

REVIEW ARTICLE

# The Impact of Food Vitamins and Minerals on Proliferation, Differentiation, Homeostasis and Regenerative Capacity of Body Mesenchymal Stem Cells: A Narrative Review

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## ABSTRACT

Several lines of evidence confirmed the idea that stem cells are among the major players in orchestrating the response of our body to nutrients, mainly due to their crucial role in tissue homeostasis as dietary components and nutritional status can significantly impact stem cell survival and performance in human body and subsequently health status. This review concentrated on literature findings to determine the impact of food components on function, proliferation, differentiation, homeostasis, and regenerative capacity of body mesenchymal stem cells by searching related databases and focusing on related keywords from June 2000 to June 2026. Even many studies regarding the impact of vitamins and mineral components on proliferation, differentiation, homeostasis and regenerative capacity of body mesenchymal stem cells are *in vitro* and require *in vivo* validation; but the positive physiological effects of vitamins and minerals through several mechanisms in the literature reflect their pivotal role in regenerative medicine. It seems that improving nutritional intake and biochemical status of key micronutrients (e.g. vitamins and minerals) can be supportive for the efficacy of MSCs in therapies and immune function and subsequently the recovery and clinical outcome of patients. A proper food intake can particularly target the enhancement of stem cell activity, epigenetic regulation, redox-inflammatory pathways and cellular metabolism. In this review, mitochondrial metabolic checkpoint regulating stem cell maintenance was highlighted. It was discussed how diet affects the metabolism of stem cells through the nutrient sensing pathways, thereby affecting stem cell fate decision and tissue regeneration.

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## Introduction

Nutrients can directly affect stem cells or indirectly via regulating the stem cell niche. Also, nutrients can regulate hormone production, which in turn can impact the behavior of stem cells and their niche (1). Several lines of evidence confirmed the idea that stem cells are among the major players in orchestrating the response of our body to nutrients, mainly due to their crucial role in tissue homeostasis as dietary components and nutritional status can significantly impact stem cell survival and performance in human body and subsequently health status (2-7). In doing so, tissue stem cells not only use nutrients for their metabolic needs but also adapt their activities, such as self-renewal, autophagy or differentiation to the metabolic environment and nutrient availability (1). Micronutrients and dietary components are among the major signaling molecules that not only influence the cell metabolism; but also can modulate stem cell activity. In particular; minerals, vitamins, etc. are important to maintain stem cell proliferation and self-renewal via signaling pathways and gene expression networks and epigenetic regulation. So the regulation in nutrition can be an emerging target to control stem cell function, survival and pools in body tissues (8-10). In this relation, the concept of functional food components is crucial to provide a physiological and health benefits relevant to stem cell function (11). The functional food micronutrients can potentially enhance regenerative outcomes and protect stem cells from stress and to be novel perspectives for health promotion and disease prevention (12).

Among the functional food micronutrients, vitamins and minerals are provided to human body from natural sources of vegetables, fruits, oils, nuts, meat, dairy products, etc. So selected micronutrients found in foods can have specific effects at cellular level (13). It was shown that functional food components have various physiological advantages in human body as plausible modulators of stem cell function and enhancing regenerative outcomes in several diseases (3, 14).

Food-gene interaction was depicted as a leading risk factor for some diseases like inflammatory bowel disease (IBD) and colorectal cancer (CRC). Recent studies in stem cell biology demonstrated that diet and nutrition by signaling to intestinal MSCs (I-MSCs) by shifting nutrient-sensing transcriptional functions could impact barrier integrity and susceptibility to inflammation and tumorigenesis (15). Some nutrient ingredients and dietetic regimens were shown to have beneficial effects on the regulation of stem cells and tissue homeostasis and can lead to inhibition of

the cancer transformation process and progression and prevention of the onset of a drug resistance (16). Nutrients can normally affect the physiology of stem cells due to capability of several nutrient derived metabolites, released during the catabolic process, to induce chromatin reshaping, epigenetic modifications and gene expression modulation (17).

Indeed, nutrients may play a direct or indirect role by regulating the stem cell niche and can regulate hormone production, which in turn can affect the behavior of stem cells and their niche. In response to these stimuli, stem cells can activate signaling pathways, reprogram their metabolism and gene expression, and convert the dietary input into fate decisions. For stem cells, the main molecular node connecting diet and function was depicted by the adenosine monophosphate-activated protein kinase (AMPK)-mammalian target of rapamycin (mTOR)-sirtuin 1, (SIRT1) pathway (1). Even though these pathways are common to stem cells, the impact of diet on stem cells may be dramatic for various reasons. Stem cells have unique metabolic needs, which can be different based on their developmental stage (18-20).

Activation of these metabolic pathways is necessary for stem cell activities, inducing nutrient dependencies more profound than those in differentiated cells (21). Also, stem cells are characterized by lower levels of reactive oxygen species (ROS) when compared to their more differentiated counterparts; which are greatly affected by diet and nutrients and are important regulators of the balance between cell selfrenewal and differentiation (22). Therefore, this review has searched findings available in the literature to determine the impact of food components on body mesenchymal stem cells' function, proliferation, differentiation, homeostasis and regenerative capacity.

## Materials and Methods

A comprehensive literature search was carried out utilizing databases of Scopus, Web of Science, PubMed, Cochrane, Science Direct, Ovid and Google Scholar by focusing on keywords of "food", "nutrition", "diet", "minerals", "vitamins", "mesenchymal stem cells", "cell function", "cell proliferation", "cell differentiation", "homeostasis", "regenerative capacity" and "healing" from June 2000 to June 2026.

### *Mesenchymal stem cells*

Mesenchymal stem cells (MSCs) as multipotent adult stem cells having self-renewal and differentiation properties into specialized cell types

such as osteoblasts (bone cells), adipocytes (fat cells), and chondrocytes (cartilage cells) in order to maintain homeostasis and tissue regeneration in human being based on their anti-inflammatory and immunomodulatory characteristics and activities to repair damaged tissues (23-25). Their immunomodulatory characteristics can impact the activity of different immune cell types. They can promote polarization of macrophages from a pro-inflammatory (M1) to an anti-inflammatory (M2) phenotype, and enhance regulatory T cell populations making MSCs beneficial in conditions such as inflammation during tissue damages (26).

They secrete several bioactive factors such as cytokines and growth factors, which not only protect tissue regeneration and repair; but also modulate the local immune responses. This regenerative potential is enhanced by their involvement in the process of new blood vessel formation, which is crucial to supply injured tissues with nutrients and oxygen in order to promote wound healing by facilitating cellular communication and extracellular matrix (ECM) remodeling (27). They have the regenerative potential of migrating to sites of injury from distant organs and have the potential to exert paracrine effects *in situ* making them a proper candidate to counteract many diseases and degenerative conditions (28). MSCs have been dispersed throughout the body in various tissues such as bone marrow (29), adipose tissue (30), dental pulp (31), Wharton's jelly (32) endometrium (33) and menstrual blood (34). The therapeutic application of MSCs is intrinsically correlated to their potential for robust proliferation, effective self-renewal, and resistance to cellular senescence (3). They have been successfully utilized in treatment of many diseases such as infertility (35), spinal cord injury (36), burns (37), osteoarthritis (38), liver injuries (39), etc. MSCs have been labeled to track the cell fate after transplantation to confirm their share in healing process too (40).

Biological function of MSCs was shown to be modulated by environmental factors such as dietary components including minerals, vitamins, etc. which can affect cell proliferation, aging, inflammatory response and resistance to oxidative stress (3). Growing body of evidences revealed that minerals and vitamins are pivotal modulators in MSCs function, proliferation, differentiation, and homeostasis (5, 7, 41-45). The profound immunomodulatory capabilities of MSCs are crucial for their therapeutic efficacy in inflammatory and autoimmune diseases. These activities are not static; but are modulated by microenvironmental factors such as vitamins A, B3, B6, C, D, E and K together with minerals like magnesium, selenium,

zinc, iron and lithium chloride which are important for immunosuppressive and anti-inflammatory characteristics of MSCs because of a change in the profiles of cytokine secretion, surface marker expression, and intracellular signaling (3).

### Vitamins

Vitamins are involved in various cellular activities, and their deficiency often leads to serious symptoms to people, sometimes even death. Most vitamins can be obtained through balanced food intake, and vitamin supplements are also extensively applied in healthcare practices. Different vitamins possess regulatory mechanisms at cellular level, particularly in stem cells. Functional stem cells need a culture system in which all components including water, inorganic salts, growth factors, amino acids, buffering reagent, energetic substrates, extracellular matrix, vitamins, vitamin-like organic factors are suitably balanced. So the regulation of nutrition is emerging as a viable target for stem cell modulation, which can impact not only cell survival; but also pluripotency and cell fates (41).

Human vitamins are generally divided into two groups of water-soluble vitamins and fat-soluble vitamins. Water-soluble vitamins are consisted of the B type vitamins and vitamin C, and fat-soluble vitamins compromise vitamins A, D, E and K. Some vitamins can be synthesized in the body, but at a very low rate; but all vitamins can be provided from food to fulfill the nutritional needs. Vitamins B1, B3, B6 and B7 participate in glucose metabolism of glycolysis, pentose pathway, glycogenolysis and gluconeogenesis; while vitamins B2, B3 and B5 are involved in fatty acid synthesis and degradation and vitamins B3, B6, B9 and B12 are essential in amino acid degradation. Vitamin C as an antioxidant suppresses generation of ROS. Vitamin A acts as an antioxidation and transcriptional regulation factor; vitamin D is a hormone that binds to nuclear receptors and regulates transcription, and is involved in calcium absorption; vitamin E is a strong fat-soluble antioxidant and modulates signal transduction and vitamin K is a cofactor for  $\gamma$ -glutamyl carboxylase that is crucial in blood clotting. (41). Six vitamins of B1, B2, B3, B5, B6 and B9 are necessary in cell proliferation. So in cell cultures, Basal Medium Eagle (BME), Minimum Essential Medium (MEM), Dulbecco's Modified MEM (DMEM) and DMEM, Ham's F12, RMPI, IMDM and  $\alpha$ -MEM were developed with various vitamins (41).

The MSCs potentials to facilitate tissue repair is prominently affected by the local biochemical environment of different vitamins that can play a

direct role in modulating regenerative activities. It was shown that the differentiation of MSCs is effectively modulated by a wide range of vitamins that play a crucial role in tissue homeostasis and regenerative applications (3). In this relation, vitamins A, B, C, D, E and K have been highlighted as key micronutrients for stem cell activity (41, 46).

### Vitamin A

Vitamin A is practically a group of compounds known as retinoids, including retinol, retinal and retinoic acid (RA). Vitamin A compounds are normally present in food of animal origin; while their precursor known as carotenoid is found in plants. Humans can synthesize vitamin A from carotenoids like  $\beta$ -carotenes that can be converted into two retinals that can be further reduced to retinol. Retinol either is then esterified into retinyl palmitate for storage, or is oxidized into RA. Vitamin A has also distinctive roles in embryogenesis and stem cells in culture as retinol and retinal are readily oxidized in culture and function as antioxidants to promote cell survival and growth (41).

RA, also known as tretinoin, is a bioactive derivative of vitamin A that mediates transcriptional programs critical for cell proliferation, differentiation and development (47). RA can enhance MSCs potential in suppression of T cell proliferation (48) and activate pro-inflammatory pathways within MSCs (49). RA *in vitro* with human umbilical cord-MSCs (UC-MSCs); *in vivo* in mouse model of liver diseases and *ex vivo* in liver inflammation co-culture model of human periodontal ligament-MSCs (PDL-MSCs) could enhance immunosuppression by suppressing proliferation of CD4<sup>+</sup> and CD8<sup>+</sup> T cells; reduction in programmed death-ligand-1 (PD-L1) expression; a significant rise in expression of human leukocyte antigens (HLA) class I and class II; a decrease in tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) secretion and activating the pro-inflammatory nuclear factor kappa-light-chain-enhancer of activated B cells/nucleotide-binding-domain, leucine-rich repeat containing protein 3 (NF- $\kappa$ B/NLRP3) axis and promoting the production of the proinflammatory cytokine of interleukin-1 beta (IL-1 $\beta$ ) (48, 49).

Vitamin A (retinol) and its metabolites (4-OH-RA and 4-Oxo-RA) roles in cell development were exhibited (50). In weaned piglets, dietary vitamin A could significantly affect I-MSC differentiation and stemness (51).

### Vitamin B3

Vitamin B3 is a water-soluble B vitamin found naturally in many foods in common forms of niacin (nicotinic acid), nicotinamide (NAM)

and nicotinamide riboside (NR) as precursors of nicotinamide adenine dinucleotide (NAD) and nicotinamide adenine dinucleotide phosphate (NADP) that are cofactors or substrates in a wide range of metabolic reactions. Nicotinamide in medium can easily cross plasma membrane and enter the cytoplasm (41). Niacin acts in the body as a coenzyme, with more than 400 enzymes dependent on it for several reactions to help converting nutrients into energy, create cholesterol and fats, create and repair DNA, and exert antioxidant effects (52).

Vitamin B3 when treated with mouse adipose tissue derived-MSCs (Ad-MSCs) could regulate histone deacetylation and telomere maintenance via activating SIRT1, nicotinamide adenine dinucleotide (NAD<sup>+</sup>)-dependent histone deacetylase to postpone senescence and support differentiation (53). It was shown that nicotinamide and pyridoxine could stimulate muscle stem cell expansion and enhance regenerative capacity during aging as skeletal muscle is dependent on resident muscle MSCs (Mu-MSCs) for growth and repair. Nicotinamide and pyridoxine synergize through CK1-mediated cytoplasmic  $\beta$ -catenin activation and protein kinase B (AKT) signaling to promote amplification and differentiation of Mu-MSCs. Oral intake of nicotinamide and pyridoxine can accelerate muscle regeneration *in vivo* by stimulating Mu-MSCs, increase muscle strength and overcome Mu-MSC dysfunction and regenerative failure during aging (54).

### Vitamin B6

Vitamin B6 is a water-soluble vitamin naturally found in several foods. Pyridoxal 5' phosphate (PLP) and pyridoxamine 5' phosphate (PMP) are the active coenzyme forms of vitamin B6. This vitamin is involved in gluconeogenesis and glycogenolysis, immune function, and hemoglobin formation (55). Administration of vitamin B6 was depicted to accelerate the clearance of transplanted MSCs from the body in a murine model that can be important in therapeutic applications (48). In murine model of hepatitis treated with UC-MSCs, an acceleration in clearance of MSCs from the body happened. It led to lower numbers of detectable UC-MSCs 4h post-injection, especially when combined with retinoic acid (48). Vitamin B6 can modulate the immunogenic and immunoregulatory profile of MSCs via a rise in the surface expression of HLA molecules; while upregulates PD-L1 immunomodulatory molecule and interleukin-1 receptor antagonist (IL-1RA) anti-inflammatory factor (48).

### Vitamin C

Vitamin C, or l-ascorbic acid (AA/LAA), is a

water soluble vitamin due to its sugar-like structure. It is a strong antioxidant that reduces ROS that acts as a kinase inhibitor too. Its roles in promoting cell proliferation and survival, cell differentiation and reduction of cell senescence during reprogramming was demonstrated via suppressing p53 (41). It is an enzyme cofactor of critical importance in synthesis of collagen that can strongly support formation of ECM, which is necessary in tissue integrity, regeneration and remodeling (56, 57). It can improve neovascularization and tissue repair (58). In *in vivo* mice model of ischemic limb, transplantation of subchondral bone mesenchymal stem cells (SCB-MSCs) and AdMSCs was shown to enhance regeneration and tissue repair in bone defects acting as a cofactor in supporting ECM formation and deposition, collagen synthesis and improving blood perfusion and neovascularization (8, 56-66). Vitamin C contributes to immune regulation by suppressing the senescence-associated secretory phenotype (SASP) in MSCs and a decrease in production of proinflammatory cytokines, thereby helping maintain the functional integrity of MSCs and supporting the activity of immune effector cells (58, 67). Vitamin C as a potent antioxidant can directly scavenge ROS and protect mitochondrial homeostasis, and as a result can support MSCs from oxidative damage and the enhanced senescence via inhibiting ROS production through key signaling pathways (56, 63, 68-71). Vitamin C in presence of human bone marrow derived stem cells (BM-MSCs) and Ad-MSCs could induce osteogenesis in senescent MSCs and activate telomerase and expression of runt-related transcription factor 2 (Runx2), alkaline phosphatase (ALP) and collagen type I alpha 1 chain (COL1A1) which are necessary in collagen synthesis and enhancing mineralization (56, 72, 73). Vitamin C when exposed to mouse embryonic mesoderm-derived MSCs could contribute to adipogenesis by a suppression of adipocytes differentiation (74). It was shown that vitamin C in addition to Glial-derived stem cells (GS-MCs) and Ad-MSCs resulted in chondrogenesis through enhancing differentiation and supporting chondrocytes from oxidative stress of hydrogen peroxide ( $H_2O_2$ ) (7, 75). In *in vivo* mice model of ischemic limb, SCB-MSCs and Ad-MSCs in addition to vitamin C could enhance regeneration in bone defects and support ECM formation and tissue repair via acting as a cofactor in collagen synthesis and deposition and improving blood perfusion and neovascularization (8, 56-66). This vitamin with lung MSCs in rat model could promote vascular repair, bone regeneration and lung development because of modulating the immune environment; promoting the osteogenic differentiation; improving adhesion

and migration of endothelial progenitor cells (EPCs) and alleviating TNF- $\alpha$ -mediated inflammation (44, 76-78). Vitamin C when treated with SCS-MSCs were indicated to decrease proinflammatory phenotype of SASP, TNF- $\alpha$ , IL-1 $\beta$ , IL-6 and IL-8 and support activation of natural killer (NK) cells and cytotoxic T lymphocytes (58). This vitamin *in vitro* when added to Ad-MSCs and lithium chloride increased cell proliferation and protected the cells from apoptosis via an increase in expression of the Bcl-2 gene and a significant reduction in Bax gene (14). Vitamin C with Ad-MSCs *in vivo* in mouse model of acute radiation syndrome (ARS) increased the survival rate following a lethal irradiation and reduced the proinflammatory cytokines, ECM formation, adhesion properties and boosted anti-inflammatory properties, detoxification and anti-oxidative stress control (79). This vitamin with Ad-MSCs demonstrated strong antioxidant activity and decreased ROS due to scavenging and inhibition of ROS production via protein kinase B/AKT/mTOR axis (56, 59, 63, 68, 80). Vitamin C in combination with gingival MSCs and mouse Ad-MSCs could directly modulate DNA and histone demethylation by participating as a cofactor for ten-eleven translocation (TET) enzymes, promoting an active DNA demethylation from 5-methylcytosine (5mC) to 5-hydroxymethylcytosine (5hmC); supporting Jumonji (JHDM) histone demethylases such as histone H3 lysine 36 dimethylation/trimethylation/2/3 (H3K36me2/3) and lead to an increase in cellular myelocytomatosis/Krüppel-like factor 4 (c-Myc/Klf4) and repression of protein 21 (p21) (7) (64) (81).

### Vitamin D

Vitamin D (also named calciferol) is fat-soluble and biologically inert that is naturally present in a few foods and is produced endogenously when ultraviolet (UV) rays from sunlight is exposed to the skin and stimulate vitamin D synthesis. It must undergo two hydroxylations in liver and kidney for activation converting vitamin D to 25-hydroxyvitamin D [25(OH)D], also known as calcidiol 1,25-dihydroxyvitamin D [1,25(OH) $_2$ D], also known as calcitriol (82). The key role of the nutrient environment, and vitamin D signaling was illustrated in defining contribution of at least two different stem cell populations to mucosal homeostasis (83). Vitamin D was shown to directly enhance the regenerative capacity of MSCs, promote bone regeneration by modulating the local immune environment and directing osteogenic differentiation (44, 46). Also, it participates in angiogenesis and vascular repair by improving the endothelial progenitor cells activity (76, 78). In rat model, lung

MSCs were demonstrated to promote vascular repair, bone regeneration and lung development via modulation of the immune environment; promotion in osteogenic differentiation; improvement in endothelial progenitor cells (EPC) adhesion and migration; and alleviation of TNF- $\alpha$ -mediated inflammation (44, 76-78). Vitamin D has a potent immunomodulatory impact via the decrease in secretion of proinflammatory cytokines mediated by an inhibition in NF- $\kappa$ B signaling (84-87). This mechanism can enhance the capability of MSCs in suppression of proliferation of T cells and can further strengthen their immunosuppressive potential (49, 85, 88). Also, vitamin D participates in redox balance by an activation in vitamin D receptor (VDR) and upregulation of antioxidant enzymes which can further preserve mitochondrial activity, decrease ROS accumulation, and support MSCs from oxidative injury (89, 90). Li *et al.* in their *in vivo* study found that VDR can protect against radiation-induced intestinal injury in mice via inhibition of intestinal crypt stem/progenitor cell apoptosis (91). It can improve autophagy and promote resistance to oxidative stress, specifically when combined with other metabolic modulators (59, 92-95). Vitamin D together with BM-MSCs has induced osteogenesis via enhancing expression of osteocalcin (OCN), ALP and Runx2 through VDR and a synergism with transforming growth factor-beta1 (TGF- $\beta$ 1), bone morphogenetic protein 2 (BMP-2), dexamethasone and metformin to activate Wnt signaling pathway-catenin (Wnt/ $\beta$ -catenin) and BMP2 signaling and a reduction in ROS (43, 44, 90, 96-99). Addition of vitamin D to human BM-MSCs has resulted in adipogenesis too due to a reduction in lipid accumulation and downregulation of adipocyte-specific genes and inhibition of transcription factor peroxisome proliferator-activated receptor gamma 2 (PPAR $\gamma$ 2) (44, 100-102). This vitamin *in vitro* together with human periodontal ligament MSCs (PDL-MSCs) and with mouse BM-MSCs *in vivo* participated in bone fracture healing. Also, it showed strong anti-inflammatory effects *in vivo* in mouse model of acute and chronic diseases when used with lipopolysaccharide (LPS) and high fat diet. These changes happened via a decline in secretion of TNF- $\alpha$ , IL-1 $\beta$  and IL-6 by blocking NF- $\kappa$ B signaling; enhancing MSC-mediated suppression of CD4 $^{+}$  T cell proliferation; suppression of M1 macrophage differentiation; promotion in M2 macrophage differentiation and inhibition of M1 macrophage-mediated MSC migration in a dose-dependent manner (84, 85, 87). Vitamin D in *in vitro* addition to human and mouse BM-MSCs and *in vivo* with mouse model of high fat diet (HFD)-

induced osteoporosis could maintain redox balance based on activating VDR to upregulate superoxide dismutase 2 (SOD2) and preserving mitochondrial function (89, 90).

Recent studies illustrated the effect of the active form of vitamin D (vitamin D3) on maintenance of I-MSCs and inflammation in crypts. Supplementation of vitamin D3 and calcium to the diet can abrogate the adverse impact of NWD1 on I-MSC function. Vitamin D3 was shown to enhance the differentiation of I-MSCs into various specialized epithelial cells like Paneth, enterocytes, enteroendocrine and goblet cells. The crucial role of vitamin D in I-MSC regulation in Vdr knockout mouse model has been validated. Vitamin D3/VDR signalling pathway can protect I-MSCs and progenitor cells against DNA damage and apoptosis due to ionising radiation (50, 91, 103, 104).

### Vitamin E

Vitamin E is fat-soluble antioxidant vitamin with eight known natural isoforms of four tocopherols and four tocotrienols, each designated as  $\alpha$ ,  $\beta$ ,  $\gamma$  and  $\delta$  based on the position of methyl groups on the chromanol ring. It is found in almost all the tissues in the human body, with the highest level in the adipose tissue and adrenal gland that plays a role as chain-breaking antioxidant, neutralizing free radicals and terminating chain reactions in the oxidation of polyunsaturated fatty acids. Vitamin E also can modulate cellular signal transduction through kinases, phosphatases, lipid mediators and transcription factors. Vitamin E was frequently utilized in primary cell culture to inhibit cell death and preserve cell activity when exposed to stress conditions. So commercial cell culture supplements that contain vitamin E are available (41).

Vitamin is essential for the maintenance of healthy skin. It is a group of eight compounds related in molecular structure enrolling four tocopherols and four tocotrienols (105). Pretreatment of MSCs with vitamin E was demonstrated to protect the stem cells from oxidative stress-induced damage and enhance the survival and preserve the regenerative capacity of MSCs (70). These findings can be promising in cartilage regeneration, as vitamin E-treated MSCs can promote chondrogenic differentiation and can slow the progression of osteoarthritis by an inhibition in apoptosis and senescence processes (106, 107). In *in vitro* preconditioning of MSCs and *in vivo* osteoarthritis rat models; an enhancement in MSC survival and cartilage regeneration was noticed. Preconditioning protected MSCs from oxidative stress (H<sub>2</sub>O<sub>2</sub>); downregulated apoptosis genes, reduced vascular endothelial growth factor

(VEGF) and lactate dehydrogenase (LDH) release, upregulated TGF- $\beta$ , and increased proteoglycan content in cartilage (70, 106, 107). Vitamin E as a major fat-soluble antioxidant is vital to support cell membranes from lipid peroxidation and as a result can protect the MSC lipid bilayer from oxidative stress and has an anti-aging protection role and maintains MSC viability and activity, especially under the challenging conditions in tissue injuries (70, 108, 109). When vitamin E is added to human dental pulp MSCs (DP-MSCs), osteogenesis was noticed via enhancing osteogenic commitment (7, 98). Vitamin E when added *in vitro* to human DP-MSCs; porcine Ad-MSCs and rat BM-MSCs and *in vivo* in rat model of osteoarthritis (OA); it could protect from oxidative stress by preventing lipid peroxidation of cell membranes; reduction of oxidative stress and aging caused because of H<sub>2</sub>O<sub>2</sub>; maintenance of cell membrane integrity; protection against apoptosis and promoting survival and enhancing proliferation (70, 71, 110).

### Vitamin K<sub>2</sub>

Vitamin K<sub>2</sub> is found in animal foods such as liver, egg yolks, high fat dairy products, organ meats and fermented foods like sauerkraut and natto. The gut bacteria can also produce some K<sub>2</sub>. It can help to decline the risk of cardiovascular diseases (CVDs) by preventing calcium buildup in arteries. It is divided into different subtypes like MK-4 and MK-7 (111). Vitamin K<sub>2</sub> may also support dental health by activating osteocalcin, a protein that helps stimulate new bone and dentin growth. Talk with a healthcare professional before adding vitamin K<sub>2</sub> supplements to the diet, especially if someone takes blood thinning medications like warfarin. Vitamin K<sub>2</sub> in combination with diet-induced obesity in mouse model and synergistically with vitamin D3 can lead to osteogenesis via enhancing the expression of osterix, osteocalcin and Runx2 (112).

### Folic acid

Folic acid is a water-soluble B vitamin which has critical roles in neural tube development and neonatal gut maturation and overall gut health. Zheng *et al.* illustrated that folic acid promoted renewal, proliferation, differentiation of intestinal stem cells (ISCs) and demonstrated that folic acid could enhance ISC-driven epithelial regeneration in a  $\beta$ -adrenergic signaling-dependent manner and epithelial barrier integrity and homeostasis and could modulate epithelial function through the upregulation expression of tight junction components and nutrient transporters (113). Zhang *et al.* revealed that supplementation of maternal folic

acid can improve the intestinal health of porcine newborns through promoting the proliferation and differentiation of I-MSCs, increase in Ki67-positive cells and the expression of proliferation-related marker genes [(C-Myc, CyclinD1, and proliferating cell nuclear antigen (PCNA))] in piglets' intestinal stem cells (114).

### Minerals

Essential minerals were exhibited to be integral to MSC-mediated repair. The differentiation of MSCs is prominently modulated by many minerals; thereby they have an important impact on tissue homeostasis and in regenerative medicine (3). Minerals such as iron, magnesium, zinc, calcium, selenium, etc. were highlighted as key micronutrients for stem cell activity (41, 46).

### Iron

Iron is a key element in the metabolism of all living organisms and is found in two biologically oxidation states of the ferrous form (Fe<sup>2+</sup>) and the ferric form (Fe<sup>3+</sup>). It naturally exists in several foods, is added to some food products, and is available as a dietary supplement. Iron is an essential component in hemoglobin, an erythrocyte (red blood cell) protein that transfers oxygen from the lungs to the tissues. As a component of myoglobin as another protein can provide oxygen and support muscle metabolism. Iron is also essential for cellular functioning, neurological development, physical growth and hormonal synthesis (115-118).

Iron as an essential cofactor was demonstrated to have a prominent role for many proteins involved in critical biological processes, such as mitochondrial electron transport, DNA synthesis, and oxidative phosphorylation that make iron a fundamental metabolic currency. Its deficiency can impair intestinal mucosal structure and activity and affect intestinal stem cells and their differentiation potential (119). The dysregulated iron dynamics can lead to a significant decline in numbers and proliferative activity of intestinal stem cells as documented by a reduction in expression of the canonical stem cell marker leucine-rich repeat-containing G-protein coupled receptor 5 (Lgr5) and antigen Kiel 67 (Ki67)-positive proliferating cells. The correlation between nutrient deficiency and impaired proliferation of intestinal stem cells has been noticed in many models of malnutrition, revealing a potential common pathway in nutrient stress responses (120, 121).

It was suggested that iron delivered via iron oxide nanoparticles (IONPs) can enhance the migration of MSCs to the site of tissue injury and to facilitate

angiogenesis and wound healing; while IONP-labeled MSCs were also successfully employed to improve tissue repair in *in vivo* studies. These properties were successfully documented by magnetic resonance imaging (MRI) tracking (37, 40, 122-127) MSCs treated with iron and delivered to cells as IONPs displayed enhanced anti-inflammatory properties with a change in their cytokine profile toward the declined secretion of proinflammatory factors and a rise in anti-inflammatory cytokines (128).

Mouse model of dermal wounds; mouse model of hind limb ischemia for angiogenesis by using human Ad-MSCs and rat model of liver fibrosis utilizing rat BM-MSCs denoted to an improvement in wound healing and a reduction in liver fibrosis. It could enhance migration of MSCs to the site of tissue injury and led to an improvement in angiogenesis (122-124). Iron can illustrate a dualistic role too, as a decrease in its level can stimulate adaptive healing mechanisms, while excessive iron level can result in accumulation of toxic ROS that can underscore the importance of tightly regulated iron homeostasis (122, 129-131). Iron when treated with Ad-MSCs in mouse model of skin wounds and in mouse model of hindlimb ischemia (angiogenesis) and with BM-MSCs in rat model of liver fibrosis could improve wound healing and decrease liver fibrosis by enhancing migration of MSCs to the site of injury and lead to an improvement in angiogenesis (123-124).

Iron *in vitro* exposed to rat BM-MSCs and *in vivo* in rat model of laser burn wound could enhance anti-inflammatory properties through modification in cytokine profile and a decrease in pro-inflammatory factors (IL-2 and TNF- $\alpha$ ) and a rise in secretion of anti-inflammatory cytokines of IL-4 and IL-10 (128). Iron in combination with human Ad-MSCs, human BM-MSCs and rat BM-MSCs revealed dualistic adaptive vs. toxic effects; while in low concentrations was associated with mild ROS for adaptive response [hypoxia-inducible factor 1 subunit alpha (HIF-1 $\alpha$ ) stimulation] and in high concentrations was with toxic ROS (122, 129-131).

### Magnesium

Magnesium is an abundant mineral in the body and a cofactor found in more than 300 enzyme systems that regulate various biochemical reactions in the body, like muscle and nerve function, protein synthesis, blood pressure regulation and blood glucose control. It is naturally found in various foods, available as a dietary supplement, added to food products, and seen in some medicines (e.g., antacids, laxatives) essential in oxidative phosphorylation, energy production and glycolysis.

It contributes to the structural development of bone and is necessary in RNA and DNA synthesis and the antioxidant glutathione. Magnesium also plays a role in the active transport of calcium and potassium ions across cell membranes to facilitate muscle contraction, nerve impulse conduction and normal heart rhythm (132).

Magnesium in addition to bone homeostasis is pivotal for both cartilage regeneration. Shimaya *et al.* reported that it can enhance the adhesion of synovial MSCs to injured sites, promote cartilage matrix synthesis, and induces apatite crystal growth on tissue surfaces as a key step in bone formation and remodeling (133, 134). *In vivo* study using a rabbit model of osteochondral defect with rabbit synovial MSCs; in *ex vivo* study employing osteochondral tissue and human synovial MSCs and in *in vitro* study of chondrogenesis assessment and cell adhesion utilizing human synovial MSCs and human Ad-MSCs, bone homeostasis and cartilage regeneration were supported. Magnesium could enhance MSC adhesion to defects; improve cartilage matrix synthesis and induced apatite crystal growth on scaffolds for mineralization (133, 134).

Magnesium has anti-inflammatory properties too that can significantly decrease secretion of proinflammatory cytokines from MSCs. It can simultaneously increase anti-inflammatory mediators such as prostaglandin E2 (PGE2) and IL-10 and modulate key inflammation-related transcription factors like NF- $\kappa$ B to enhance the overall immunosuppressive activity of MSCs (135). Magnesium in combination with BM-MSCs could trigger osteogenesis by enhancing early differentiation, Notch and Wnt signaling and autophagy; while high concentrations were shown to impair late-stage mineralization (133, 136-141). When added to synovial MSCs, chondrogenesis was noted due to the support of differentiation and synthesis of cartilage-specific ECM via integrin-mediated signaling (133).

This mineral with synovial MSCs *in vivo* in rabbit model of osteochondral defect, in *ex vivo* with human synovial MSCs in osteochondral tissue; in *in vitro* with synovial MSCs in cell adhesion and chondrogenesis assessment; and *in vitro* with Ad-MSCs could support bone homeostasis and cartilage regeneration by promoting cartilage matrix synthesis; enhance MSC adhesion to defects and induce apatite crystal growth on scaffolds for mineralization (133, 134). Magnesium with murine MSCs and macrophages *in vitro* displayed strong anti-inflammatory and immunosuppressive impacts via a decrease in IL-1 $\beta$ , IL-6; an increase in IL-10 and PGE2 and the modulation of nuclear factor NF- $\kappa$ B

and signal transducer and activator of transcription-3 (STAT-3) (135).

### Zinc

Zinc is an essential mineral that helps cell metabolism, growth, signaling and division. It is mainly stored in muscles and bones and is naturally present in some foods and is available as a dietary supplement. Zinc is involved in many aspects of cellular. It is required for the catalytic activity of hundreds of enzymes and is essential for protein and DNA synthesis, to enhance immune function and improve wound healing. Its homeostasis is maintained via absorption of zinc from the diet, excretion into the gastrointestinal tract, and reabsorption in gastrointestinal lumen. Zinc Supplementation can be beneficial in glycemic control, insulin resistance, inflammation and oxidative stress in diabetes too (142).

Zinc was described to improve the therapeutic efficiency of MSCs via enhancing the migration and adhesion of stem cells, which are important processes in homing of MSCs to the site of injury (4). Zinc-containing biomaterials were also tissue engineered to simultaneously improve angiogenesis and osteogenesis to support the complex tissue repair (143). *In vitro* scratch assays of human UC-MSCs and human Ad-MSCs with zinc promoted tissue repair via enhancing cell homing. It significantly improved migration and adhesion of MSCs and when scaffolds co-doped with copper and zinc, they promoted both angiogenesis and osteogenesis (4, 143).

Zinc is also essential in immune response regulation and its deficiency can be associated with an enhanced inflammation. Conversely, its supplementation has anti-inflammatory effects and can modulate the expression of genes involved in inflammatory signaling pathways of MSCs (144). It can enhance cellular defense via modulation of pathways that can promote the transcription of antioxidant genes (144, 145). Zinc when comes with Ad-MSCs can provide osteogenesis via enhancing matrix formation, osteoblast differentiation, and mineralization (143). Zinc and human UC-MSCs showed anti-inflammatory effects through upregulation of genes for cytokine receptor interactions and IL-17/TNF pathways. The deficiency was found to increase the TNF- $\alpha$ , IL-1 $\beta$  and IL-8 (144).

Zinc in combination with human UC-MSCs could enhance antioxidant defense by modulating nuclear factor erythroid 2-related factor 2/sirtuin 3 (Nrf2/Sirt3) pathway to promote antioxidant gene transcription (144, 145). Zinc treated with rat Ad-MSCs could regulate histone deacetylation and telomeric stability by activating SIRT3 including histone deacetylase; functioning as a structural

component for zinc finger transcription factors and chromatin remodelers and an increase in telomerase reverse transcriptase (TERT) expression (146).

### Calcium

Calcium is the most abundant metal and the 5<sup>th</sup>-most abundant element in the human body. Calcium ion (Ca<sup>2+</sup>) as an electrolyte plays a crucial role in the physiological and biochemical processes of cells: in signal transduction pathways where they play a role as a second messenger; in contraction of all muscle cell types; in neurotransmitter release from neurons; as cofactors in several enzymes and in fertilization. Its ions outside cells are important to maintain the potential difference across excitable cell membranes, protein synthesis, and bone formation (147). Presence of calcium with BM-MSCs and MSC immunoselected with stromal elements1 (STRO1) antibody provided the chance for osteogenesis. It happened because of upregulation of bone sialoprotein (BSP), OCN and ALP expressions and mediation through L-type calcium channels and calcium/calmodulin-dependent protein kinase II (CaMKII) signaling (148-150).

### Selenium

Selenium is an ingredient in various multivitamins and dietary supplements, and in infant formulas. It is a component of the antioxidant enzymes glutathione peroxidase and thioredoxin reductase and in three deiodinase enzymes. Although trace amounts of selenium are essential in cellular function; but they can be toxic in even small doses and cause selenosis with symptoms of fatigue, diarrhea, hair loss, nail brittleness, joint pain or discoloration, headache, nausea, vomiting, tingling and fever (151). Selenium as a trace element is essential for antioxidant defense and specifically in nanoparticle forms that can present a strong, dose-dependent supportive influence against oxidative stress. At optimal levels, it can decrease intracellular ROS and activate signaling pathways to increase the expression of antioxidant enzymes and consequently improves MSCs viability (43).

Human embryonic stem cells-derived MSCs with selenium induced adipogenesis and osteogenesis. They happened through a change in MSC fate towards osteogenic lineage and an increase in ALP function and osteogenic gene transcription (43). Also it occurred via the suppression in adipocyte differentiation (43). Selenium addition to human ESC-derived MSCs and rat BM-MSCs showed a protecting effect against oxidative stress by activating c-Jun N-terminal kinase forkhead box O3a (JNK/FOXO3a) pathway and increasing

SOD and catalase (43, 152, 153). Selenium in combination with human BM-MSCs could support methylation cycle and chromatin integrity because as a component of selenoproteins, it can ensure the availability of S-adenosylmethionine (SAM), the universal methyl donor for DNA methyltransferases, histone H3K36me2/3 (DNMTs) and histone methyltransferases (HMTs) and decrease DNA damage indicators (micronuclei) by up to 58% (154).

### Lithium chloride

Lithium is a fine, white, deliquescent granular or crystalline powder with a feeble alkaline taste. Its salts can influence the central nervous system (CNS) in a variety of ways and used to treat bipolar disorder (BPD) (14). Lithium chloride (LiCl) *in vitro* could enhance the proliferation and growth kinetic of Ad-MSCs and protect the cells from apoptosis via an increase in expression of the Bcl-2 gene and a significant decrease in Bax gene (155). LiCl intake with MSCs and a ketogenic diet can be successful in treatment of BPD. This happens by an improvement in neurogenesis and an increase in expression of neurotrophic factors such as brain derived neurotrophic factor (BDNF), nerve growth factor (NGF) and insulin-like growth factor-1 (IGF-1) that enhance the survival and differentiation of neurons (156).

### Conclusion

Even many studies regarding the impact of vitamins and mineral components on proliferation, differentiation, homeostasis and regenerative capacity of body mesenchymal stem cells are *in vitro* and require *in vivo* validation; but the positive physiological effects of vitamins and minerals through several mechanisms in the literature reflect their pivotal role in regenerative medicine. It seems that improving nutritional intake and biochemical status of key micronutrients (e.g. vitamins and minerals) can be supportive for the efficacy of MSCs in therapies and immune function and subsequently the recovery and clinical outcome of patients. A proper food intake can particularly target the enhancement of stem cell activity, epigenetic regulation, redox-inflammatory pathways and cellular metabolism. In this review, the mitochondrial metabolic checkpoint regulating stem cell maintenance was highlighted. It was discussed how diet affects the metabolism of stem cells through the nutrient sensing pathways, thereby affecting stem cell fate decision and tissue regeneration.

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### Authors' Contribution

Conceptualization: DM and SJM; Investigation: SM, ASM, MH and MN; Data curation: SM and MN; Writing original draft preparation: DM and MN; Writing review and editing: DM and SM; Supervision: DM and SJM. All authors have read and agreed to the published version of the manuscript.

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### Conflict of Interest

The authors declare no conflicts of interest.

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