Progress in Lipid Research 58 (2015) 121–145

Contents lists available at ScienceDirect

Progress in Lipid Research

journal homepage: www.elsevier.com/locate/plipres

Review

Pros and cons of fatty acids in bone biology

Fabien Wauquier, Laurent Léotoing, Claire Philippe, Mélanie Spilmont, Véronique Coxam, Yohann Wittrant *

INRA, UMR 1019, UNH, CRNH Auvergne, F-63009 Clermont-Ferrand, France
Clermont Université, Université d'Auvergne, Unité de Nutrition Humaine, BP 10448, F-63000 Clermont-Ferrand, France
Equipe Alimentation, Squelette et Métabolismes, France

ARTICLE INFO

Article history:
Received 31 January 2013
Received in revised form 6 March 2015
Accepted 23 March 2015
Available online 30 March 2015

Keywords:
Fatty acids
Bone
Nutrition
Osteoporosis

ABSTRACT

Despite the growing interest in deciphering the causes and consequences of obesity-related disorders, the mechanisms linking fat intake to bone behaviour remain unclear. Since bone fractures are widely associated with increased morbidity and mortality, most notably in elderly and obese people, bone health has become a major social and economic issue. Consistently, public health system guidelines have encouraged low-fat diets in order to reduce associated complications. However, from a bone point of view, mechanisms linking fat intake to bone alteration remain quite controversial. Thus, after more than a decade of dedicated studies, this timely review offers a comprehensive overview of the relationships between bone and fatty acids. Using clinical evidences as a starting-point to more complex molecular elucidation, this work highlights the complexity of the system and reveals that bone alteration that cannot be solved simply by taking ω-3 pills. Fatty acid effects on bone metabolism can be both direct and indirect and require integrated investigations. Furthermore, even at the level of a single cell, one fatty acid is able to trigger several different independent pathways (receptors, metabolites…) which may all have a say in the final cellular metabolic response.

Contents

Abbreviations: AA, arachidonic acid; ALP, alkaline phosphatase; ALX, G protein-coupled lipoxin A(4) receptor; AMP, adenosine monophosphate; BAT, brown adipose tissue; BMC, bone mineral content; BMD, bone mineral density; BMI, body mass index; CKD, chronic kidney disease; CLA, conjugated linolenic acid; CLD, chronic liver disease; Col1a, collagen 1a; COX, cyclooxygenases; CTR, calcitonin receptor; CTX, c-terminal telopeptide; DC-STAMP, dendritic cell-specific transmembrane protein; DHA, docosahexaenoic acid; EFA, essential fatty acid; EPA, eicosapentaenoic acid; ESRD, end-stage renal disease; FFA, free fatty acid; GHSR, growth hormone secretagogue receptor; GIP, glucose-dependent insulinotropic peptide; GLP-1, glucagon-like peptide-1; GPCR/GPR, G protein coupled receptor; IGF, insulin-like growth factor; GSIS, glucose-stimulated insulin secretion; H_2O_2, hydrogen peroxide; HFD, high fat diet; HSC, hepatic stellate cells; IFN, interferon; Ig, immunoglobulin; IKK, inhibitor of kappaB kinase; Il, interleukine; iNOS, inducible nitric oxide synthase; IRS, insulin receptor substrates; IsoP, isoprostan; JNK, c-Jun N-terminal kinases; KO, knock-out; LA, linoleic acid; α-LA, α-lipoic acid; LCFA, long chain fatty acid; LDL, low-density lipoprotein; LnA, α-linolenic acid; LOX, lipoxygenases; LTB4R, leukotriene B4 receptor; MCP-1, monocyte chemoattractant protein 1; M-CSF, macrophage colony-stimulating factor; MIP1A, macrophage inflammatory proteins 1α; MMP-9, Matrix metalloproteinase-9; MUFA, mono-unsaturated fatty acid; NALP3, NACHT, LRR and PYD domains-containing protein 3; NADPH, nicotinamide adenine dinucléotide phosphate; NFATc-1, nuclear factor of activated T cells cytoplasmic calcineurin dependent 1; NO, Nitric oxide; NOX, NADPH Oxidase; N-Tx, N-telopeptide; OA, oleic acid; OPG, osteoprotegerin; OVX, ovariectomized; PBMC, peripheral blood mononuclear cell; PGE, prostaglandin; PKC, protein kinase C; PPAR, peroxisome proliferator-activated receptor; PTH, parathyroid hormone; PUFA, poly-unsaturated fatty acid; RAMPS, receptor activity modifying proteins; RANKL, receptor activator of NF-κB Ligand; ROS, reactive oxygen species; Runx-2, runt-related transcription factor 2; RvE, resolvin; SAMP8, senile osteoporosis senescence-accelerated prone mouse 8; SFA, saturated fatty acid; SREBP-1, sterol regulatory element binding protein 1; STZ, streptozotocin; TGF, transforming growth factor; TIMP, tissue inhibitor of metalloproteinases; TLR, toll like receptor; TNF, tumor necrosis factor; TRAP, tartrate-resistant acid phosphatase; WAT, white adipose tissue.

* Corresponding author at: UMR 1019, Centre de Recherche INRA de Clermont-Ferrand/Theix, France. Tel.: +33 (0)4 73 62 47 84; fax: +33 (0)9 57 05 99 12.
E-mail address: yohann.wittrant@clermont.inra.fr (Y. Wittrant).

http://dx.doi.org/10.1016/j.plipres.2015.03.001
0163-7827/

1. Introduction

Industrialized countries face a greater prevalence of metabolic disorders as a consequence of the increased amount of fat in daily food intake [1]. These disorders have reached record proportions in the last three decades and mostly include obesity and the onset of type 2 diabetes. However, the main social and economic burdens of these pathologies lye in their morbidity. In fact, obesity and type 2 diabetes alter tissue functions and are associated with complications such as cardio-vascular diseases, cancers, sarcopenia and osteoporosis [2].

Regarding locomotor dysfunctions, when associated with age-related bone loss, HFD have a dramatical impact on the onset of osteoporosis [3–5], with an increase in associated-mortality [6]. In fact, osteoporotic fractures can result in up to 20% excess mortality within one year. Additionally, up to 50% of patients will be disabled, with half of them requiring long-term nursing home care, while only one-third fully recover from hip fracture. Current osteoporotic treatments are limited to drug-based strategies, but major side-effects have been reported, including a greater prevalence of breast cancer and to a lesser extent osteonecrosis of the jaw [7]. These clinical observations strongly emphasise the need for alternative strategies in the prevention of bone loss.

As a consequence, the epidemic of obesity has led to an increased number of guidelines encouraging low-fat and low-energy diets as well as the development of low-fat products or fat substitutes, in order to reduce associated complications. However, from a bone point of view, mechanisms linking fat intake to bone alteration remain quite controversial.

Previous epidemiological studies have demonstrated a positive correlation between body mass index (BMI) and bone mineral density (BMD) [2–5]. Nevertheless, this correlation may be attributed to mechanical stimulation of bone formation or obesity-related enhanced estrogen level [3,8,9], independently of the adiposity effect on bone. Indeed, when the mechanical loading effect of total body weight was statistically removed, fat mass was negatively correlated with bone mass and positively associated with bone fractures, suggesting a detrimental effect of excess adiposity on bone [10–13].

On the other hand, fat quality is also a crucial determinant for bone tissue behaviour. Indeed, far from being only energy substrates, a growing body of evidence demonstrates that the influence of fatty acids on bone metabolism widely relies on their origin, structure, relative concentration and metabolic context. As a matter of fact, depending on their group, fatty acids may be either beneficial or detrimental to bone [14,15]. For instance, clinical observations, consistent with *in vivo* and *in vitro* data, would indicate bone loss induction by the ω-6 group, while ω-3 are believed to protect bone health [16–19]. Nevertheless, this debate is rather simplistic considering the wide range of fatty acid molecules present in the human diet, and the mechanisms of action are far from