which strongly suggested a better recovery of those patients with a better nutritional status before their surgeries (Table 1). Therefore, an insufficient nutritional reserve is associated to abnormal level of osteoporotic indexes, and the association between nutritional status and osteoporosis was clear.

Part 2. Key nutritional factors mediated osteoporosis and fragility fractures

To investigate more about which key nutritional factors are the most important causes of osteoporosis after part 1, we made a logistic regression study. In all of the 138 patients, 122 of them suffered from an abnormal bone metabolism with an average \( T \)-value of BMD < −1. According to the definition of osteoporosis, we separated these 122 patients into two groups: the osteoporosis group with the average \( T \)-value of BMD ≤ −2.5, and the osteopenia group with the average BMD ∈ (−1, −2.5). After PSM analysis, there were 32 patients in osteoporosis group and 42 patients in osteopenia group. The basic characteristics were summarized in Table 2.

The key indexes in measuring the nutritional status included Albumin, BMI, 25OHD, erythrocyte sedimentation rate, and highly-sensitive C-reactive protein, as well as the DM history and liver function disorders. The initial inclusion criteria was set as \( P < 0.10 \) [5]. Since no significant differences were observed for DM and hepatic disorders as \( P = 0.453 \) and 0.128, respectively, these two indexes were excluded in the first step (Table 2). Compared with other indexes, BMI (range 16.2–25.8 kg/m\(^2\)) and 25OHD level were identified to be significantly lower in osteoporosis group than that in osteopenia group (\( P = 0.044 \) and 0.037, respectively) (Table 2). Consequently, BMI and 25OHD were key nutritional factors which mediated the progress of osteoporosis and fragility fractures.

Discussion

NR was proposed assuming the indications for nutritional therapy are the severity of malnutrition and the increasing nutritional requirements due to the disease [6, 7]. Being nutritionally “at-risk” is associated with many adverse clinical outcomes [8]. Hence, adequate screening and necessary nutritional management have been proved [7]. Although many screening tools for nutritional assessment are available, there is no “gold standard” till now. As the most widely used method, NRS 2002 has been very popular [3]. The premise of NRS 2002 relates to the assumption of NR, so that both a measurement of current potential undernutrition and a measurement of disease severity should be included [9].

However, there are still some suggestions about whether NRS 2002 should include more elements or indexes to get a better assessment for nutritional status. For example, 25OHD played an important role in NR mediated osteoporosis according to our study [10]. Vitamin B, zinc and magnesium are all necessary factors in body’s routine works, and there had been many articles proving that they would stay below normal when patients were suffering from nutritional problems. Thus, key trace elements should be considered in nutritional evaluation.

Another vital medium in NR induced osteoporosis in our study is BMI. Our results prompted an important topic: whether the BMI classification now is a proper evaluation for people at different ages. Since BMI is most frequently used in young people and adults [1], whether it should have another categories in the old is worthy of a specific discussion. According to our study, the average level of BMI in osteopenia group was 22.43 kg/m\(^2\), while that in osteoporosis group was 19.99 kg/m\(^2\). Thus, the cut-off BMI level should be within 21.37–21.72 kg/m\(^2\) (mean \( ± 3 \times \) SEM), blow which might be underweight for the elder people in the aspect of bone metabolism. However, more studies with more patients and data are needed, and we will devote ourselves in continuing this study, to give more evidence...
Table 1  Demographic, clinical characteristics, osteoporotic indexes and postoperative status of patients in part 1

|                        | NR group | Rational-nutrition group | P    |
|------------------------|----------|--------------------------|------|
|                        | NRS2002 ≥ 3 | NRS 2002 < 3             |      |
| No. patients           | 30       | 52                       |      |
| Age, mean ± SEM, yr.   | 73.00 ± 2.40 | 67.65 ± 1.69            | 0.0702|
| Sex (male/female)      | 10/20    | 12/40                    | 0.488 |
| Menopausal age of female patients, mean ± SEM, yr. | 50.60 ± 0.76 | 49.50 ± 0.77            | 0.375 |
| Causes of fractures, n (%) |          |                          |      |
| Trauma                 | 6 (20.00) | 28 (53.85)               | 0.0346|
| Mild activities        | 24 (80.00) | 24 (46.15)               |      |
| Past medical history, n (%) |          |                          |      |
| Diabetes mellitus      | 10 (33.33) | 20 (38.46)               | 0.767 |
| Hepatic diseases       | 14 (46.67) | 16 (30.77)               | 0.321 |
| Others chronic illness | 10 (33.33) | 16 (30.77)               | 0.869 |
| None                   | 8 (26.67)  | 16 (30.77)               | 0.788 |
| Fracture positions, n (%) |          |                          |      |
| Compression fractures of spine | 2 (6.67)    | 8 (15.38)               | 0.251 |
| Femoral neck           | 4 (13.33)  | 8 (15.38)               | 0.803 |
| Femoral intertrochanter | 8 (26.67)  | 8 (15.38)               | 0.219 |
| Distal radius          | 2 (6.67)   | 2 (3.85)                | 0.573 |
| Proximal humerus       | 0         | 2 (3.85)                | —     |
| Ankle                  | 0         | 4 (7.69)                | —     |
| Kneecap                | 2 (6.67)   | 2 (3.85)                | 0.573 |
| Others                 | 12 (40.00) | 18 (34.62)              | 0.631 |
| Osteoporotic Indexes, mean ± SEM |          |                          |      |
| 25OHD, ng/ml           | 17.22 ± 2.12 | 26.48 ± 1.23            | 0.0003|
| Bone mineral density   |           |                         |      |
| Hip                    | −2.61 ± 0.24  | −1.55 ± 0.26            | 0.0113|
| Lumbar vertebrae       | −2.59 ± 0.28  | −1.64 ± 0.30            | 0.0387|
| Osteocalcin, ng/ml     | 1.30 ± 0.21  | 3.66 ± 0.45             | 0.0003|
| Serum calcium, mmol/L  | 2.15 ± 0.05  | 2.20 ± 0.01             | 0.212 |
| Serum beta-CrossLaps, ng/ml | 0.43 ± 0.08 | 0.55 ± 0.49            | 0.178 |
| Parathyroid hormone, pg/ml | 13.03 ± 5.62 | 20.95 ± 2.06          | 0.118 |
| 24 h urine Ca, mmol/L  | 6.69 ± 1.30  | 5.17 ± 0.77             | 0.327 |
| 24 h urine P, mmol/L   | 12.09 ± 1.29 | 16.86 ± 2.84            | 0.353 |
| Fragility fracture, n (%) | 24 (80.00)  | 24 (46.15)              | 0.0346|
| Alkaline phosphatase, U/L | 89.20 ± 16.02 | 77.00 ± 5.52          | 0.371 |
| Postoperative results, n (%) |          |                          |      |
| Mortality              | 0         | 0                       | >0.99 |
| Overall complications (≥Clavien grade 3) | 0     | 0                       | >0.99 |
| Postoperative hemorrhage | 0         | 0                       | >0.99 |
| Incision infection     | 0         | 0                       | >0.99 |
| Thromboembolism        | 0         | 0                       | >0.99 |
| Length of the hospital stay after surgery, mean ± SEM, d | 15.62 ± 3.56 | 7.13 ± 0.91             | 0.0055|

Other past medical histories: hypertension, Parkinson disease, chronic obstructive pulmonary disease, asthma, umbilical hernia, chronic renal insufficiency, and so on

Other fracture positions: tibia, fibula, clavicle, olecranon, and so on

NR nutritional risk, NRS nutritional risk screening
and suggestions for the management of nutrition-associated osteoporosis.

**Conclusion**

Nutrition is important in many aspects, including the bone metabolism and the absorption of related trace elements. As crucial factors of nutrition, BMI and 25OHD played important roles in NR mediated osteoporosis. A better nutritional status, better BMI level, and higher 25OHD level, could reduce the incidence of fragility fracture, as well as the negative effects of osteoporosis. Thus, nutrition should be an indispensable part of anti-osteoporosis treatment.

**Author contributions** Li was in charge of the clinical data collection and analysis, and Hui was in charge of PSM analysis and logistic regression analysis in our study; Zhang was in charge of the surgical treatment of osteoporotic fractures, and Yu was in charge of clinical nutritional treatment. Xiao Chang helped in data collection and analysis; ML and YW gave many necessary suggestions in the aspect of osteoporosis, 25OHD and Ca treatment.

**Conflict of interest** The authors declare that they have no conflict of interest.

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**Table 2** Demographic, clinical characteristics, and nutritional indexes related to osteoporosis of patients in part 2

|                      | Osteoporosis group | Osteopenia group | P     |
|----------------------|--------------------|------------------|-------|
|                      | BMD ≤ −2.5         | BMD ∈ (−1, −2.5) |       |
| No. patients         | 32                 | 42               |       |
| Age, mean ± SEM, yr. | 67.19 ± 4.26       | 67.10 ± 2.28     | 0.984 |
| Sex (male/female)    | 2/30               | 10/32            | 0.160 |
| Menopausal age of female patients, mean ± SEM, yr. | 49.50 ± 0.96 | 50.60 ± 0.66 | 0.348 |
| Past medical history, n (%) |                   |                  |       |
| Diabetes mellitus    | 8 (25.00)          | 16 (38.10)       | 0.453 |
| Hepatic diseases     | 6 (18.75)          | 18 (42.86)       | 0.128 |
| Others               | 8 (25.00)          | 8 (19.05)        | 0.674 |
| None                 | 14 (43.75)         | 10 (23.81)       | 0.210 |
| Causes of fractures, n (%) |               |                  |       |
| Trauma               | 6 (18.75)          | 24 (57.14)       | 0.0178|
| Mild activities      | 26 (81.25)         | 18 (42.86)       |       |
| Fracture positions, n (%) |               |                  |       |
| Compression fractures of spine | 10 (31.25) | 2 (4.76) |       |
| Femoral neck         | 4 (12.50)          | 6 (14.29)        |       |
| Femoral intertrochanter | 6 (18.75) | 8 (19.05) |       |
| Distal radius        | 4 (12.50)          | 2 (4.76)         |       |
| Proximal humerus     | 0                  | 2 (4.76)         |       |
| Ankle                | 2 (6.25)           | 2 (4.76)         |       |
| Kneecap              | 0                  | 4 (9.52)         |       |
| Others               | 6 (18.75)          | 16 (38.10)       |       |
| Nutritional Indexes, mean ± SEM |             |                  |       |
| 25OHD, ng/ml         | 17.14 ± 1.83       | 26.09 ± 1.10     | 0.0001|
| 25OHD deficiency, n (%) | 20 (62.50) | 6 (14.29) | 0.0016|
| Albumin, g/L         | 35.69 ± 1.01       | 38.33 ± 1.09     | 0.0917a|
| Body mass index, kg/m² | 19.99 ± 0.58 | 22.43 ± 0.35 | 0.0006|
| ESR, mm/h            | 50.29 ± 7.80       | 32.05 ± 5.35     | 0.0550a|
| hsCRP, mg/L          | 48.11 ± 10.42      | 26.31 ± 5.35     | 0.0725a|
| NRS 2002 score       | 2.58 ± 0.31        | 1.91 ± 0.28      | 0.129 |
| Diabetes mellitus    | 8 (25.00)          | 16 (38.10)       | 0.453 |
| Hepatic diseases     | 6 (18.75)          | 18 (42.86)       | 0.128 |

**Logistic Regression Analysis**

|                      | B      | S.E. | Significance OR | EXP (B) 95% CI |
|----------------------|--------|------|-----------------|----------------|
| 25OHD, ng/ml         | −0.214 | 0.103| 0.037           | 0.807 0.660–0.988|
| Albumin, g/L         | 0.034  | 0.107| 0.751           | 1.034 0.839–1.275|

**Table 2 (continued)**

|                      | B      | S.E. | Significance OR | EXP (B) 95% CI |
|----------------------|--------|------|-----------------|----------------|
| ESR, mm/h            | −0.001 | 0.025| 0.972           | 0.999 0.952–1.049|
| hsCRP, mg/L          | −0.005 | 0.027| 0.866           | 0.995 0.944–1.050|
| Body mass index, kg/m² | −0.845 | 0.419| 0.044           | 0.430 0.189–0.977|

*Statistically significant: P < 0.10
Other past medical histories: hypertension, Parkinson disease, chronic obstructive pulmonary disease, asthma, umbilical hernia, systemic lupus erythematosus, and so on
Other fracture positions: tibia/fibula, clavicle, olecranon, and so on
BMD bone mineral density, ESR erythrocyte sedimentation rate, hsCRP highly sensitive C-reactive protein, NRS nutritional risk screening
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