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# Impact of non-cancer related malnutrition on bone metabolism

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## ABSTRACT

Malnutrition, defined as an imbalanced nutritional intake due to different causes, still represents an open issue for clinicians. Cancer is the leading cause of malnutrition, even though other forms of nutritional chronic deficits as obesity, sarcopenia, aging and undernutrition should also be considered as important factors in non-oncological patients.

Malnutrition can damage all body systems; in particular, it determines a reduction in mineral density and an alteration of microarchitecture on bone, thus enhancing the risk of pathological fractures. Therefore, avoiding malnutrition by a correct ob approach appears to be necessary to ameliorate bone health, even though the best dietary habit is not fully established.

The aim of this narrative review is to evaluate the pathological alteration of bone metabolism induced by non-cancer related malnutrition and the effect of different dietary habits on nutrients deficiencies and on bone architecture to suggest the best clinical practice to restore normal bone structure in malnourished patients.

## KEYWORDS

OBESITY

OSTEOPOROSIS

SARCOPENIA

UNDERNUTRITION

## INTRODUCTION

Malnutrition can be defined as "a state resulting from lack of intake or uptake of nutrition that leads to altered body composition (decreased fat-free mass) and body cell mass leading to diminished physical and mental function and impaired clinical outcome from disease"[1]. It refers to deficiencies, excesses, or imbalances in a person's intake of energy and/or nutrients in relation to their dietary requirements. Cancer cachexia is the most common form of malnutrition, even though acute diseases/inflammation, aging, obesity and micronutrient imbalances are recognized by World Health Organization (WHO) as pivotal causes too[1,2].

Since 2002, the European Society for Clinical Nutrition and Metabolism (ESPEN) has recommended the use of the Nutritional Risk Screening tool (NRS-2002), which includes parameters such as body mass index (BMI), weight loss, and disease severity to assess nutritional status in clinical settings.

Nevertheless, none of them consider criteria such as muscle mass, muscle function, and the presence of inflammation[3].

Therefore, since 2016, the Global Leadership Initiative on Malnutrition (GLIM) was convened to correctly define malnutrition in hospital-based settings, involving phenotypic criteria as non-voluntary weight loss, low BMI, reduced muscle mass on validated body composition measures, decline in muscle strength by handgrip measurement and etiological criteria as reduced food intake and/or absorption due to inflammation or acute and chronic diseases[4].

To date, malnutrition has been recognized as a pivotal risk factor for infectious complications, poor wound healing, and mortality in hospitalized patients, thus representing an open issue for clinicians. In acute clinical settings, the definition of malnutrition should still involve reduced food intake, micronutrient deficiencies, weight loss or obesity, muscle mass quantification and laboratoristic parameters such as serum levels of albumin, prealbumin, C-reactive protein (CRP), or white blood cell count, as well as clinical signs of inflammation (i.e., fever, hypothermia, or systemic inflammatory responses with tachycardia, hyperglycemia)[3].

Recently, another validated score, the COntrolling NUTritional status (CONUT) score, a simple index calculated using serum routine analysis (albumin, total lymphocyte count, and total cholesterol), has been developed to correlate either with short-term and long-term prognosis in several diseases and in-hospital mortality or with immune nutritional status[5,6].

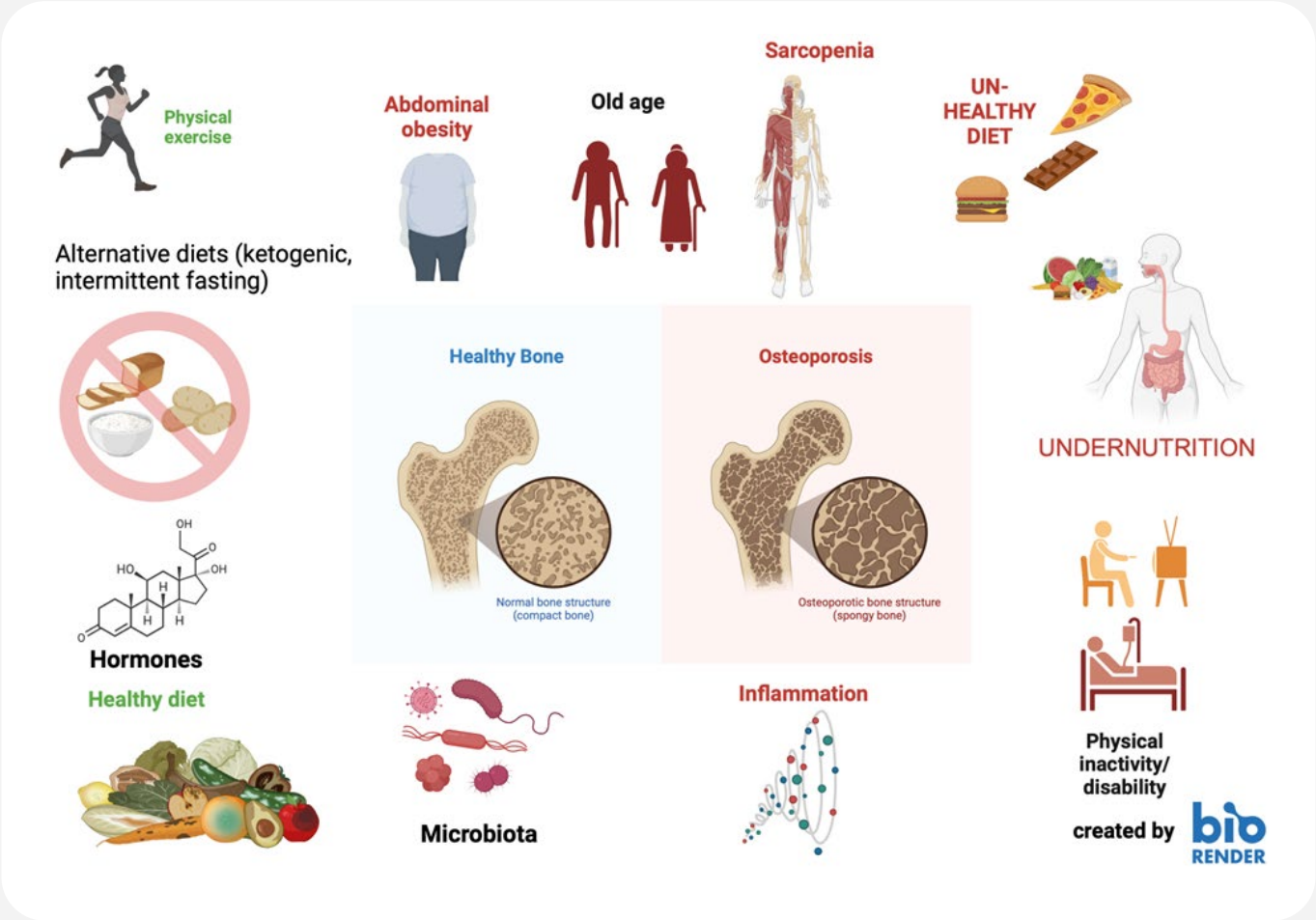


**Figure 1.** Life-style habits directly affect bone composition: obesity, aging, sarcopenia, un-heathy excessive or defective dietary habits, through favourating low-grade systemic inflammation and in combination with dysregulating hormonal signaling pathways (e.g., Leptin, insulin, corticosteroids) could foster dangerous alterations in bone micro-architecture, thus predisposing to osteoporosis.

In this regard, the role of the gut needs to be elucidated. Therefore, life-style modifications could become adjuvant therapy to prevent and to cure bone metabolism alterations. As an example, healthy diets (e.g., Mediterranean diet) combined with regular physical exercise and micronutrient supplies (e.g., calcium, magnesium, vitamin D) as well as a correct protein intake could avoid excessive bone mineral density loss. At the same time, for obese patients, encouraging weight loss through specific dietary advice (e.g., ketogenic diet, intermittent fasting) could prevent excessive bone loss and foster muscular strength.

## MATERIALS AND METHODS

Malnutrition should be considered a systemic syndrome, negatively affecting every body functions. The most important type of malnutrition is cancer-related cachexia, even though many other causes have been recognized in clinical practice. Importantly, malnutrition represents an important risk factor for fractures and for bone-related postoperative complications, as it can produce pathological alterations on bone composition[7].
Therefore, we perform a literature narrative review through PubMed, Google, Cochrane, Embase, and Science Direct to clarify the current point of view on the effect of non-cancer-related malnutrition on bone metabolism, with the aim of evaluating potential nutritional beneficial interventions.

## BONE METABOLISM ASSESSMENT

The most frequently used technique to assess bone mineral density (BMD) is dual X-ray absorptiometry (DXA), as it can exactly quantify bone mineral content (BMC) and areal bone mineral density. Peripheral quantitative computed tomography is a three-dimensional technique that can be used to assess volumetric bone mineral density and bone geometry at appendicular skeletal sites, evaluating the distinction between trabecular and cortical bone and providing measures of total and cortical bone area, cortical thickness, and estimations of bone strength.
These instruments are mostly used for research purposes and can be further combined with other techniques to estimate bone mechanical characteristics. The assessment of fracture risk is the ultimate outcome in bone research[8].
Alternatively, bone turnover markers (BTMs) are surrogate factors evaluating changes in bone formation and bone resorption rates, as they reflect acute changes in bone metabolic activity with a shorter period of assessment than a serial collection of BMD/BMC. They can be divided into bone resorption markers, as products of type I collagen breakdown generated during bone resorption (C-terminal cross-linking telopeptide of type I collagen (CTX), NTX, pyridinium cross-links) or indicators of osteoclast activity (tartrate-resistant acid phosphatase), and bone formation markers, as post-translational processing of type I collagen molecules (procollagen type I N propeptide (P1NP), procollagen type I C propeptide (P1CP), matrix proteins (osteocalcin) or enzymes (bone-specific alkaline phosphatase) released in the circulation from osteoblasts during their activity of bone matrix synthesis[8].
Bone is a dynamic tissue in which remodeling of its components is a continuous cycle formed by five phases: in the activation phase, local mechanical or systemic hormonal signals (e.g., TGF-β, M-CSF, RANKL, vitamin D, calcium, PTH, estrogen, androgen, and glucocorticoids) recruit progenitor of osteoclasts and osteoblast to initiate the process. In the resorption phase, mature osteoclast secrete metalloproteinases (MMPs) to digest mineral and organic bone matrices; then, in the reversal phase, Osteoprotegerin (OPG) block the receptor activator of nuclear factor-κB (NF-κB) (RANK)-RANK ligand (RANKL) complex formation and reduce resorption by inhibiting osteoclast differentiation and promoting apoptosis. In the formation phase, osteoblasts are recruited to the reabsorption site and are activated by local and systemic regulators, such as Wnt, sclerostin, and PTH, to induce osteoblastogenesis to replace the old bone; finally, in the termination phase, the immature osteoid is gradually mineralized through the incorporation of hydroxyapatite[9].
In particular, crystalline hydroxylapatite is embedded in a flexible organic matrix, composed of collagenous fibers. Calcium ions can be substituted by other bivalent metal ions, such as magnesium, strontium, copper or zinc ions, and in minor percentage by other anions, such as fluoride. In particular, zinc has been reported to exert a protective action against bone loss by suppressing osteoclastogenesis via the downregulation of RANKL/RANK, resembling the action of the drug denosumab. Therefore, dietary intake, together with intestinal absorption, influences the concentrations of minerals and trace elements detected in human bone[10,11].

In addition, skeletal muscle applies forces on the bone to stimulate high-magnitude strains, which in turn induce adaptations of bone mass, structure, and strength. Furthermore, muscle and fat as contributors to body weight offer mechanical stimuli for increasing bone mass to support a higher body weight, while absolute reductions in muscle/fat and the resulting mechanical unloading have been proposed to partially explain the effects of weight loss on bone health. The interaction between the three tissues is mediated by molecules produced by muscle (myokines such as IL6 and IL15, irisin) or fat (adipokines such as leptin and adiponectin) which act on bone, (ii) molecules secreted by bone (e.g., osteocalcin) with action on muscles/fat and iii) local/systemic endocrine factors (e.g., sex steroids) with effects on multiple tissues[12].

## NON-CANCER MALNUTRITION AND BONE METABOLISM

All considered, an imbalance of bone remodeling may lead to pathological conditions, such as osteoporosis. Osteoporosis is characterized by low bone mineral density (BMD) and microarchitectural deterioration of bone tissue, leading to decreased bone strength and increased risk of fractures. To date, DXA remains the gold standard for diagnosing and monitoring osteoporosis, as it has been shown to be linearly associated with fracture risk: in fact, a diagnosis of osteoporosis is made when the bone mineral density (BMD) is 2.5 standard deviations or more below the mean peak BMD for healthy adults, as measured by dual energy X-ray absorption (DXA)[13,14].

Osteoporosis can be caused by nutrient deficiencies, especially in calcium and vitamin D, which may lead to secondary hyperparathyroidism with calcium mobilization from the skeleton; systemic inflammations is another contributing factor, as it is known that pro-inflammatory cytokines, including IL-6 and TNFα, in addition to nutrient deficiencies, can produce bone loss in other gut disorders such as celiac disease and inflammatory bowel syndrome[15].

Bone morphogenetic proteins (BMPs), a member of the transforming growth factor-(TGF)-β superfamily, are involved in the remodeling process of the human skeleton by stimulating the osteoblastic differentiation of mesenchymal stem cells and by fostering the osteoclastogenesis: BMP ligands interact with combinations of type 1 and type 2 receptors, which, in turn, activate effectors called receptor-activated-(RA-) SMADs[16].

In addition, BMPs are important regulators of adipogenesis and of obesity-related metabolic disorders including glucose metabolism via increasing glucose uptake in mature 3T3-L1 adipocytes by PPARγ and GLUT4 upregulation[17].

BMP9 (also known as growth and differentiation factor-(GDF)-2) is the most important BMPs implicated in bone formation as it increases the expression of mRNA levels of the osteoblast differentiation markers, such as ALP, Cola1, and OCN in MC3T3-E1 cells by upregulating LGR6 and activating the Wnt/β-catenin pathway. It also increases the expression of two key transcription factors (OSX and RUNX2) that regulate the target genes of osteoblastic differentiation. Meanwhile, BMP9 suppresses RANKL-induced osteoclast differentiation of bone marrow macrophages (BMMs) by inhibiting the Akt-NF-κB-NFATc1 pathway[18].

BMP4 is a bone-inducing factor as it stimulates the synthesis of osteocalcin and osteoprotegerin via activation of the P38/MAPK signaling pathway in osteoblasts[19].

BMP7, known as osteogenic protein-1 (OP-1), has an osteoinductive activity too, as it induces osteoblast proliferation and inhibits osteoclast formation from monocyte precursor cells[20].

On the contrary, Sclerostin, an osteocyte product, encoded by the SOST (sclerosteosis) gene on chromosome 17, inhibits bone formation, as it decreases osteoblast activity while maintaining osteoclast function, leading to a shift of the bone remodeling balance towards bone resorption and bone loss[21].

BMP2 increases sclerostin levels to prevent overstimulation of the anabolic processes or ectopic bone formation through the Wnt signaling pathway[22].

In addition, RANKL, along with its cognate receptor RANK and osteoprotegerin (OPG), have been involved in bone remodeling and metabolic bone diseases. As aforementioned, RANKL, produced by osteoblasts, binds to RANK on the surface of osteoclast precursors and promotes osteoclastogenesis and bone resorption. On the other hand, OPG, also produced by osteoblasts, attenuates RANKL-RANK interaction through binding to RANKL, thus serving as a negative regulator of osteoclastogenesis and an inhibitor of bone loss[23].

Another important factor in bone metabolism is Leptin, whose receptors are plentiful in skeletal muscle, as well as in bone stromal cells; in fact, leptin can decrease bone marrow lipogenesis centrally via its receptors in the hypothalamus and directly via its receptors in bone marrow stem cells. It stimulates the differentiation of stromal cells to osteoblasts, increases the proliferation of osteoblasts, and inhibits osteoclastogenesis, while mature osteoclasts seem to be unaffected. However, hyperleptinaemia, observed in obese individuals, may exert a detrimental effect on BMD due to the development of peripheral leptin-resistance. All considering, leptin has been positively correlated with body mass index and subcutaneous fat mass and negatively with brown adipose tissue[24].

Leptin action is counterbalanced by adiponectin, which in turn stimulates osteoblastic proliferation, alkaline phosphatase activity, and the formation of type I collagen and osteocalcin, all markers of differentiation and maturation of osteoblasts, via phosphorylation of P38/MAPK, which enhances COX-2 (cyclooxygenase2) and BMP2 expression[25].

Insulin-like growth factor-1 (IGF-1) is another important bone anabolic factor, and incretin hormones, such as glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide 1 (GLP-1), can indirectly favourate bone anabolism via enhancing insulin secretion[26].

Cortisol, a hormone deregulated in malnutrition-related conditions, has a negative impact on bone health; 11β-hydroxysteroid dehydrogenase type 1(11β-HSD1),

the enzyme converting cortisone to active cortisol, is also upregulated by pro-inflammatory cytokines (TNF-α, IL-6), favoring bone loss in systemic inflammatory diseases[27]. Other pro-inflammatory cytokines (i.e., TNF-α, IL-6) have been related to alterations in bone metabolism via stimulating osteoclastogenesis through RANKL signaling[28].

## OBESITY AND BONE METABOLISM

The interaction between obesity and bone metabolism is complexly related to many mechanical and biochemical factors: even though the traditional view pointed out that obesity is associated with increased BMD due to a major mechanical overload on the bone, sarcopenic obesity is a risk factor for the development of osteoporosis, suggesting that the positive effects of body weight on BMD cannot counteract the detrimental effects of obesity on bone quality. To date, increased fat mass is associated with decreased bone mass in the so-called "obesity paradox"[29].

Obese patients show reduced levels of BMP9, which in turn reduces body weight, decreases the percentage of white adipose tissue (WAT), enhances the activity of brown adipose tissue (BAT), and increases the percentage of BAT as well as "browning"[30].

In addition, low levels of BMP7, an inducer of BAT differentiation, have been observed in obese patients. BMP7 can regulate brown adipogenesis and energy expenditure through a leptin-independent pathway via affecting P38/MAPK, PRD/M16, PGC-1, UCP-1, and mitochondrial signaling, and it is involved in body weight reduction by increasing energy expenditure and decreasing food intake via mTOR-p70S6 kinase pathway[31].

On the contrary, BMP4 levels are increased in obese patients, as it stimulates adipocyte formation, size, and activity while inhibiting the acquisition of a brown phenotype during terminal differentiation due to lipolysis suppression via regulation of hormone-sensitive lipase expression linked to reduced PPAR activity[32]. BMP2 levels are also increased in obese patients, as it contributes to the partition of energy storage into visceral (VAT) and subcutaneous adipose tissue (SAT) and to maintaining a pro-inflammatory status. In particular, a genetic variant rs979012 within BMP2 has been associated with the waist-to-hip ratio (WHR)[33].

Nevertheless, in obese patients a deregulation of the OPG-RANKL-RANK axis occurs in bone with a consequent inhibition of bone formation and an acceleration of bone resorption via an enhanced osteoclastogenesis in response to a low-grade systematic inflammation and to an increased adipogenesis in bone marrow[34]. Interestingly, this deregulated axis has been involved in perpetuating systemic inflammation and metabolic changes in a vicious cycle[35].

Obesity is related to reduced expression of adiponectin in VAT: adiponectin levels, in turns, have been negatively correlated with the amount of VAT, suggesting that the decrease in obesity-related adiponectin levels could potentially contribute to VAT over-accumulation on the whole body, and on its detrimental systemic effect in obese subjects[36].

In the skeleton, VAT can directly foster a reduction in trabecular volume, in bone formation rate and in bone stiffness, and an increase in cortical porosity; in addition, it can indirectly affect bone health by inducing systemic inflammation[37].

Obese individuals are also exposed to vitamin D deficiency due to reduced sunlight exposure, deficient calcium status, increased accumulation of fat-soluble vitamins in enhanced percentage of adipose tissue, and reduced milk apport in the diet because of excessive content of sugar-rich or phosphate-containing soft drinks, not bringing about adequate quantities of vitamins, minerals, and trace elements. Circulating levels of magnesium, another nutrient important for bone health, are also reduced in obese individuals due to fewer fruits and vegetables[38].

Although obesity is dangerous for bone heath, bariatric interventions for reducing body weight likely lead to bone loss over time too, even if the effects on BMD are dependent on the type of surgical procedure. Today, the most used bariatric procedures are divided into malabsorptive, as Roux-en-Y gastric bypass (RYGB), and non-malabsorptive, as sleeve gastrectomy (SG).

Recent evidence underlines that after bariatric surgery, BMD at the femoral neck decreased compared with nonsurgical controls[39,40].

Preoperative malnutrition consisting of vitamin D deficiency increased parathyroid hormone levels, and subnormal levels of zinc, copper, folic acid, and manganese can contribute to post-operative bone loss[41,42].

Bariatric surgery, especially malabsorptive procedures such as RYGB, has been found to aggravate or precipitate vitamin D deficiency, despite the recommended supplementation with about 15 µg vitamin D daily, due to the bypass of intestinal segments with vitamin D absorption. Deficits in the other fat-soluble vitamins, such as vitamins A, E, and K, are also frequently observed[43].

In particular, vitamin K seems to have a synergistic effect on bone mineral density with vitamin D, as it could lead to increased bone resorption due to reduced activation (carboxylation) of osteocalcin. Moreover, vitamin K acts as an essential component for the synthesis of the metal-chelating groups on Ca2+-binding proteins

that transfer calcium into the hydroxylapatite crystals.
Vitamin K occurs in the diet in two major forms: Vitamin K1 (phylloquinone) from green leafy vegetables such as spinach and cabbage, and Vitamin K2 (menaquinones). Nevertheless, postoperative vitamin K supplementation is not clearly recommended[44-46].
In addition, post-operative deficiency of vitamin B12, folic acid (vitamin B9) and vitamin C are associated to reduced bone health and osteoporosis due to disturbed collagen crosslinking: therefore, oral supplementation, routinely administered as a multivitamin tablet taken daily is strongly recommended[47].
Hypocalcemia after RYGB occurs in 5-25% of patients, suggesting that an adequate supplementation of both calcium and vitamin D is crucial to reduce the risk of postoperative bone loss and osteoporosis[48]; in particular, when serum calcium levels are too low, parathyroid hormone (PTH) is released from the parathyroid glands to increase renal, intestinal and bone reabsorption of calcium, with the purpose to normalizing calcemia[49].
Copper and zinc deficiencies have also been reported after malabsorptive bariatric procedures. Nevertheless, restrictive surgery as SG seems to represent an increased risk of reduced bone health due to impaired micronutrient uptake too.
In summary, the increased risk of osteoporosis after bariatric surgery is related to micronutrient deficiencies, which can alter bone mineral density for years after the intervention. For prevention, the bisphosphonate zoledronate, when given as monotherapy, has been found insufficient, but the postoperative periodically follow-ups, including determinations of calcium, albumin, phosphate, and PTH, as well as bone densitometry are strongly recommended after all bariatric surgery[50,51].
Molecularly, after bariatric surgery, a decrease in BMD and areal BMD (aBMD) with endocortical resorption, evidenced by the decrease in the number of trabeculae and a great increase of cortical porosity, an early and dramatic increase of biochemical markers of bone turnover, such as serum C-terminal telopeptide (CTx) and an overall increased risk of fractures in wrist, humerus, spine, hip, femur, clavicle, scapula, sternum, foot have been observed. As mentioned, the mechanisms involved are intestinal malabsorption of nutrients and minerals, reduction in lean mass and hormonal imbalances[52-54].

## SARCOPENIC OBESITY

Sarcopenia is a syndrome characterized by progressive loss of skeletal muscle mass, strength, power, and performance associated with a risk of disability, poor quality of life, and death. It has been classified in primary, age-related, and secondary, associated with lack of physical activity (after prolonged bed rest, reduced physical activity, and sedentary lifestyle), diseases (advanced organ failure, inflammatory diseases, malignant diseases, and endocrine abnormalities), and nutrition (macronutrient and micronutrient deficient diet, malabsorption, gastrointestinal disorders, and drug-induced anorexia)[55].
Sarcopenia can foster metabolic alteration of muscle and bone due to increased intramuscular fat deposition, decreased growth hormone (GH) secretion, and elevated production of pro-inflammatory cytokines such as interleukin-6 (IL-6), interleukin-1 (IL-1). Adipokin and leptin imbalance secondary to aging, inadequate protein synthesis, development of insulin resistance, and impaired fatty acid oxidation due to mitochondrial dysfunction and oxidative stress are also correlated with sarcopenia[56].
Moreover, sarcopenia-induced release of specific muscle cytokines, such as myostatin, can impair bone formation by inhibiting osteogenic differentiation of bone marrow stem cells (BMSCs), osteoblast differentiation, and bone mineralization[57].
Sarcopenic obesity (SO), characterized by a decline in both muscle and bone mass and an increase in adipose tissue, is defined as muscle mass >2SD less than the mean of muscle mass in adults aged 18-39 years with a gait speed < 0.8 m/sec[58].
It combines sarcopenia with concomitant obesity, leading to an increased risk of osteopenia, osteoporosis, fractures, falls, and mortality. It has a prevalence of 20% in older adults, in whom a gradual increase in total adipose tissue mass, redistribution of fat tissue with preference for fat surrounding the internal organs, muscles and bone, and reduction in subcutaneous peripheral fat is accompanied with a total skeletal muscle mass reduction[59].
As skeletal alterations have been strictly associated with sarcopenic obesity, a new clinical entity has recently been defined as osteosarcopenic obesity (OSO), but the exact mechanisms of these abnormalities are still almost unknown[60].
Metabolic alterations have been hypothesized to play a pivotal role in sarcopenia-induced bone rearrangements: in particular, increased cortisol levels, insulin resistance, and decreased levels of growth hormone, insulin-like factor 1, dehydroepiandrosterone-sulfate and sex hormones, as well as enhanced pro-inflammatory cytokine milieu (i.e., IL-6, IL-1, and TNF-α) have been observed in sarcopenic obese individuals[61].
In addition, decreased adiponectin in sarcopenic obese subjects can promote adhesion of the macrophages to endothelial cells, where they release RANKL/OPG/RANK pathway-stimulating cytokines, specifically TNF-α, IL-

1β, and IL-6, fostering local and systemic inflammation, which in turn promotes bone reabsorption[62].
Conversely, increased levels of serum leptin can lead to peripheral leptin resistance and reduced Skeletal Mass Index (SMI), via fostering TNF-α and Il-6-mediated systemic inflammation and insulin resistance[63].

## SARCOPENIC OSTEOARTHRITIS

Sarcopenic osteoarthritis is the coexistence of sarcopenia and osteoarthritis (OA). OA of the lower limbs is the most common joint dysfunction due to the mechanical stress they sustain; it is characterized by destruction of articular cartilage (synovitis), reduction of the inter-articular space, and development of osteophytes resulting in alteration of the joint architecture. Symptoms include pain, edema, stiffness, grinding of the affected joint, limited range of motion, and, in the final stage, atrophy of muscles supporting the affected joint[64].
Metabolic syndrome and central obesity (measured by waist circumference and waist-to-hip ratio) are also associated with radiographic osteoarthritis of the knee[65,66].
Leptin has a catabolic effect on articular cartilage; in a recent study, leptin was detected in the synovial fluid of patients with OA with a positive correlation with the disease severity, suggesting that its increased levels in the osteoarthritic joint and the expression of receptors on the cartilage cells surface could be used as a possible biomarker for OA. Moreover, increased levels of resistin, a pro-inflammatory mediator, in synovial fluid and in peripheral blood have been found in patients with OA[67].
Interestingly, the effects of reconstituted adipokine compounds on subchondral bone tissue from femoral heads of patients with hip OA who underwent total hip arthroplasty have been investigated. After stimulation of the subchondral bone from patients with normal body weight with reconstituted resistin, visfatin, or leptin, it was found that only resistin resulted in a significant rise in non-normal collagen type, which was also detected in obese patients with hip OA[68].

## OTHER FACTORS

Even though obesity represents a risk factor for abnormal bone metabolism, other factors may contribute to pathological bone metabolism derangements.
Anorexia exerts a negative impact on bone composition as it leads to hypoglycaemia, leucocytopaenia, hypoalbuminemia, hypophosphatemia, hypoinsulinaemia and electrolyte imbalances due to a hypercatabolic state. Reduced BMD is almost always present in anorexic patients, and nutritional interventions are necessary either with oral supplements or with enteral/parenteral feeding, even avoiding re-feeding syndrome[69].
Ageing is strongly associated with sarcopenia, predisposition of fat mass, osteoporosis, and osteoarthritis, due to a loss of osteocytes in the bone matrix and a reduction in the proliferative capacity of osteoprogens in the periosteum, which weakens the reaction of bone to muscle contraction and normal mechanical stimuli[70].
In addition, in older patients, a reduction in leptin sensitivity with concomitant hyperleptinemia due to central hypothalamic leptin resistance has been associated with increased bone marrow adipogenesis and bone marrow fat deposition with age[71].
Hyperglycaemia, excess insulin levels, and insulin resistance (i.e., in type 2 diabetes) are purported to be associated with low bone turnover, impaired bone microstructure, and bone matrix quality. Conversely, weight loss enhances insulin and leptin resistance but reduces their absolute concentrations, thus producing weight-induced bone loss[12].

### Dietary patterns and bone metabolism

As malnutrition represents an important etiological factor for bone health, dietary habits affecting nutrient absorption could become either causes or solutions for bone metabolic abnormalities.
Low-calorie ketogenic diet (LCKD) and very-low-calorie ketogenic diet (VLCKD) are diets low in carbohydrates and high in lipids, effective in losing weight quickly and safely, improving body composition, athletic performance and markers of cardiovascular and metabolic health[72].
It provides less than 20% of daily caloric intake as carbohydrates (<50 g/day), more than 50% from lipids, and a moderate but variable amount of proteins to preserve glycogen and lean tissue protein utilization, increase lipolysis and fatty acid oxidation, and generate marked elevation of plasma ketone bodies (KB), like acetate, acetone, and ß-hydroxybutyrate (3-ßOH), as effective alternative fuel source for tissues. These keton bodies can also exert anti-inflammatory and anti-catabolic effects on skeletal muscle by inhibiting activation of the NF-kB pathway[73]. Keton diet is effective in reducing body weight and fat mass without inducing loss of muscle mass and fat-free mass (FFM), thus preventing the risk of sarcopenia[74]. Nevertheless, it can also induce bone mineral density (BMD) loss, as it alters vitamin D levels, lowers growth factors, and brings a high “acid load” via ketone body accumulation. Moreover, it has been associated with hypercalciuria, urine acidification, and hypocitraturia due to increased renal

excretion of acid to compensate for the dietary acid overload: in fact, the skeleton acts as a buffer system through its active resorption to tamponade acid pH secondary to keton bodies excess[75]. Molecularly, in an in vitro model of osteoblasts (OBL) cultures, the mineralization activity appears to be upregulated by acetoacetate and downregulated by 3ßOH-B[76].

However, in 2023 a systemic review of 7 trials demonstrated no significant changes in bone mass density after ketogenic diet; no significant effect on bone resorption by measuring urinary N-telopeptide levels, as neither effect on bone formation by measuring bone-specific alkaline phosphatase, or alterations in overall bone turnover were reported. However, patients on KD lost significantly more weight than controls, associated with an increase in serum vitamin D levels and a reduction in plasma parathyroid hormone levels[77].

A balanced diet with adequate intakes of certain nutrients (i.e., calcium (Ca) and proteins) and foods (e.g., dairy products, fruits, and vegetables) is important for maximizing and maintaining bone properties. Conversely, an unbalanced Western-type diet typically high in ultraprocessed foods, saturated fats, refined sugars, and salt appears to compromise bone health through direct (e.g., salt-induced increases in urinary Ca excretion) and indirect (chronic inflammation, contribution to obesity and associated metabolic diseases) mechanism[78,79].

A recent RCT trial of 102 patients demonstrated that vegetable consumption following the Dietary Guidelines for Americans recommendations (between 44 and 80 g for people at an energy need of 2000 kcals/d) could benefit bone health via reducing serum and urinary acidity and urinary calcium excretion. In fact, in the experimental group a greater urinary pH ($p < 0.05$) and a lower urinary excretion of titratable acid ($p < 0.01$), ferrum ($p < 0.01$), and magnesium ($p < 0.05$) as well as a lower serum concentration of C-terminal telopeptide of type I collagen (CTX) and a higher serum level of bone-specific alkaline phosphatase have been reported[80].

Two previous clinical trials[81,82] also demonstrated that a diet with a greater intake of carotenoid-rich fruits and vegetables, as well as greater consumption of green tea, could increase bone formation and decrease bone resorption markers. In addition to providing essential nutrients to bone, such as vitamins and minerals, vegetables contain bioactive components such as flavonoids and carotenoids with antioxidant properties, which can decrease the production of proinflammatory cytokines and bone resorption[83,84].

Olive oil, which is rich in olive polyphenols that effectively reduce oxidative stress and inflammation, can contribute to prevent bone loss and improve bone loss markers too[85].

Current evidence supports additional musculoskeletal benefits from higher protein intakes (≥ 1·2 g/kg/d) for older individuals, while, to maximize protein synthesis, distribution of protein intake over waking hours, and consumption of ≥ 2 meals per day with ~0·4 g protein/kg are encouraged[86]. In fact, dietary proteins provide amino acids essential for the synthesis of bone matrix and skeletal muscle, foster the expression of insulin-like growth factor-1, and decrease bone and muscle breakdown during aging[87].

In 2017, Heer et al88 found that 60 days increased protein intake (1.45 g/kg/d + 0.72 g/d branched chain amino acids versus 1 g protein/kg/d) could enhance circulating bone turnover markers levels as Procollagen type 1 N-terminal propeptide (p1NP), C-terminal telopeptide type-1 collagen (CTX), thus ameliorating bone remodelling.

In 2023, an umbrella systematic review (PROSPERO: CRD42018082395) confirmed the beneficial effect of protein intake above the recommendation (1.0 g/kg BW/day) in adults > 65 years of age for bone health, even though authors did neither reveal positive nor negative effects on bone turnover markers due to insufficient strong evidence[87].

However, a recent RCT of 64 patients allocated to receive either 60 g/d of whey protein hydrolysate or maltodextrin in combination with either high (30 g/d) or low dietary fiber intake (10 g/d) for 12-weeks reported only a non-significant positive association between protein intake and positive changes in P1NP and CTX[89].

Supplementation with fermented dairy products as yogurt appears useful to improve micronutrient adsorption, as symbiotic yogurts enriched in inulin and in the probiotic *Lactobabacillus rhamnosus* increased intestinal absorption of calcium and phosphorus[90].

As aforementioned, high-fat diet (HFD) is associated with increased bone quantity (larger bone size and mineral content) but decreased bone quality (lower size-independent mechanical properties due to a reduction in trabecular bone density, an increased bone resorption due to RANKL/RANK/OPG-dependent osteoclastic hyperactivity and an increased bone marrow adiposity, which in turns inhibit the differentiation of bone marrow stem cells into osteoblasts[27].

This particular decrease in bone trabecular density, bone trabecular volume fraction, bone mineral content, and quantity is probably due to the hypersensitivity of cancellous bone to bone turnover for its larger surface to volume ratio[91].

Among ultraprocessed foods, sugar-sweetened beverages consumption, particularly carbonated beverages, is inversely correlated to BMD[92]. However, literature evidence reported that undernutrition by caloric restric-

tion with a subsequent decrease in body weight is associated with reduced bone mass[93,94].

In addition, selective dietary patterns could lead to nutrient deficiencies, thus representing a sort of dietary-induced malnutrition. Among them, strict adherence to a vegan diet has been associated with low calcium intake and low vitamin D levels. Vegetarian and vegan patterns have been associated with lower bone mineral density and increased fracture risk[95] in a BMI-dependent manner, as lowest BMI is most likely to develop osteoporosis and bone metabolism alterations[96].

A 6-week intervention trial in healthy men investigating whether the partial replacement of red and processed meat by nonsoya-vegetables would modify bone turnover demonstrated no changes either in the circulating levels of bone specific alkaline phosphatase nor of tartrate-resistant acid phosphatase[97]. However, 2 years earlier, the same research group reported that plant proteins as compared with animal protein accelerated bone turnover[98], suggesting that literature evidence is still controversial[99].

To date, compared with omnivores, peripheral skeleton trabecular and cortical microstructure are altered in vegan people, with a slightly different in vegan people practicing regular exercise training and calcium-vitamin D supplements[100].

Another dietary habit called intermittent fasting (IF) has been reported to exert a protective effect on bone health. The 5:2 diet, alternate-day fasting (ADF), alternate-day modified fasting and time-restricted eating (TRE)/time-restricted feeding are the most adopted and researched types of IF regimens. The '5:2' diet alternates severe energy restriction (consuming ~25% of energy requirements) on 2 days of the week with ad libitum eating on the remaining 5 days, leading to 4-7% weight loss over 8-52 weeks and improving insulin sensitivity[101].

Alternate-day fasting (ADF) involves a day of fasting alternated with a day of adequate or ad libitum eating: even though achieving weight loss; it is supposed to reduce lean mass to a greater extent than traditional energy restriction[102]. In animal studies, it has been shown to inhibit osteoclast proliferation and osteogenic differentiation, determining lower levels of bone resorption markers and higher levels of bone formation markers[103]. However, in human observational studies, no differences were seen in total body BMC or BMD among healthy adults who were following ADF over periods ≥ 6 months and healthy controls[104].

A study in healthy lean males and females compared the effects of ADF with net energy restriction (25% energy deficit) with continuous energy restriction (matched 25% energy deficit applied daily) and ADF without energy restriction over 3 weeks. Despite weight loss after continuous energy restriction was largely achieved by reducing body fat mass, ADF led to lesser reductions in fat mass accompanied by a reduction in lean mass. No significant changes were seen in the plasma concentrations of the bone resorption marker CTX or total body BMD (assessed by DXA)[102].

Another 6-months RCT, comparing ADF versus non-ASF diet, confirmed no significant changes for total body BMC or BMD (by DXA) and none alteration in circulating levels of surrogate markers of bone formation (osteocalcin, bone alkaline phosphatase) and bone resorption (CTX) in all groups[105].

In another RCT, although total body BMC (by DXA) was not affected, BMD at the level of the lumbar spine (extracted from regional analysis of total body DXA scans) decreased in the ADF group[104].

Time-restricted eating (TRE) is based on restricting food intake to short daily windows (4-12 h), thereby extending the overnight fasting to at least 12 h, by skipping a meal or delaying the time of the meals101. This approach has been reported to reduce femoral BMD in animal eating a high-fat diet during the ad libitum periods, as the greater fat deposition inhibited osteoblasts differentiation from bone marrow mesenchymal cells[106].

In two human cross-sectional analyses[107,108], people who skipped breakfast ≥3 times per week had lower hip BMD compared with those who consumed breakfast daily.

In a subanalysis, Lowe et al[109] found that the TRE group decreased their body mass from baseline by a small amount (–1·7 kg) with an increase in total body BMC and no changes in body weight or bone. In another trial, Lobene et al[110] reported reductions in the bone formation marker P1NP with no changes in other bone metabolism molecules (NTX or PTH) in the TRE interventional group. In another cross-over RCT TRE had no impact on participants' body mass, lean mass, total body or regional BMD (by total body DXA)[111].

Furtherly, a longer-term (6 months) TRE intervention (employing a 12-h ad libitum eating window) had no unfavourable effects on bone metabolism (BTMs and bone-related hormones) or bone loss (total body BMC/BMD by DXA) compared with the provision of standard dietary advice. In particular, the control group experienced a modest loss of total body BMC, which was supported by small, albeit non-significant increases in bone resorption (CTX). By contrast, when weight loss was achieved by TRE, BMC was preserved with CTX concentrations tending to decrease. These findings suggest a possible benefit of TRE on bone health during weight loss[112]. However, studies on the effect of IF on bone metabolism were too short (max 6 months follow up) and had a too small sample size to reach statistically significant conclusions.

## PHYSICAL EXERCISE AND BONE METABOLISM

Interestingly, the effect of dietary habits on bone composition could be influenced by physical activity, as exercise, especially resistance training, is often promoted as a strategy to attenuate bone loss during weight loss[113]. Kotarsky et al[114] compared the effects of 8 weeks of TRE in combination with an aerobic and resistance exercise program with a habitual diet and the same exercise programme in obese adults, demonstrating that TRE+exercise reduced total body mass (3·3% versus 0·2%) and fat mass (9·0% versus 3·3%) to a greater extent than the control group. Lean body mass tended to increase due to exercise, with no differences between groups.
Meta-analyses of exercise interventions have shown that programs incorporating moderate- to high-intensity resistance and impact exercise can either increase or maintain areal bone mineral density (aBMD); a subanalysis at the femoral neck also demonstrated that bone loss was more attenuated in adults aged >60 years and that only 12 weeks of treadmill walking exercise performed at 70% maximum heart rate during diet-induced weight loss was sufficient to significantly ameliorate lumbar spine and total hip aBMD (+5.2%)[115,116].
A well-known training principle to consider when designing osteogenic exercise regimens is the "progressive overload": as loads or strains imparted on bone via muscle or gravitational forces must exceed typical loading patterns experienced during everyday activities for osteogenesis to occur, and as bone adapts to them, loading stimulus should be increased progressively. Load pattern (distribution), rate, and frequency are other parameters to adequate progressively[117].

## MICROBIOTA, DIET, AND BONE METABOLISM

Recent evidence demonstrates a particular interaction between gut and bone health, as microbiota can influence the absorption of nutrients required for skeletal development. Moreover, microbial fermentation of dietary fiber to short-chain fatty acids (SCFAs) also plays an important role in maintaining bone density either indirectly via regulating nutrient absorption in the intestinal tract, or directly via inhibiting osteoclast differentiation and favoring osteoblast proliferation. Further researches are still evaluating the potential implication of the gut in the regulation of bone health via the immune system and hormonal modulation in a sort of "gut-bone axis"[118-120]. Alterations of gut microbiota have been reported in malnourished patients, with a reduction in beneficial SCFAs-producers and an increase in pro-inflammatory strains, thus suggesting that modulation of gut microbiota could represent a new adjuvant therapy to avoid bone abnormalities, although evidence in the literature is still lacking and need further investigation[121].

## CONCLUSIONS

Malnutrition is a well-established risk factor for bone loss and reduced bone mineral density: dietary patterns, aging, undernutrition, sarcopenia, and obesity are the most common non-cancer-related causes of micronutrient deficiencies which could lead to significative alteration in bone composition, thus increasing the risk of osteoporosis and fractures.
Therefore, following a balanced diet with adequate supplementation of calcium and vitamins seems to be the best lifestyle modification to avoid pathological bone loss in all individuals. Even though in obese patients other dietary habits to lose weight should be suggested, avoiding bone loss by regular physical exercise preventing sarcopenia and by micronutrient supplementation should be considered. Nevertheless, literature evidence suggests that the gut microbiome could affect bone health in a sort of "gut-bone axis", suggesting that it could become a future target therapy to ameliorate bone metabolism. All considering, dietary treatments to foster consumption of fruit, vegetables and unsaturated fats (i.e., olive oil) and to avoid fat-rich foods, in addition to moderate aerobic activity still represent the gold standard to beneficially modify bone composition in all malnourished patients, thus preventing pathological complications as osteoporosis and fracture risk.

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

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