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INFORMATIVE NOTE

An opinion on the regulation of bone marrow adipose tissue by dietary fatty acids

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SUMMARY: Obesity has a significant impact on predisposition to various diseases and also affects the viability and choice of haematopoietic stem cells (HSCs) to favour myeloid cell production and/or turnover, all of which are extremely important for the functioning of immune system. As the production of blood cells and mobilization of HSCs and their progeny are regulated, at least in part, by multifaceted interactions through signals that come from the bone marrow (BM) microenvironment, it does not seem astonishing to assume that circumstances that cause alterations in BM structure will unavoidably cause alterations in mesenchymal cells such as adipocytes and lineages from HSCs. The existence of adipose tissue in BM or marrow fat (BMAT) is well known, although its origin, expansion, and functions are poorly understood. Inspired by other studies showing the potential role for olive oil and omega-3 long chain polyunsaturated fatty acids (omega-3 PUFAs) on BM health, and by our own preliminary findings showing the effects of monounsaturated (olive oil) but not saturated (milk cream) dietary fats to contain neutrophils and $CD14^{high}$ monocytes in BM during postprandial periods in healthy volunteers, herein we asked whether dietary fats (saturated fatty acids, SFAs, monounsaturated fatty acids, MUFAs, and omega-3 PUFAs) may be a candidate lifestyle factor to modulate the expansion, composition, and function of BMAT, the infiltration of adipose tissue macrophages (ATMs) in BMAT and the mobilization of HSCs and mature myeloid cells from BM during high-fat-induced obesity in mice. This is the first time that the interplay between different dietary fatty acids, obesity, and BM is addressed.

KEYWORDS: *Adipose tissue; Bone marrow; Olive oil; Omega-3 PUFAs; Saturated fats*

RESUMEN: ***Una opinión sobre la regulación del tejido adiposo de médula ósea por los ácidos grasos de la dieta.*** La obesidad aumenta de forma significativa la susceptibilidad a diversas enfermedades y también afecta a la viabilidad y elección del destino de las células madre hematopoyéticas (HSCs) y las cinéticas de producción de los leucocitos que provienen de ellas, todo ello de extrema importancia para el funcionamiento del sistema inmune. Considerando que la producción de células sanguíneas y movilización de HSCs y su progenie están reguladas, al menos en parte, por interacciones complejas a través de señales que provienen del microambiente de la médula ósea (BM), no parece sorprendente suponer que condiciones que causen alteraciones en la estructura de BM inevitablemente causarán alteraciones en las células mesenquimales como los adipocitos y los linajes procedentes de las HSCs. Es bien conocida la existencia de tejido adiposo en BM (BMAT), aunque su origen, desarrollo, y sus funciones son muy poco conocidas. Basándonos en los resultados de otros autores, quienes han descrito que el aceite de oliva y los ácidos grasos poliinsaturados omega-3 de cadena larga (omega-3 PUFAs) pueden tener efectos beneficiosos en la salud ósea, y no en menor medida en nuestros estudios previos que sugieren la capacidad del aceite de oliva, al contrario que las grasas saturadas, de inducir la retención de neutrófilos y monocitos con CD14 en BM de voluntarios sanos durante periodos postprandiales, en esta propuesta se pretende evaluar si las grasas de la dieta (ácidos grasos saturados, SFAs, ácidos grasos monoinsaturados, MUFAs, y omega-3 PUFAs) tienen relevancia en la expansión, composición, y funcionalidad de BMAT, en la infiltración

de macrófagos de tejido adiposo (ATMs) en BMAT, y en la movilización de HSCs y células maduras mieloides de BM durante la obesidad inducida por dietas ricas en grasas en animales de experimentación. Es la primera vez que se aborda la posible interacción entre diferentes ácidos grasos de la dieta, la obesidad, y BM.

PALABRAS CLAVE: *Aceite de oliva; Ácidos grasos omega-3; Grasas saturadas; Médula ósea; Tejido adiposo*

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In previous studies, we have identified atherosclerosis, thrombosis, and inflammatory risk factors associated to the ingestion of dietary fats during the postprandial period in humans (Lopez *et al.*, 2018, 2011, 2010, 2008; Ortega-Gomez *et al.*, 2017, 2012; Montserrat-de la Paz *et al.*, 2016; Naranjo *et al.*, 2016; Bermudez *et al.*, 2014, 2011; Varela *et al.*, 2011; Lopez-Miranda *et al.*, 2010; Pacheco *et al.*, 2008, 2006; Abia *et al.*, 2003, 2001, 1999). Our findings included some of the putative mechanisms by which exogenous fatty acids modulate cellular and molecular targets in the aetiology and pathogenesis of cardiovascular disease (Varela *et al.*, 2015, 2014, 2013; Lopez *et al.*, 2013, 2007; Bermudez *et al.*, 2012, 2008; Bellido *et al.*, 2004; Pacheco *et al.*, 2003, 2002, 2001). Recently, our research team has also discovered that neutrophils and monocytes/macrophages undergo phenotype/functional dynamic switch in response to the microenvironment signals during the period that follows the ingestion of dietary fats (manuscripts in preparation). We found that circulating neutrophil number was transiently increased after the ingestion of saturated (milk cream) but not of monounsaturated (refined olive oil) dietary fats. In addition, while total number of circulating monocytes was not postprandially affected, those monocytes expressing CD14 and CD16 at high density were characteristic after the ingestion of saturated and monounsaturated dietary fats, respectively. These observations are the first evidence of a potential crosstalk between exogenous fatty acids and bone marrow (BM) function, and suggest that dietary fats, in a fatty acid-dependent manner, could trigger myeloid cell mobilization in BM.

Hematopoietic stem cells (HSCs) exist in the BM and are in charge to generate all the cells necessary to refill the blood and immune systems. It is hierarchical and firmly orchestrated by a proper environment of cells and factors for controlling the fate decision of HSCs to preserve a steady platelet, erythrocyte, and leukocyte supply (Eaves, 2015; Boulais and Frenette, 2015). HSCs are rare (1 in 10000 BM cells), relatively quiescent (<5% are in cell cycle), and constitute the apex of a differentiation cascade of hematopoietic progenitor cells with gradually reduced regeneration competence while augmented ability of conversion into multiple blood cell lineages. The existence of subpopulations with different phenotypes among the progenitor cells involved in the reconstitution of haematopoiesis and able to produce the entire range of haematopoietic progeny cells has already been documented for a long time (Morrison and Scadden, 2014). According to the latest model of haematopoiesis, the multipotency of HSCs is conserved by the presence of long-term HSCs (LT-HSCs) that differentiate to yield short-term HSCs (ST-HSCs) in BM and no other population of HSCs is devoted to sustaining a certain lineage, but the potential lineage appears as the HSC grow (Adler *et al.*, 2014). Blood and immune system have the requirement of a proper supply of red cells and mature leukocytes with a finite lifespan throughout life. It is more evident after stress situations in which both host defence and repair mechanisms are mobilized. Furthermore, intravenously injected HSCs during BM transplantation can also promote homing and engraftment of HSCs to BM and regenerate the HSC pool to meet the demand of blood and immunity (Lapidot *et al.*, 2005). The endosteal and perivascular regions in bone are anatomical locations for HSCs within the BM. Several stromal cells, including mesenchymal stem cells (MSCs), secrete messengers [e.g. granulocyte-macrophage colony-stimulating factor (GM-CSF), macrophage colony-stimulating factor (M-CSF), and stromal cell-derived factor 1 (SDF-1)/C-X-C motif chemokine ligand 12 (CXCL12)] that bind to cell-surface receptors on HSCs for modulating their survival and functional role (Morrison and Scadden, 2014; Mendelson and Frenette, 2014). In addition, HSCs are retained in restricted hematopoietic niches via adhesion molecules, including vascular cell adhesion molecule-1 (VCAM-1), cadherins, annexin II, and E-selectin, where they receive and integrate extrinsic regulatory cues through the activation of transcription factors of the ETS family and partners, the main of which

are crucial to divert the production to myeloid cells (Pittet *et al.*, 2014).

Once neutrophils and monocytes are produced in mature form, they can leave the bone marrow into circulation. The release is tightly controlled by numerous signals such as C-C motif chemokine receptor 2 (CCR2) ligands [e.g. monocyte chemoattractant protein-1 (MCP-1)] and CXCL12. Migration of HPCs is limited, as only a few hundred are normally found outside BM (Massberg *et al.*, 2007). However, proteases [neutrophil elastase (NE), cathepsin G, and metalloproteinases (MMPs)] produced by BM myeloid cells have been noticed to be involved in the cleavage and inactivation of CXCL12 and KIT ligand throughout mobilization of myeloid cells from BM in stress situations (Shen *et al.*, 2010; Klein *et al.*, 2015). Serine protease inhibitor α1-antitrypsin (A1AT) is expressed in BM to prevent the accidental cleavage of niche components by NE and cathepsin G, and extracellular matrix (ECM) disarrangement (Kuiperij *et al.*, 2009). Genes encoding the small Rho guanosine triphosphatases Rac1 and Rac2 that control cell migration further promote the rapid mobilization and entry of HSCs into circulation (Gu *et al.*, 2003). We have preliminary data showing that monounsaturated, when compared to saturated dietary fats, promote: (i) a higher content of A1AT in lipoproteins of intestinal origin, neutrophils, and monocytes (manuscript in preparation); and (ii) the activation of the phosphoinositide 3-kinase (PI3k)-Rac1-Jun N-terminal kinase (JNK) and Rac1-MMP-2 pathways in human perivascular smooth muscle cells (Varela *et al.*, 2014). Therefore, it is tempting to speculate that dietary fats, in a fatty acid-dependent manner, may be involved on migratory capacity and release of HSCs.

In BM, cells of the osteoblast and adipocyte lineages have a common precursor, which comes from MSCs (Tian and Yu, 2015). Tracking the fate of MSCs in aged BM has revealed that close proximity between osteoblasts and adipocytes underscores the reciprocal relation of bone mass and BM adipogenesis. As a result, bone loss caused by osteoporosis is accompanied by a progressive BM adiposity, which suggests that differentiation of MSCs into adipocytes predominates over osteoblasts. To support MSC differentiation into either osteoblasts or adipocytes, it is essential that MSCs be recruited to proper density and confluence. Involved in modulating the lineage commitment, a variety of external stimuli delicately balanced include the release of growth factors [e.g. transforming growth factor-β (TGF-β) family members, bone morphogenic proteins (BMPs), and Wnt proteins] and transcription factors [e.g. peroxisome proliferator-activator gamma 2 (PPARγ2) for adipogenesis and runt-related transcription factor 2 (RUNX2) for osteogenesis]. The canonical Wnt/β-catenin pathway plays a major role in regulating these two differentiation processes (Yuan *et al.*, 2016). Soluble Wnt proteins such as Wnt10b, Wnt1, Wnt6, Wnt7a, and Wnt10a have pro-osteogenic activity and prevent phosphorylation, and thereby degradation of β-catenin. Unphosphorylated β-catenin may then translocate into the nucleus to form transcriptional complexes along with members of the T-cell factor (Tcf)/lymphoid enhancer-binding factor (Lef) nuclear protein family and RUNX2. These processes facilitate the osteogenic differentiation of MSCs, the mineralization by increasing alkaline phosphatase (ALP) activity in pre-osteoblasts, and the expression of the anti-bone resorption osteoprotegerin (OPG). During bone formation, pro-osteogenic Wnt proteins (Wnt10b, Wnt1, Wnt6, Wnt7a, and Wnt10a) coordinate each other and bind to low-density lipoprotein receptor-related protein (LRP) family, most likely LRP5/6. This crosstalk stabilizes β-catenin and allows its translocation, promoting osteoblastogenesis whereas blocking adipogenesis (Cawthorn *et al.*, 2012). However, other Wnt proteins (Wnt4, Wnt5a, and Wnt5b) obstruct these communications and networks, enabling degradation of β-catenin and inducing adipogenesis (Cristancho and Lazar, 2011). Previous studies noticed that MSCs are by-default programmed to differentiate into adipocytes (Lecka-Czernik, 2006; Kirkland *et al.*, 2002). By contrast, when the nuclear envelope intermediate filament lamin A/C is overexpressed, as it occurs in the bone in youth, MSCs enter the osteogenic lineage, preventing MSCs to differentiate into adipocytes (Pajerowski *et al.*, 2007; Bermeo *et al.*, 2015). Disruption of nearly all of these conditions takes place with aging and therefore the balance between MSC osteogenesis and adipogenesis will move towards adipogenic differentiation. In a setting of PPARγ activation, adipogenesis in BM-MSCs is positively regulated. Through mechanisms mediated by PPARγ signalling pathways, Wnt proteins are inhibited, β-catenin is degraded, and lamin A/C expression is suppressed. Interestingly, systemic adipokynes that regulate insulin sensitivity can also influence the fate of MSCs in BM. Insulin impedes the production of OPG in osteoblasts, thus, an increased ratio of OPG to receptor activator of nuclear factor-kB ligand (RANKL) supports the release of active osteocalcin from bone ECM giving rise the release of insulin from pancreas (Chen *et al.*, 2012). We have previously demonstrated that β-cell function and insulin sensitivity are modulated by meals enriched with refined olive oil (source of oleic acid) when compared to meals enriched with butter/milk cream (source of SFAs) (Lopez *et al.*, 2011; Lopez *et al.*, 2008), in agreement with a local action of meal-derived oleic and palmitic acids on pancreatic β-cells (Bermudez *et al.*, 2014). The adipocyte/osteoblast balance is also highly regulated at the level of gene transcription by the transfer of adipogenic microRNAs from adipocytes to osteoblasts, which enhances BM adiposity (Martin *et al.*, 2015).

Exponential accumulation of BM fat begins at birth. This happens more quickly in distal than in proximal bones, so that at 25 years old, BM is approximately 70% fat (Fazeli *et al.*, 2013; Cawthorn *et al.*, 2014). Apart from age, certain conditions such as metabolic diseases (type 1 and 2 diabetes) (Kurra and Siris, 2011), oestrogen withdrawal (Taxel *et al.*, 2008), immobilization (Lau and Guo, 2011), glucocorticoid treatment (Havashi *et al.*, 2009), Cushing's disease (Geer *et al.*, 2012), and caloric restriction (Devlin *et al.*, 2010) favour fat accumulation within BM instead of bone formation. These risk factors encourage the MSCs to change into its default lineage: adipocytes. BM adipose tissue (BMAT) formation is further induced by several treatment modalities such as radiation, chemotherapy, and thiazolidinediones (Suchacki *et al.*, 2016). Until the last few years, adipocytes were perceived by many as metabolically inactive cells in the BM niche, even as cells only intended to fill trabecular bone holes. It is now clear that the adipocyte within bone is indispensable for the normal function of other neighbouring cells in the marrow microenvironment. BM adipocytes are scattered throughout the hematopoietic tissue, instead of grouped in lobules as in other fat depots (Hardouin *et al.*, 2014). It is relevant that subcutaneous and visceral adipose tissues (white adipose tissue, WAT) have a fatty acid composition different to that found in BM adipose tissue (BMAT), which is richer in saturated fatty acids (SFAs) and poorer in monounsaturated fatty acids (MUFAs) than subcutaneous or visceral WAT (Griffith *et al.*, 2009). Observations from randomized controlled trials and population-based observational studies have shown that a high intake of fatty fish strongly correlates with a reduction in the burden of fragility fracture (Longo and Ward, 2016), suggesting that omega-3 long chain polyunsaturated fatty acids (omega-3 PUFAs), as demonstrated for oleic acid (Gillet *et al.*, 2015; Garcia-Martinez *et al.*, 2014), have potential benefits on BM cells and microenvironment. Under high levels of adipogenesis, BM adipocyte products (free fatty acids and adipokynes) may induce osteoblast apoptosis, even the fat tissue can undergo dramatic and repetitive sequences in the remodelling to allow tissue expansion and removal of dead adipocytes, which is a process mediated by adipose tissue macrophages (ATMs). This scenario causing a vicious circle is known as lipotoxicity (Ng and Duque, 2010). Conversely, when co-cultured with adipocytes having inhibited the fatty acid endogenous biosynthesis, osteoblasts increase survival and improve mineralization (Elbaz *et al.*, 2010). There is now plenty evidence that lipotoxicity by ectopic fat accumulation in BM is common in other organs, including pancreas, muscle, and liver. In pancreas, newly arrived adipocytes (deposition of fat inside and around the pancreas) affect the function and induce the death of β-cells (Long *et al.*, 2014). Interestingly, this fat-induced process may be orchestrated by fatty acids. For example, exposure of human islet cells to palmitic acid [the main SFA in the diet] impairs glucose-stimulated insulin secretion, reduces insulin gene transcription, and induces β-cell apoptosis, whereas oleic acid [the main MUFA in the diet] is cytoprotective for β-cells and even attenuates the pro-apoptotic effects of palmitic acid (Lopez *et al.*, 2010). Similarly, among the adipocyte-secreted factors in BM, palmitic acid has negative effect on osteoblasts in co-culture (Gunaratnam *et al.*, 2014; Wang *et al.*, 2013): (i) lowering mineralization, ALP activity, and expression of osteogenic mRNA markers; (ii) increasing intracellular reactive oxygen species (ROS); and (iii) disrupting the Wnt signalling and BMP2/RUNX2/SMADs pathways. Evidence from proteomic analysis of adipocytes suggests the occurrence of changes during ageing BM from pro-osteogenic, anti-adipogenic, and anti-apoptotic phenotype in young mice to a toxic and pro-adipogenic phenotype in old mice through paracrine mechanisms involving local secretion of adipokynes particularly involved in BM function (Gasparrini *et al.*, 2009). Recent studies have reported that secretion of leptin and adiponectin (the adipokynes whose receptors are expressed by osteoblasts and osteoclasts) is greater from BMAT than from visceral WAT (Cawthorn *et al.*, 2014) and that adiponectin from BM adipocytes has a relevant role in mobilizing HSCs/HPCs into blood to participate in tissue repair and remodelling (Yu *et al.*, 2015).

The link between progressively sedentary lifestyle and cumulative consumption of high-dense foods, exemplified by the "Western style" high-fat diet, has contributed to the global pandemic of obesity and related disorders. This diet-induced adiposity is generally localized in subcutaneous or visceral WAT. There are important metabolic differences between adipocytes in different anatomical compartments; therefore, the location of fat pads at any of these regions is not their only distinctive characteristic. In fact, this adipose heterogeneity is also visualized by their different roles in disease susceptibility. BMAT seems to be a special class of fat depot with unique functions. Despite a similar appearance to subcutaneous and visceral adipocytes, BM adipocytes have divergent physiological, hormonal, and metabolic responses. In the C57BL/6J and C3H/HeJ mouse strains, by using the osmium staining technique for comparative morphology, BMAT may be found in two different groups: constitutive BMAT (cBMAT) and "regulated" BMAT (rBMAT). cBMAT is formed very early after birth in distal region of tibia and in caudal vertebrae, its adipocytes look like those in WAT and are poorly responsive to systemic disturbances. On the other hand, rBMAT is developed later as smaller adipocytes scattered with other BM

cells in proximal skeletal sites, being responsive to a range of environmental, metabolic, and genetic cues (Scheller et al., 2014). Strikingly, the analysis of lipids, gene expression patterns, and functions in rBMAT is different from cBMAT (Scheller *et al.*, 2015). It is possible that the origin of BMAT, still unveiled, is dissimilar to that of other fat depots. Thus, the origin of WAT and brown adipose tissue (BAT) is even a matter of on-going debate. After body weight loss induced by caloric restriction or by starvation in an eating disorder such as anorexia nervosa, there is an increase of BMAT. This fat tissue accretion in BM is to some extent unexpected because other fat depots (for example, visceral WAT) are being mobilised to meet energy demands when excessive catabolic activities. It is unclear why this happens. Several hypotheses have been proposed to explain this apparent paradox, including the occupation by BMAT of BM cavity space in response to the eventual loss of trabecular bone, the expansion of BMAT in response to starvation-induced stress as an adaptive strategy for supporting survival of BM cells, and the adiponectin secretion by BMAT to enhance insulin sensitivity and to stimulate appetite (Scheller *et al.*, 2014). Notwithstanding the relevance of BMAT for metabolic and hematopoietic outcomes, it remains unexplored whether dietary fatty acids are instrumental in BM adiposity and in the phenotype of BM adipocytes, which could balance the likely adverse effects of increased adipogenesis on BM organization and function.

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