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Osteosarcopenic adiposity syndrome update and the role of associated minerals and vitamins

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The objectives are to present an updated synopsis on osteosarcopenic adiposity (OSA) syndrome and evaluate the roles of selected micronutrients in its prevention and management. OSA refers to the concurrent deterioration of bone (osteopenia/osteoporosis), muscle (sarcopenia) and adipose tissue expansion. It portrays the most advanced stage in a continuum of body composition disorders. Although OSA has been widely studied involving the populations of different backgrounds, its prevalence is hard to collate because different methodologies and criteria were used for its diagnosis. Another critical health aspect is the presence of low-grade chronic inflammation (LGCI) which contributes to OSA and *vice versa*. Nutrition is important in the prevention and management of both OSA and LGCI. Although micronutrients act in numerous metabolic and physiological processes, their roles here are presented in relation to OSA (and its components) and LGCI in general and relevant to the COVID-19 pandemic. These include calcium, magnesium, phosphorus, potassium, sodium and vitamins D and K; their interactions, physiological ratios and synergism/antagonism are discussed as well. In conclusion, calcium, magnesium and vitamin D have a profound impact on OSA and its components, and the latter two also on LGCI. Potassium and vitamin K are vital in bone, muscle functioning and possibly adipose tissue modification. Both, but particularly vitamin D, surfaced as important modulators of immune system with application in COVID-19 infections. While both phosphorus and sodium have important roles in bone, muscle and can impact adiposity, due to their abundance in food, their intake should be curbed to prevent possible damaging effects.

Micronutrients: Minerals: Vitamins: Osteosarcopenic adiposity: Osteosarcopenic obesity

Apart from the current SARS-CoV-2 (COVID-19) pandemic (2020–2021) that resulted in declining health and premature deaths of millions of people, the life expectancy in the past 100 years has been steadily increasing throughout the world[1]. Subsequently, as the number of older adults grows, so are the numerous comorbidities associated with ageing. Some could be avoided with proper care and lifestyle, while some are inevitable. Among the latter is the low-grade chronic inflammation (LGCI) and the deterioration of body composition

Abbreviations: Gla, γ-carboxyglutamic acid; LGCI, low-grade chronic inflammation; OSA, osteosarcopenic adiposity; OSO, osteosarcopenic obesity; PTH, parathyroid hormone.

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components, namely bone, muscle and adipose tissue; ultimately leading to osteopenia/osteoporosis, sarcopenia/dynapenia and overweight/obesity, respectively[2–4]. Each of these body composition disorders has been studied throughout the years particularly in older individuals, although for the most part, as separate entities. The research converging bone and muscle health (osteopenic sarcopenia) or muscle and adipose tissue (sarcopenic obesity) has been gaining attention in the past decade. However, the research investigating the simultaneous deterioration of all three tissues, their interactions and their reciprocated influences compounded by the presence of LGCI, has started relatively recently[2].

Such research led to the identification of the osteosarcopenic adiposity (OSA) syndrome, initially termed osteosarcopenic obesity (OSO) syndrome[2] (see discussion later), reflecting coexisting impairments of all three tissues. OSA presents a good model for studying body composition changes under various conditions and influences; it could be relatively easily assessed[3] and subsequently acted upon with reasonably effective measures[5–7]. Nutrition and lifestyle play important role in both OSA and LGCI. Single nutrients, food components and/or food as a whole have been investigated mostly in relation to only one of the impaired conditions, not necessarily to the combination of OSA components and LGCI and not for longer periods.

Among the single nutrients, vitamins and mineral elements (minerals) are receiving increasing attention in the COVID-19 pandemic due to the anti-oxidative and anti-inflammatory properties and immune system modulation which some of them exert (2020–2021)[6,7]. In this context, it is important to keep in mind that micronutrients are not consumed alone. They also do not act alone but are involved in complex processes with other nutrients, enzymes and/or other molecules, performing multiple tasks along the different metabolic pathways. Moreover, some of them have synergistic or antagonistic effects, play different roles in different tissues and/or may be affected by epigenetic influences[8,9]. These are probably the main reasons why so many studies investigating nutritional effects on health outcomes result in different and even controversial findings. The complexity of nutrients' action and difficulties in assessing their requirements and intake in human subjects was addressed recently, where the concept of nutrient ratio was introduced[10,11], possibly providing a better way for linking dietary intake with health outcomes, as well as offering better estimates for the nutrient recommendations.

Although micronutrients act in numerous metabolic and physiological processes, their roles here are presented in relation to OSA and LGCI, focusing on those having the highest influence. These include calcium (Ca), magnesium (Mg), phosphorus (P), potassium (K), sodium (Na) and vitamins D and K. Therefore, the purpose of this paper is to: (a) present an updated synopsis on OSA; (b) evaluate the roles of and recommendations for selected micronutrients with regard to influencing OSA and LGCI, bearing in mind their interactions, physiological ratios and their synergism and antagonism. Because of a scarcity of interventional clinical trials, this evaluation includes the results from the observational studies and *post hoc* analyses and the findings inferred from the studies with similar conditions.

What do we know about osteosarcopenic adiposity?

The OSA concept was substantiated based on the common precursors of three body composition tissues in the mesenchymal stem cells (namely, osteoblasts, myocytes and adipocytes), the hormonal interactions among the three tissues, and the common aetiologies in the impairment of each, leading to osteopenia/osteoporosis, sarcopenia/dynapenia and compromised adipose tissue[2]. It could then be speculated that OSA has multiple causes, including ageing, chronic inflammation, stress, inadequate nutrition, immobilisation and/or some chronic diseases (cancer, diabetes), as those also may be the causes for each individual disorder within OSA[6,7,12].

OSA is a complex entity reflecting the most advanced stage on the spectrum of body composition disorders, starting at the place where the adipogenesis expansion originated; most likely at adipose tissue itself. Therefore, it could begin with one or two conditions (e.g. osteopenic adiposity, sarcopenic adiposity) and evolve into the full-blown OSA syndrome (Fig. 1). The underlying LGCI exacerbates the OSA and *vice versa*, creating a vicious cycle with everlasting and worsening outcomes[6,7,12].

What do the results from other studies show?

A detailed review evaluating the studies on OSA/OSO was published in 2019[13]. For an update, a quick search in February 2021 on PubMed using 'osteosarcopenic obesity' as a key phrase returned only fifty articles, with four in each 2014 and 2015; five in 2016; eleven in 2017; seven in each 2018 and 2019; sixteen in 2020; and one in 2021. This seems to be an underestimated reflection of the overall number of published articles about the issue, since the search with various other key words/phrases, including three body composition compartments, returned hundreds of hits. Evaluation of these studies revealed that osteopenia/sarcopenia/adiposity was addressed in many of them, but the condition was not specified as OSA/OSO. Some other studies had databases from which OSA/OSO could have been identified[13], but the objectives were different, or the authors were simply unaware of or did not use the term.

After the proof of concept was established in 2014[2], among the first published original studies was one in Caucasian overweight/obese postmenopausal women. The study depicted significant inferior functionality (handgrip strength, walking speed, balance) in women with OSA, compared to their counterparts who were obese only[14]. Subsequently, several other studies reported similar findings in which OSA was associated with inferior functionality[15–18] and higher frailty scores[19] in older individuals with OSA compared to those with only one or two impaired body composition outcomes. These studies suggest that individuals with OSA may be at increased risk of falls and subsequent

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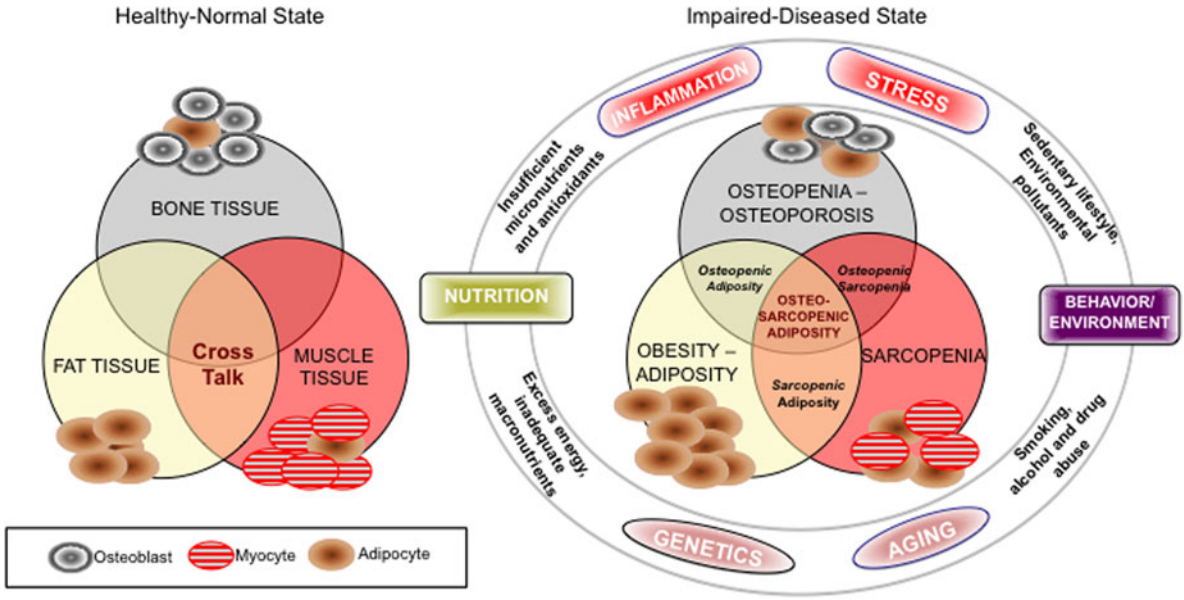

Fig. 1. (Colour online) Conceptual model of bone, muscle and fat tissue development from each tissue-specific cells in healthy (left) and impaired (right) states. Osteosarcopenic adiposity is the most advanced condition of body composition impairment with various possible influences depicted (right). Genetics and ageing are inevitable and most powerful influences that could not be manipulated or changed. Other influences could potentially be mitigated. Modified from Ilich *et al.*[3] and Ilich[7]. Creative Commons Attribution License (https://creativecommons.org/licenses/by/4.0/).

fractures (although the direct connection with fractures was not established), as well as other disabilities and poorer quality of life[7]. Other researchers reported that individuals with OSA, compared to those without OSA, had poorer cardiometabolic disease markers (both men and women) and lower serum vitamin D[20]; higher prevalence of hypertension even after adjusting for confounders[21]; worsened lipid profile[22]; and lower serum vitamin D[23]. The results of these studies indicate possible elevated metabolic disorders in individuals with OSA.

Evaluation of body composition in patients with other chronic diseases was also conducted in a few studies. For example, in a sample of about 40-year-old women with rheumatoid arthritis, 42·2 % were identified as having OSA[24], obviously indicating impaired overall body composition status. In the study among older men with and without HIV, those identified as having OSA (although such term was not used, but patients' characteristics clearly pointed to its existence) had significantly higher fragility scores, compared to men without OSA, regardless of the HIV status[25]. Carsote *et al.* conducted a mini-review evaluating some forty studies in patients with various malignancies, concluding that obesity with underlying sarcopenia may worsen the oncology outcomes[26]. Considering increased proinflammatory state and catabolic features of cancers, as well as the consequences of cancer therapy, the bones and adipose tissue may have been impacted as well, although not specifically addressed in that review. Thus, all three tissues when impaired could lead to worse cancer prognosis while malignancy itself may worsen the OSA, contributing to a vicious cycle. A recent pilot study evaluated body composition in breast cancer survivors (mostly stage I and at least 5 years into survivorship) comparing them with their age-matched healthy counterparts[27]. About 94 % of women in each group were obese and the prevalence of OSA in breast cancer survivors was 5·9 % compared to 0 % in control group. This study needs to be taken with caution because of the small number of participants (*n* 35 total); however, some other studies reported compromised body composition in breast cancer survivors, although not explicitly determining the prevalence of OSA[28–30].

Studies reporting nutritional associations with osteosarcopenic adiposity

At the time of writing, there are no published clinical trials with nutritional intervention to assess their effects on OSA. A few of the published studies were observational or retrospective, utilizing *post hoc* analyses or cross-sectionally comparing the intake of individuals with OSA to those with normal or milder body composition impairments. Among them, the most studied were macronutrients and rarely micronutrients. For example, de França *et al.* reported that protein intake as g/kg body weight (but not as a percent of energy) was significantly lower in individuals with OSA[17]. In that study, participants (*n* 218; both males and females age 59–69 years) were divided into eight groups: from normal body composition to OSA. None of the other nutrients examined (including Ca and vitamin D) were significantly different among the groups. Although the categorisation of participants into eight groups based on the body composition status was commendable as it included

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all possible variations, the study was probably underpowered. Some groups had only six, eleven or fourteen participants and dietary intake was not separated for men and women.

Choi and Bae, utilizing the database from the Korean National Health and Nutrition Examination Survey, reported that men (age >50 years) with OSA had lower plant-based and overall protein intake compared to control men[31]. Other Korean researchers utilizing the same databases collected in different years showed poorer diet quality[23], higher dietary inflammatory index[32] and lower fruit intake[33] in OSA individuals compared to those in other groups. Obviously, more studies are needed to bring insight into the full influence of diet, as well as specific nutrients, on OSA. Further refinement in personalised nutrition may bring a breakthrough in this area.

Difficulties in diagnosis and subsequent controversies in the prevalence of osteosarcopenic adiposity

Of note is that the studies identifying OSA used different methodologies and criteria to diagnose OSA components (osteopenic adiposity, sarcopenia, sarcopenic adiposity or adiposity alone), which resulted in ununiformed diagnosis of OSA itself. Therefore, it is of no surprise that the overall prevalence of OSA is hard to infer and it ranges from about 3 to 20 %[13], typically (but not always) lower in men than in women.

While the consensus on diagnosing osteopenia/osteoporosis has been established many years ago and followed worldwide, even for specific ethnicities[34], that is not true for osteopenic adiposity, or other body components within OSA. There is still no uniform diagnosis for sarcopenia; some utilise the criteria based on functional performance, others on the appendicular lean mass index, while others use both[3]. Additionally, sarcopenia is diagnosed mostly by measuring the appendicular lean mass (a proxy for muscle), thus presents just an approximation of a true muscle mass.

Discrepancies in cut-offs for overweight/obesity determination: Another problem in the standardisation of OSA diagnosis is a lack of consensus for cut-offs in determining adiposity. Using BMI is still the most common way to categorise individuals into weight categories, but due to its numerous limitations[6,13] its use is being discouraged in research settings, as well as for more accurate determination of body composition and associated risks[35].

Regarding the use of some popular technologies, e.g. dual-energy x-ray absorptiometry or bioelectrical impedance, the cut-offs for determining obesity based on the total body fat range from 32 to 40 % for women and 25 to 35 % for men[36,37]. Therefore, due to the lack of consensus, it is up to each researcher to choose the cut-offs. However, a much bigger problem is the heterogenic feature of adipose tissue, addressed recently[6]. Briefly, visceral fat surrounding the organs (mostly in abdominal area) and infiltrated/ectopic fat in bone and muscle can be accurately detected only with limited technologies (e.g. MRI or computed tomography), thus, not widely available. In fact, the heterogeneity of adipose tissue was the main reason why the original term OSO was changed into OSA; obesity typically referring to the overt overweight-phenotype and adiposity, in addition to the overweight-phenotype, also reflecting the complexity of fat tissue[36]. Additionally, the term OSA also aligns better with the original definition of the syndrome[2,6]. However, since the term OSO was depicted in the earlier studies, either term reflects the same condition and is used interchangeably.

Of note is that the potential breakthrough could be the development of biomarkers for each tissue which in combination may indicate the existing impairments and presence of OSA. A pilot study showed increased levels of serum sclerostin (bone resorption marker), skeletal muscle troponin (muscle breakdown marker), inferior lipid profile and increased leptin in women with OSA compared to their counterparts with only one or two impaired conditions[38]. However, more refinement is necessary, and the series of omics will need to be determined to serve as potential markers. It is encouraging that omics research, applying artificial intelligence, big data and systems research is advancing biomedical sciences, particularly toward personalised medicine, diagnostics and therapeutics to promote healthy longevity.

Overall, despite the shortcomings, OSA has been studied worldwide in populations of different sex, age, background and ethnicity (Caucasians, Koreans, Chinese, Latin Americans), bringing more insight into the issue, which was the goal and aspiration when the syndrome was first identified[2]. However, identifying OSA still depends on each researcher's abilities, institutional infrastructure and available equipment.

Osteosarcopenic adiposity: a cause, a consequence or both?

As reported earlier, it is likely that the health consequences of OSA with comorbidities are greater than the sum of its individual components[6,7], especially considering the underlying LGCI. Since the results from reported studies are mostly based on associations, it is hard to distinguish whether OSA is a cause or a consequence or both for various impairments. The most frequent impairments associated with OSA are frailty and functional deteriorations, including, but not limited to hand-grip strength, balance and walking abilities, which all increase the risk for falls[14–19]. Vulnerability to chronic poor health probably due to metabolic deregulations, leading to higher susceptibility to infection, including COVID-19 (2020–2021), as well as worsening the oncological and other chronic diseases[20–25,27–30], are other possible causes/consequences. The presence of OSA–LGCI may also contribute to a worsened quality of life accompanied by another set of comorbidities, premature nursing home placement, and even premature death[6,7,13].

In view of the afore-mentioned, it is important to continue research on OSA, even with the existing limitations for its global and/or ethnic-specific diagnoses. Only continued research will bring more insight into its causes and

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Table 1. Micronutrients affecting osteosarcopenic adiposity (OSA) components and low-grade chronic inflammation (LGCI) with best food sources for each and current daily recommendations for older individuals in USA[47] and Europe[48]

Micronutrients	OSA	LGCI	Best food sources	DRI or AI* (USA) DRV or AI* (EFSA)
Calcium	†		Milk and dairy foods, sardines with bones, tofu, broccoli, kale, collard greens	1200 mg/d 950 mg/d
Magnesium	†	‡	Nuts, seeds, beans, legumes, whole grains, chocolate	320 (F), 420 (M) mg/d 300 (F), 350 (M) mg/d*
Phosphorus§	¶	Implicated	Abundant in all foods, present in soft drinks and processed foods	700 mg/d 550 mg/d*
Potassium	¶	Implicated	Bananas, potatoes, beets, beans, spinach, tomatoes, other fruits and vegetables	2600 (F), 3400 (M) mg/d* 3500 mg/d*
Sodium§	**		Abundant in all foods, used widely in processed foods	1500 mg/d* 2000 mg/d*
Vitamin D	†	‡	Butter, egg yolks, fatty fish, cod-fish-liver oil, fortified dairy (in the USA)	20 μg/d 15 μg/d*
Vitamin K	¶	Implicated	Kale, cabbage, spinach, Brussels sprouts, asparagus, broccoli, fermented dairy foods	90 (F), 120 (M) μg/d* 70 μg/d*

DRI, dietary reference intake[47]; AI, adequate intake; DRV, dietary reference values; EFSA, European Food Safety Authority[48]; F, females; M, males (when recommendations are different).
* When DRI or DRV is not available, AI is used.
† Confirmed positive modulation for all three OSA components.
‡ Confirmed benefits for LGCI.
§ Excess could be damaging.
¶ Confirmed modulation for two OSA components (bone and muscle) and implicated for adipose tissue.
** Possible negative effect on bone when in excess.

consequences, and more importantly, to its possible management and treatment.

Micronutrients most closely related to osteosarcopenic adiposity

The minerals and vitamins most closely related to OSA syndrome and its components are Ca, Mg, P, K, Na, vitamin D and vitamin K. Based on national surveys and other reports, all of these minerals (except P and Na) and vitamins are at lower or marginal intake in the US population[8,39,40], as well as globally[41–45], when compared to each nation's official recommendations. This is particularly true for vitamin D, probably due to its scarcity in food. It is worth noting that some improvements in the intake of these nutrients could be achieved with the consumption of supplements (although uncontrolled supplementation is not recommended), or even in the case of home-delivered or congregate meals in community-dwelling older adults[46]. Table 1 summarises the roles of the discussed minerals and vitamins in relation to OSA and LGCI and provides the best food sources and dietary recommendations for each, both in the USA[47] and Europe[48].

Calcium

Ca together with P and fluorine (the latter mostly in teeth) comprise the mineral part of bone known as hydroxyapatite ($Ca_{10}(PO_4)_6(OH)_2$) which is interlaced in collagen fibrils extruded by osteoblasts (bone-forming cells) and gives bones the mechanical strength. Additionally, other mineral cations, namely Mg, Zn, Cu, Fe, as well as some anions and their salts (citrates, hydro-carbonates) are also present in the hydration layer of hydroxyapatite (although not as its structural part), indicating their important roles in bone metabolism[49,50].

The role of Ca in the mineralisation of bone, where 99 % of its total amount is present, is well understood, particularly from the aspect of its homeostasis and tight regulation of extracellular and intracellular Ca concentration via calcitropic hormones; active metabolite of vitamin D, parathyroid hormone (PTH) and calcitonin[50]. Numerous studies have investigated bone status and susceptibility to fractures with or without Ca supplementation or its dietary intake in osteoporotic or healthy individuals; thus, those will not be elaborated here. See the latest reviews[51,52]. Patients at risk for fractures or those with insufficient dietary intake or impaired Ca absorption may benefit from additional Ca and vitamin D, either as a supplement or increased food consumption; however, the recommendations need to be scrutinised, considering each individual's circumstances, and possibly necessitating personalised/precision nutrition[7].

Regarding muscle functioning where ionised Ca^{++} is involved, increased intracellular concentration is required for muscle contraction. For those purposes, Ca^{++} is released either from sarcoplasmic reticulum (and subsequently pumped back into circulation via Ca^{++}-ATPase when contraction stops) or it is guided into the cells from extracellular fluid (where Ca^{++} concentration is about 10 000 times higher than in the intracellular fluid)[50]. Although it is obvious that adequate Ca is important for muscle work, locomotion and functionality, studies in human subjects returned equivocal results[8]. It is safe to assume that due to the tight

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homeostasis of intra- and extracellular Ca^{++} governed by hormonal regulation, any lower dietary Ca intake in healthy individuals would be corrected (via bone resorption, renal reabsorption and increased intestinal absorption) to keep normal intra- and extracellular concentrations for muscle and other physiological functioning.

The exchange between intra- and extracellular Ca^{++} has been investigated in view of its possible modulation of obesity. Lower Ca intake results in lower serum (extracellular Ca^{++}) concentration upon which PTH and calcitriol are stimulated promoting its immediate serum normalisation. At the same time and paradoxically, these hormones promote the influx of extracellular Ca^{++} into adipocytes. Higher intracellular adipocyte concentration stimulates lipogenic gene expression and *de novo* lipogenesis via fatty acid lipase. However, higher Ca diets, which suppress this hormonal response, result in an up-regulation of lipolysis[53]. Some published reviews of these effects show either verification[54] or contradiction[55]. A recent 6-month weight loss study in postmenopausal overweight/obese women showed that the best outcomes in weight and body fat losses, as well as in bone preservation and lipid profile, were achieved in women who consumed more low-fat dairy foods (4–5 servings/d). The women with supplemental Ca (total about 1500 mg/d plus about 15 µg/d vitamin D) followed closely, compared to the women who were on their regular (low Ca diet) and showed the least favourable outcomes. All women were on similar energy restriction protocols[56]. It is safe to assume that the synergism between Ca in dairy food with other components (e.g. protein, Mg, K) probably contributed to the best outcomes in the dairy group, underpinning the effect of the foods on health, not necessarily single nutrients.

Overall, Ca alone, or as part of dairy foods, profoundly influences all three tissues and has an essential role in the physiology of OSA and its possible prevention and management. However, its relatively scarce bioavailable food sources (Table 1) and dependence on vitamin D and interaction with other nutrients in the absorption (P, Mg), or excretion (Na), discussed later, should be kept in mind when evaluating its overall impact.

Magnesium

Mg plays essential roles in numerous cellular and enzymatic processes. Its intake in the US population is marginal[8,39] with regard to the dietary reference intake[48], but not at the level to lead to clinical hypomagnesemia. Ca, Mg and P compete for the common gastrointestinal absorptive pathways and higher intake of Ca and P (especially the latter) may precipitate Mg depletion and raise its requirements[50]. Certain diseased states including diabetes, hypertension, coronary artery or renal disease, as well as alcoholism, malabsorption and energy malnutrition may induce true Mg deficiency. In those instances, the PTH secretion is affected resulting in hypocalcaemia and altered calcitriol synthesis, subsequently leading to serious disturbances in bone metabolism. Although Mg is not a structural part of hydroxyapatite (as are Ca and P), Mg deficiency (in addition to the afore-mentioned processes) impairs its crystallinity and lowers the strength of the bone. It was reported earlier that even suboptimal Mg intake (not necessarily a true deficiency) may result in osteopenia/osteoporosis and in animal models to uncoupling of bone turnover[57].

The most apparent symptoms of Mg deficiency or marginal intake regarding the muscle are related to a disturbance in balance and ataxia, muscle weakness and spasms, especially pronounced with ageing, as well as the heart muscle dysrhythmias which may lead to a sudden death[50]. Particularly interesting is a recent study which showed that intracellular Mg^{++} (measured by ^{31}P magnetic resonance spectroscopy) is a better indicator of Mg status than serum Mg concentration (where Mg is partially bound to albumin) and is a more reliable indicator of ageing and muscle functioning[58]. In that study conducted in over 400 men and women of wide age range, a negative correlation with age and a positive correlation with knee extension (indicating muscle strength/functioning) were found with intracellular Mg^{++}, while serum Mg did not show any relation. Since serum Mg is most often used as an indicator of Mg status, it may be a reason why many studies are not finding a clear connection between Mg status and various physiological outcomes.

The role of Mg in obesity, a state typically characterised by low intracellular Mg^{++}, was reviewed recently. In that context, the regulation of serum lipids and lipid metabolism is impaired when Mg^{++} is low and may predispose these individuals to a higher incidence of CVD[59].

A recent article addressed the ratios of Ca and Mg in the US dietary supplements, arguing that both high (>2·6) and low (<1·7) Ca:Mg ratios may have multiple adverse health consequences, including disturbances in vitamin D and PTH secretion[39]. Within the cell, Mg^{++} and Ca^{++} are physiological antagonists and their intracellular concentrations regulate several signalling pathways. For example, in cases of lower Ca^{++}:Mg^{++} ratios, Mg^{++} may displace Ca^{++} from Ca-binding sites or compete with Ca for non-specific sites on troponins and myosin to alter muscle contraction. Lower ratio can also cause inhibition of Ca^{++} release from sarcoplasmic reticulum, again interfering with muscle contraction[50]. The opposite imbalance (high Ca^{++}:Mg^{++}) also has numerous negative consequences, including altered vitamin D status, increased risk for CVD, metabolic syndrome and several cancers (for review, see[39]). Based on their analysis, Costello *et al.* suggest that the optimal Ca:Mg ratio in supplements is between 1·7 and 2·6 and that uncontrolled intakes of supplements are not advisable for general population[39] indicating again, the importance of mineral ratios and synchronised effects of nutrients[10].

In the COVID-19 era (2020–2021), some of the Mg anti-inflammatory functions and abilities to curb systemic inflammation, based on the previous animal and human studies, have received attention. Namely, in Mg deficiency, there is an increased release of inflammatory

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cytokines, free radicals, endothelial dysfunction and possibly development of metabolic syndrome, as reviewed recently[60,61].

Obviously, Mg is another nutrient with a huge impact on OSA and LGCI. In view of its marginal intake, more awareness should be given in correcting its dietary deficiencies, especially in older population.

Phosphorus

P is as important as Ca in bone and muscle health. However, due to its abundance in food, it never gained much attention other than in some chronic conditions (uncontrolled diabetes, alcoholism, Crohn's disease). The optimal ratio of Ca:P intake is about 1·5; however, it is usually much lower, especially in Western-type diets with high consumption of beverages containing phosphate acidifiers, as well as other processed food[50]. In addition to its role in bone as a structural part of hydroxyapatite, P has multiple other functions, including being a part of high-energy-releasing compounds (ATP and creatine phosphate) stored in and required for muscle contraction. P deficiency, although rare, may result in hypophosphatemia leading to serious multiorgan problems, including osteomalacia and rickets in bones and myalgia and muscle weakness[50].

More problems may occur with excessive intake. P competes with both Ca and Mg in the intestinal absorptive pathways, interfering with the absorption of each, although it decreases urinary Ca excretion, as a possible compensation. Hyperphosphatemia may produce a transient fall in serum Ca^{++} resulting in PTH secretion and potentially bone resorption, although studies are equivocal in showing decreased bone mass or heightened fracture rates with the high P consumption (e.g. carbonated beverages)[49].

Possible relation between P and adiposity has not been elucidated. There are some cross-sectional associations, the latest[62] analysing the National Health and Nutrition Examination Survey data from 2007 to 2014, where both higher P and Na intake was associated with higher BMI and waist circumference, while some other minerals (e.g. Ca, Mg, K) were negatively associated, all after adjusting for confounders. These associations probably reflect the higher intake of energy-dense foods rather than some specific action of P and/or Na on obesity. P has not been studied in inflammatory processes; however, phosphatidylethanolamine and phosphatidylcholine (both phospholipids and structural components of cell membranes) may have a role in cellular immune response[50].

Nevertheless, P is another nutrient involved in bone and muscle and possibly in adiposity and LGCI, but due to its excessive intake it may be damaging. Therefore, less processed and more whole-food consumption is advisable in order to modulate P's possible adverse effects.

Potassium

K is another widely under-consumed nutrient. Based on the National Health and Nutrition Examination Survey (2002–2012) data analysis, average intake for women and men was only 51 and 67 % respectively, of its adequate intake[8]. Being the most abundant monovalent intracellular cation (K^+) in the body, K opposes the extracellular sodium (Na^+). Virtually, every cell in the body expresses membrane-bound Na^+/K^+-ATPase pump, transporting the K^+ into and extruding the Na^+ out of the cell; the process absolutely crucial in maintaining cell-membrane potential and intimately regulating smooth, cardiac and skeletal muscle[50]. The optimal K:Na dietary intake is about 3; however, it is largely shifted towards Na in the Western-type diet[6,12], possibly resulting in overall chronic higher blood pressure. Although at marginal intake, true K deficiency rarely occurs just from the inadequate diet, but more likely from increased renal (diuretics use) or intestinal (diarrhoea, laxative abuse) losses[50].

The breakthrough awareness about possible K roles in bone health was revealed from the epidemiological studies reporting positive relation of fruit-vegetable-rich diets (containing an abundance of K, Mg and other minerals and vitamins) with bone health[63]. The simplified explanation of the mechanism is mostly attributed to the fruit-vegetable-diet alkaline-ash properties for raising the blood pH. Having an acidic blood (lower pH) promotes bone resorption in order to provide bone-buffering neutralisation although these effects have not been confirmed unequivocally[64]. Additionally, K also decreases Ca urinary excretion and could contribute to a lower age-related bone loss and kidney stone reduction[65]. Therefore, higher K intake may be particularly beneficial for older individuals.

Since muscle presents the largest storage site, it is reasonable to conclude that K deficiency is related to a decreased muscle mass[8]. Indeed, in cases of chronic hypokalaemia, the most altered function is that of all muscle types (smooth, cardiac and skeletal), with the most serious consequences exerted on cardiac muscle. The skeletal muscle dysfunction is characterised by the impaired blood flow, glycogen depletion and total impairment of cellular integrity leading to muscle-cell apoptosis[50]. Similarly, as with bones, a higher alkaline diet containing fruits and vegetables was associated with higher muscle indices in women of wide age[66]. In the opposite direction, hyperkalaemia, although not chronically observed (other than in renal disease, muscle injury, insulin deficiency), may lead to serious cardiac disturbances and even cardiac arrest[50].

The direct connection between K intake and obesity has not been established. Indirect connection stems from the studies reporting the intake of high processed foods, with low K, Mg and some vitamins, leading to higher obesity rates[67], again, pointing to the perils of Western-type diets on health in modern societies. The study in hypertensive subjects showed that those with higher abdominal obesity lost more K when on diuretics and had higher serum glucose[68], indicating that they maybe at higher risk for diabetes. Although it is unclear whether obesity causes K loss or the general low K status contributes to increased obesity, it is possible that obese individuals require higher K intake.

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Regarding the K role in LGCI, no direct connection has been established. However, adequate K status may be a marker of high fruit and vegetable intake (rich in antioxidants); thus, it could be speculated that indirectly, K will be beneficial for LGCI.

Obviously, adequate K intake is crucial in bone health, muscle functioning and possibly adipose tissue balance, making it one of the important nutrients to keep in check with OSA. However, the prudent approach would be to follow adequate K consumption with increased fruit and vegetables rather than obtaining it via uncontrolled supplementation.

Sodium

As well established, Na consumption is in excess nationwide because of its abundance in all, but particularly in processed foods[6]. The adequate intake in the USA is about 1500 mg/d (about 3·8 g salt)[47]; however, it typically averages at about 4000 mg/d[69] and in some countries (Japan) the intake is much higher. As discussed earlier, the Na^+/K^+-ATPase pump is crucial for electrolyte balance, membrane potential, muscle contraction and blood pressure regulation[50], thus any sudden changes in intra- and extracellular concentration of both Na^+ and K^+ could affect muscle functioning.

While the influence of Na on blood pressure is still controversial in some instances, its hypercalciuric effect is well established. It has been repeatedly shown in animals and human subjects that dietary Na (as NaCl) has a calciuric effect[69–71]. On average, for every 100 mmol (2300 mg) Na excreted in urine, there is about 0·6–1 mmol (24–40 mg) loss of Ca in healthy adult population[71]. Older studies in animals with NaCl loads showed bone loss, especially at low Ca intakes. However, despite the evidence of detrimental effect of Na on bone in animals (probably due to overstressed physiological conditions with Na loads), the studies in human subjects did not show similar results, especially when Ca intake was adequate[69]. Nevertheless, it is important to keep in mind the interaction between Ca and Na within the trends in the intakes of each: low Ca–high Na. However, whether a habitual salt excess decreases bone mass and increases the risks for fractures is still not established.

The concentration of Na in blood is important regarding its influence on body composition in view that total body water (sum of extracelluar and intracelluar) is the main determinant of body weight. In other words, rapid weight change even without concurrent changes in energy intake may probably be attributed only to the change in salt intake. In this context, the change in total body Na is directly proportional to a change in extracellular fluid volume, where about 1 kg body weight is dietary salt-dependent but is often inappropriately exploited by weight loss claims[50]. Although there is no direct evidence between Na intake and obesity, it is safe to assume that the correlation may exist with increased intake of processed, energy-dense food and increased obesity rates[62].

Vitamin D

The active form of vitamin D, calcitriol ($1,25(OH)_2$), is crucial for the absorption of Ca, Mg and P and for maintaining their homeostasis. Calcitriol, however, has a dual role in bone. It stimulates osteoclasts (bone-resorbing cells), as well as PTH to mobilise Ca, P and other minerals from bone and normalise their serum concentration. Alternatively, calcitriol also stimulates the expression of osteocalcin, osteopontin and other proteins released from osteoblasts, thus promoting bone anabolic processes[49].

Circulating levels of serum calcidiol (25(OH)), used as a circulating vitamin D status indicator, were examined outside of its roles in bones in numerous other studies. Overall, higher levels were associated with improved balance, gait and muscle endurance, while lower levels reflected poorer muscle performance, sarcopenia and obesity[72–74]. Low calcidiol in obese individuals still presents an enigma as to what the cause and effect is, in view that adipose tissue scavenges much of circulating calcidiol, but then it also provides the source for it[75]. The current recommendations for serum calcidiol concentrations are at about 20 ng/ml (50 nmol/l). However, in the COVID-19 pandemic (2020–2021), some researchers recommend even higher concentrations (about 30 ng/ml), probably prompted by the results of recent studies reporting a significantly higher risk of infections with COVID-19 in patients with lower compared to those with adequate/higher calcidiol levels[76,77]. An even earlier study showed a much higher risk for intensive care unit admittance for patients with pneumonia whose calcidiol was inadequate[78]. These findings could be attributed to the relatively newly discovered roles of vitamin D in modulating both innate and adaptive immune system, microbial peptides, as well as proinflammatory cytokines[77]. As much as these results are promising, randomised controlled trials are needed to confirm such effects, along with the affirmation of other non-skeletal roles of vitamin D.

Obviously, adequate vitamin D intake is crucial for both OSA and LGCI and some supplements should be considered in high-risk and older individuals, within the auspices of personalised medicine[7].

Vitamin K

Based on the National Health and Nutrition Examination Survey data[8] and corroborated with other countries' intake/recommendations, the US intake of vitamin K seems to be adequate for females (but not males), especially in view that some of it could be synthetised by the colon bacteria[79]. Of three forms of dietary vitamin K; plant-derived phyloquinone (K_1), animal- or fermented-foods-derived menaquinone (K_2) and synthetic menadione (K_3) used in supplements, each may have tissue-specific effects and different health benefits[80].

The role of vitamin K in regulating vitamin K-dependent clotting factors involved in blood coagulation is undisputed, and so is its role in carboxylation of proteins containing three γ-carboxyglutamic acid (Gla) residues necessary for bone mineralisation[49]. In these

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processes, the Gla residues attract positive Ca^{++} ions, foster their incorporation into the hydroxyapatite crystals, and augment bone mineralisation. There are three Gla proteins associated with bony tissue, of which osteocalcin (synthetised by osteoblasts) is the best known and referred to as a bone formation marker. Deficiency of vitamin K results in an increase in undercarboxylated osteocalcin which has low biological activity and is often detected in osteoporotic patients[81]. As per the recent review, some studies suggest that supplementation with K_2 may improve bone quality and reduce fracture risk in osteoporotic patients, possibly by enhancing Ca and vitamin D actions, but the results are inconclusive and do not warrant the widespread use of supplements[51]. It was shown earlier that the benefits of K_2 may be enhanced by the addition of vitamin D, genistein and Zn[82] supporting the notion that nutrients do not act alone.

A recent 13-year follow-up study (longitudinal aging study Amsterdam) reported the association between lower vitamin K intake and lower functionality measures and smaller calf muscle circumference in women, although the 13-year decline in those measures was not related to vitamin K status[83]. This may indicate some role of vitamin K in muscle health, but more investigation is warranted.

Possible roles of vitamin K in modulating adiposity are not well established other than some associative connections for older individuals[84,85], or in animal studies where rats fed a high-fat diet supplemented with menaquinone gained less weight and body fat and had lower serum leptin and glucose compared to those fed the high-fat diet only[86]. Those studies suggest vitamin K may have a role in maintaining lean body mass and preventing fat mass gain, both important for the prevention and treatment of OSA.

In the COVID-19 era (2020–2021), another protein, known as matrix Gla protein containing five Gla residues and dependent on vitamin K to be carboxylated, has received attention. Matrix Gla protein is present in vascular tissue and by its ability to bind calcium ions, prevents vascular calcification and elastic fibre degradation, both detrimental in COVID-19 infection[87]. But as with any new findings related to COVID-19 and conducted rapidly, more studies are necessary to establish a clear connection or a cause.

Conclusions

The complex aetiology of OSA syndrome was revisited and the reasons why its uniform diagnosis and thus determination of its prevalence is still hard to establish were explained: either due to the lack of consensus of diagnostic criteria or to technological shortcomings. A brief updated overview of the published studies and those with nutritional focus was presented as well. OSA has multiple causes, most notably ageing, chronic inflammation, stress, immobilisation, poor nutrition and some chronic diseases (Fig. 1). It may lead to functional impairment, increased risks of falls and fractures, metabolic deregulation, decreased quality of life, increased morbidity and possibly mortality. Of note is that OSA as a whole presents higher health risks than the sum of its components[6,7].

Nutrition is of utmost importance for the prevention and management of OSA. In this review, some of the nutrients involved in all three OSA components were addressed, also emphasizing those recognised to affect LGCI (Table 1), particularly important in the COVID-19 era (2020–2021). Moreover, the interactions, synergism and antagonisms among nutrients were pointed out.

Ca alone, or as part of dairy foods, profoundly influences all three tissues, thus has an essential role in the physiology of OSA, its possible prevention and management. Mg is another nutrient with a huge impact on OSA as well as on LGCI. In view of its marginal intake, more awareness should be given in correcting its dietary deficiencies, especially in older individuals. K is vital in bone health, muscle functioning and possibly adipose tissue balance, making it another important nutrient to keep in check with OSA. While both P and Na have important roles in bone, muscle and can impact adiposity, due to their abundance in food, their intake should be curbed to prevent possible damaging effects. Both vitamins D and K have crucial roles in bone and muscle metabolism and functioning and new research is emerging for their roles in modulating adiposity. Both, but particularly vitamin D, surfaced as important modulators of immune system with application in COVID-19 infections (2020–2021). However, uncontrolled supplementation with any of these nutrients is not advisable.

In the time of COVID-19 pandemic (2020–2021), it seems that the success of health professionals to prolong (or even save) life is contested[88]. There has also been a shift in prioritisation of healthcare services and ultimate neglect of some chronic conditions in order to spare the overburdened national health systems. Some 50 years ago, Thomas McKeown, epidemiologist and historian of medicine, stated that 'the reductions in mortality asserted by medicine might be better claimed by improved nutrition, hygiene, and, only later, by superior physic'. Although this statement is criticised and debated, the fact that maintaining good nutrition and healthy behaviours becomes more important now than ever. A diet rich in antioxidant foods, fruit, vegetables, legumes, whole-grains, nuts and seeds to provide balanced vitamins, minerals and other nutrients, possibly at or above each nation's official recommendations, is the safest approach to benefit OSA and LGCI. Before personalised nutrition becomes more widespread, such a diet should be employed during COVID-19 pandemic (2020–2021), but even more importantly, should be adopted as a long-term habit.

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