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Review

Low-grade chronic inflammation perpetuated by modern diet as a promoter of obesity and osteoporosis

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Some of the universal characteristics of pre-agricultural hominin diets are strikingly different from the modern human diet. Hominin dietary choices were limited to wild plant and wild animal foods, while the modern diet includes more than 70 % of energy consumed from refined sugars, refined vegetable oils, and highly processed cereals and dairy products. The modern diet, with higher intake of fat has also resulted in a higher ratio of omega-6 (*n*-6) to omega-3 (*n*-3) polyunsaturated fatty acids (PUFA), contributing to low-grade chronic inflammation (LGCI) and thus promoting the development of many chronic diseases, including obesity and osteoporosis. In this review, we describe the changes in modern diet, focusing on the kind and amount of consumed fat; explain the shortcomings of the modern diet with regard to inflammatory processes; and delineate the reciprocity between adiposity and inflammatory processes, with inflammation being a common link between obesity and osteoporosis. We present the evidence that over-consumption of *n*-6 PUFA coupled with under-consumption of *n*-3 PUFA results in LGCI and, along with the increased presence of reactive oxygen species, leads to a shift in mesenchymal stem cells (precursors for both osteoblasts and adipocytes) lineage commitment toward increased adipogenesis and suppressed osteoblastogenesis. In turn, high *n*-6 to *n*-3 PUFA ratios in the modern diet, coupled with increased synthesis of pro-inflammatory cytokines due to adiposity, propagate obesity and osteoporosis by increasing or maintaining LGCI.

KEY WORDS: *adipocytes; cytokines; eicosanoids; mesenchymal stem cells; omega-3 fatty acids; omega-6 fatty acids; osteoblasts; osteoclasts; polyunsaturated fatty acids*

Abbreviations:

5-LOX=5-Lipoxygenase; AA=Arachidonic acid; AHA=American Heart Association; ALA=Alpha-linoleic acid; CLA=Conjugated Linolenic Acid; COX-2=Cyclooxygenase-2; CRP=C-reactive protein; DHA=Docosahexanoic Acid; EPA=Eicosapentanoic Acid; IGBP-3=Insulin like growth factor binding protein-3; IL-1=Interleukin-1; IL-6=Interleukin-6; LA=Linolenic Acid; LBT_4=Leukotriene B_4; LBT_5=Leukotriene B_5; LGCI=Low grade chronic inflammation; MSC=Mesenchymal stem cells; MUFA=Monounsaturated Fatty Acids; n-3=Omega-3; n-6=Omega-6; NHANES=National Health and Nutrition Examination Survey; OPG=Osteoprotegerin; PDE=Phosphodiesterase; PGE_2=Prostaglandin E_2; PGE_3=Prostaglandin E_3; PUFA=Polyunsaturated Fatty Acids; RANK=Receptor activator of nuclear factor kappa-B; RANKL=Receptor activator of nuclear factor kappa-B ligand (RANKL); SFA=Saturated Fatty Acids; TNF-α=Tumor Necrosis Factor-alpha; TXA_2=Thromboxane A_2

Dietary intake and other lifestyle factors (e.g. physical activity, smoking) are environmental modifiers that have changed dramatically with agriculture and animal husbandry, about 10,000 years ago (1, 2). However, a number of anthropological, nutritional, and genetic studies indicate that even more drastic changes happened very recently, some 200 years ago with the onset of industrial revolution, and that these changes could be associated with many chronic diseases or the so-called diseases of civilization (1, 3).

By examining the dietary habits along the evolutionary timeline, one can easily notice the

difference between the pre-agricultural hominine and modern human diet. Hominin dietary choices were limited to wild plant and animal foods. In contrast, 72 % of the energy consumed by modern humans includes refined sugars, refined vegetable oils, highly processed cereals and dairy products, as well as high consumption of alcohol (4).

The objectives of this review are to: a) describe the changes in modern diet with regard to several nutrients, particularly addressing the type and amount of consumed fat; b) explain the shortcomings of the modern diet with regard to inflammatory processes; and c) delineate the reciprocity between adiposity and inflammatory processes and the link that connects obesity, osteoporosis, and inflammation. We present the hypothesis that omega-6 (*n*-6) polyunsaturated fatty acids (PUFA) propagate obesity and osteoporosis by increasing/maintaining low-grade chronic inflammation (LGCI), ultimately shifting the commitment of mesenchymal stem cells (MSC) toward increased adipogenesis.

Discordance between current and past dietary habits along the evolutionary timeline

Our genetic makeup has not changed over the last few centuries, but the environment and dietary behaviors have, substantially. The spontaneous mutation rate for nuclear DNA is estimated at 0.5 % per million years; thus, very little change has occurred in our genes compared to our Paleolithic ancestors of 40,000 years ago, when our genetic profile was established. Therefore, the profound environmental and dietary changes that began with the introduction of agriculture and animal husbandry some 10,000 years ago, occurred too recently on the evolutionary timeline for the human genome to adapt, contributing to many of the chronic diseases in modern societies (5).

Some nutrients exhibit high discordance regarding their intake in the hominines compared to modern humans that may have contributed to inflammation and subsequent chronic diseases, including obesity and osteoporosis. Of note are the lower consumption of fat, carbohydrates, and sodium (high amounts of the latter might result in negative consequences on bone health via increased calcium excretion) and much higher consumption of calcium and vitamin C (both important in bone health and the former one in weight management). Additionally, with the high intake of plant foods, hominines were consuming much higher amounts of fiber (has a role in weight management) and phytochemicals, known for their anti-oxidative and anti-inflammatory properties. Table 1 compares the intake of hominines and current intake in the USA, as well as the current recommendations of selected nutrients in the USA (adapted from 2, 6, 7).

Changes in fat intake and their subsequent effect on omega-6 (n-6) and omega-3 (n-3) PUFA ratio

Among the most salient changes were those in the dietary fat intake, specifically in the type and amount of fatty acids (1, 3, 8). The amount and kind of fat reflected the consumption of primarily lean meat from

Table 1 *Estimated intake of selected nutrients and foods by hominines from the late Paleolithic (~40,000 years ago) and modern USA population and current recommendations*

Nutrients/ Foods	Late Paleolithic	Current USA Intake	Current USA recommendations
Fat (% of energy)	21	33	20-35
Carbohydrates (% of energy)	46	50	45-65
Protein (% of energy)	33	15	10-35
Alcohol (serving per day)	Minimal	N/A	1-2
P/S ratio	1.4	0.7	N/A
Cholesterol (mg per day)	520	261	<300
Fiber (mg per day)	100-150	16	38
Sodium (mg per day)	690	3463	<2300
Calcium (mg per day)	1500-2000	1029	1000-1300
Vitamin C (mg per day)	440	87	75-95

Adapted from references (2, 6, 7)
P/S - polyunsaturated to saturated fatty acid ratio; N/A - data not available

wild animals, low in saturated fatty acids (SFA) and high in both PUFA and monounsaturated fatty acids (MUFA), with low *n*-6 to *n*-3 PUFA ratio. Prior to the Neolithic (agricultural) period, or some 40,000 years ago in the Paleolithic, all animal foods consumed by hominines were limited to wild animals (9). Approximately 50 % of fatty acids in the adipose tissue of wild animals were SFAs, while the dominant type in the muscle and all other organs were PUFA and MUFA. However, for most of the year animals' subcutaneous and visceral body fat stores were usually depleted, and it was likely that PUFA and MUFA were the predominant fats of the carcass available for hominin consumption. Therefore, high amounts of SFA were probably not available to hominines feeding on these wild animals. Moreover, the consumption of seeds, nuts, various greens, and other wild plants provided the hominines with higher intake of PUFAs and MUFAs and probably with an optimal ratio of *n*-6 to *n*-3 (3, 8).

Subsequent changes that occurred with the beginning of animal husbandry and agriculture (in the Neolithic period, some 10,000 years ago) allowed for slaughtering of animals at the peak of body fat accumulation, while the production of grains and other agricultural products with higher SFA content led to an increasing consumption of *n*-6 PUFAs, creating a less favorable *n*-6 to *n*-3 ratio. Technological advances in the early and mid 19th century generated large quantities of grain (especially corn) for animals and humans, which changed the composition of the meat in the cattle, resulting in "marbled meat" characterized by excessive triglyceride accumulation and fat infiltration into the muscular tissue and higher SFA content (10). This and the modernization of food processing and preservation, as well as changes in food choices have altered the ratio between *n*-6 and *n*-3 fatty acids in the modern diet and resulted in its low *n*-3 fatty acid content (8, 9), favoring the development of chronic diseases.

According to numerous anthropological and epidemiological studies, humans evolved on a diet with a *n*-6 to *n*-3 PUFA ratio of approximately 1-2:1 (3), whereas this ratio in the current Western-type diet has increased to approximately 10-15:1 (1, 3, 8), as shown in Table 2 (adapted from 1, 3, 8). This suggests that even the current dietary guidelines (except for the recommendations from the American Heart Association for severe coronary patients, who need to lower their triglycerides) fall short of the intake of prehistoric humans. Table 3 (adapted from 1, 3, 8, 11) shows

Table 2 *Ratio between* n-*6 and* n-*3 polyunsaturated fatty acids in different population groups*

Population group	*n*-6/*n*-3 ratio
Paleolithic/Neolithic	0.8-1
Mediterranean (prior to 1960)	1-2
Current Northern Europe	15
Current USA	15-20

Adapted from references (1, 3, 8)

different recommendations for eicosapentanoic acid (EPA) and docosahexanoic acid (DHA) as well as the *n*-6 to *n*-3 ratio. The Lyon Diet Heart Study (12) showed that the ratio of 4:1 could be cardioprotective. The subjects in this study consumed less linoleic acid (*n*-6) and more of oleic (*n*-9) MUFA and α-linolenic acid (*n*-3), which resulted in higher plasma levels of oleic acid, linolenic acid, and EPA and lower levels of linoleic and arachidonic acid (AA), which was ultimately associated with a reduced risk of recurrent heart disease.

Pro- and anti-inflammatory metabolites of n-6 and n-3 fatty acids

It is known that elevated *n*-6 PUFA levels stimulate pro-inflammatory processes and promote the pathogenesis of many diseases such as cardiovascular, neurological, autoimmune, as well as cancer, arthritis, and diabetes (3, 8). Recently however, it has been realized that various pro-inflammatory actions may

Table 3 *Intake of eicosapentanoic acid (EPA) and docosahexanoic acid (DHA), the* n-*6 to* n-*3 ratio reported by NHANES, and recommendations*

Intake recommendations	EPA + DHA (g per day)	*n*-6/*n*-3 ratio
NHANES (2009-2010)	0.12	9:1
Dietary Guidelines (2010)	0.25	8:1
AHA (healthy population)	0.5	7:1
AHA (coronary patients)	1	6:1
AHA (severe coronary patients)	2-4	3:1
FDA GRAS level	3	N/A

Adapted from references (1, 3, 8, 11)
NHANES - National Health and Nutrition Examination Survey; AHA - American Heart Association

foster obesity and osteoporosis as well (11). In contrast, *n*-3 fatty acids and their derivatives have been shown to promote anti-inflammatory processes and to have some beneficial health effects on cardiovascular disease (8, 9), cognition in aging, function in the brain grey matter, and the development of eye retina (2, 8).

Eicosanoids, the metabolic products of the sequential elongation and desaturation processes of both *n*-6 and *n*-3 PUFA, are the signaling molecules responsible for the immune and inflammatory reactions in the body (13). They originate from the essential fatty acids, linoleic (*n*-6) and alpha linolenic (*n*-3). The major metabolites of *n*-6 PUFA are pro-inflammatory eicosanoids and include prostaglandin E_2 (PGE_2), leukotriene B_4 (LBT_4), and thromboxane A_2 (TXA_2), generated by lipid-oxidizing enzyme lipoxygenase-5 (5-LOX) and cyclooxygenase-2 (COX-2) (13). The major metabolites of *n*-3 PUFA are the anti-inflammatory eicosanoids and include prostaglandin E_3 (PGE_3), leukotriene B_5 (LBT_5), resolvins, and protectins, also generated by COX-2 and 5-LOX. During metabolism, *n*-6 and *n*-3 PUFAs compete for the desaturation enzymes (13, 14), and the higher amount of *n*-6 PUFA in the modern diet shifts the balance toward the production of pro-inflammatory eicosanoids (11). Figure 1 illustrates the metabolic pathways of the *n*-6 and *n*-3 PUFA series in generating various types of eicosanoids.

Acute and low-grade chronic inflammation and their resolutions

The breakdown of fatty acid metabolites and the conversion of eicosanoids generates different pro- and anti-inflammatory products (Figure 2). The pro-inflammatory lipoxins A_4 and B_4 are the metabolites of AA, and their action is focused on neutrophil regulation (15), while the E-series resolvins (both E1 and E2) are metabolized from EPA by 5-LOX, and their action is anti-inflammatory (16). Protectins, the D-series resolvins (D1 and D2), and the macrophage-specific maresins are the metabolites of DHA (17), and these are associated with resolving the inflammation (18). Overall, *n*-3 PUFA are metabolized into anti-inflammatory eicosandoids which are important to resolve inflammation otherwise triggered by any insult on the cell, ranging from a bruise to a bacterial infection or even by inflammatory signals from neighboring cells.

Acute inflammation activates the inflammatory cascade of prostaglandins, leukotrienes, and other inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and interferon-gamma which recruit neutrophils and macrophages. When the insult is dealt with, either via apoptosis and phagocytosis of the infected cells and foreign bodies or via cleaning the local inflammation, resolvins, protectins, maresins, and lipoxins all work together to stop further recruitment of immune cells and the propagation of pro-inflammatory cytokines, so that the cell can return to its basal state (19, 20).

In contrast, LGCI is a state of persistent and unresolved inflammation, where pro- and anti-inflammatory cytokines are elevated, and inflammation is not resolved (21). In the clinical context, this state results from the continuous presence of specific immune cells leading to 2-4-fold elevations in the circulating levels of pro- and anti-inflammatory cytokines, and more are recruited in a perpetual cycle (21). The exact PUFA metabolite composition of this unresolved or surplus inflammation is unknown (17), but it is likely that there is a bias towards the pro-inflammatory eicosanoids, particularly with higher *n*-6 PUFAs intake (Figure 3).

The detrimental role of low-grade chronic inflammation in obesity and osteoporosis

Obese individuals have abnormal circulating levels of TNF-α, IL-6, C-reactive protein (C-RP), adiponectin, and leptin, as these molecules are overexpressed in adipose tissue (22-24). PGE_2, a metabolite of AA, has been found to mediate locally the biological action of TNF-α and Interleukin-1 (IL-1) in the cases of fever and local inflammation. Leptin and adiponectin are adipokines produced by adipose tissue that mediate chronic inflammation. Leptin has been found to stimulate inflammatory responses (25, 26), while adiponectin acts as an anti-inflammatory adipokine (27). The constant presence of these inflammatory cytokines associated with increased adiposity promotes persistent LGCI in obese individuals (1), while adipose tissue itself increases their production, resulting in a perpetual feedback cycle from one to another (adiposity↔inflammation). For more extensive review see Kelly, et al. (11).

In the bone, inflammation also plays a detrimental role and is interconnected with adiposity. It is well established that IL-6 stimulates osteoclastogenesis (formation of bone-resorbing cells) and is considered an osteoresorptive factor (28). Simultaneously, higher amount of fat mass activates osteoclasts via increase in other cytokines like IL-1 and TNF-α, as shown in Figure 4. Osteoclasts are derived from the same

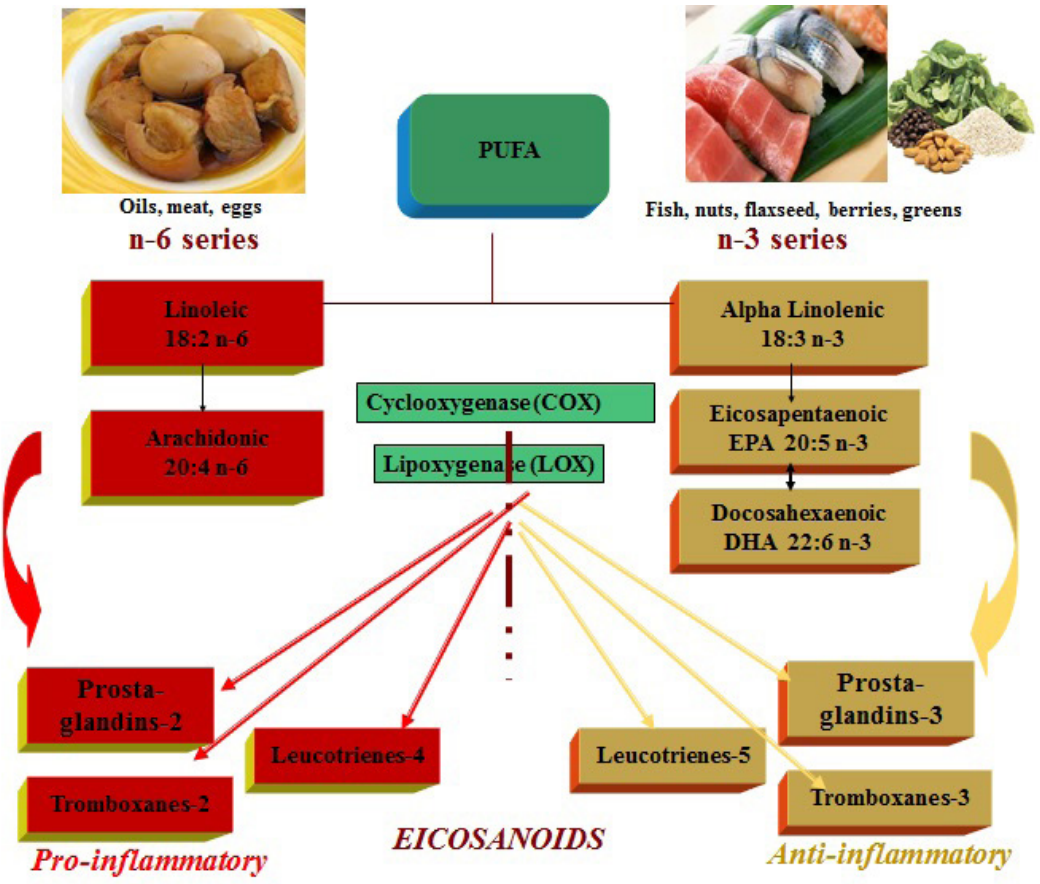

Figure 1 *Metabolism of essential linoleic (*n*-6) and alpha linolenic (*n*-3) fatty acids. An overproduction of arachidonic acid originating from the high intake of linoleic acid will metabolize into pro-inflammatory eicosanoids, which are implicated in many inflammatory and autoimmune disorders. Eicosapentanoic acid (EPA) and docosahexanoic acid (DHA), which are the derivatives of the essential* n*-3 alpha linolenic fatty acid (created from multiple elongation and desaturation reactions), form anti-inflammatory eicosanoids*

hematopoietic stem cells as the immune cells (29). In LGCI accompanied by increased T-cell activation, osteoclastogenesis and bone resorption are accelerated, as the osteoclasts are programmed to respond to inflammatory signals. Therefore, in states such as LGCI, osteoclastogenesis and bone resorption are increased (11), leading to a perpetual feedback cycle (bone resorption↔inflammation).

Mesenchymal stem cells (MSC) are the common precursors for osteoblasts (bone forming cells) and adipocytes (30). However, inflammation may deregulate the MSC lineage commitment (11, 31). Even under normal homeostatic conditions, MSC slightly favors adipogenic differentiation. In LGCI, pro-inflammatory mediators in the presence of a high *n*-6 to *n*-3 ratio and reactive oxygen species (ROS), stimulate adipogenesis and suppress osteoblastogenesis, ensuring that MSC are committed to becoming adipocytes. In addition, high levels of IL-6, C-RP, and TNF-α are associated with lower muscle mass in older people (32). Since muscle and bone mass decline with age, and fat mass increases, it is possible that age-related MSC lineage commitment dysfunction occurring in LGCI and coinciding with obesity causes both osteopenia (loss of bone) and sarcopenia (loss of muscle). For the extensive review on the connection between bone, muscle, and fat, see Ilich et al. (31).

Recently, we investigated the effect of *n*-6 and *n*-3 PUFAs in different ratios on MSC proliferation and differentiation and found that the *n*-6 to *n*-3 ratio of 4:1 resulted in maximal osteoblastogenesis and minimal adipogenesis in a cell culture system (33). This ratio is higher than in the prehistoric humans (e.g. 1:1), and is feasible for modern humans with some dietary modifications. Figure 5 illustrates the loop effect of modern (A) and prehistoric (B) diet on adipogenesis, osteoblastogenesis, and osteoclastogenesis.

Proposed mechanism of action

The enzyme COX-2 has a higher affinity for *n*-6 than *n*-3 PUFAs and the former will be metabolized at a higher rate (13, 14). However, higher presence of *n*-3, especially at the 1:1 ratio, would increase the odds of more *n*-3 being metabolized, which would lower the production of inflammatory eicosanoids. Some COX-2 inhibitors have been observed to decrease osteoblast differentiation and increase adipogenesis (34). This indicates that COX-2 and its lipid products may have a role in promoting MSC differentiation into adipocytes rather than osteoblasts, and that the ratio between *n*-6-derived COX-2 and *n*-3-derived COX-2 products may be important in MSC regulation.

Another proposed mechanism concerns the receptor activated nuclear factor kappa-B (RANK) signaling and osteoprotegerin (OPG). RANK binds to its ligand (RANKL), which is secreted by preosteoblasts, and activates osteoclastogenesis and bone resorption. Conversely, OPG, which is also produced by preosteoblasts, inhibits osteoclastogenesis by binding to RANKL, and thus promotes osteoblastogenesis. Upregulated pro-inflammatory cytokines, including TNF-α, IL-1, and IL-6 in obese state seem to mediate osteopenia and osteoporosis by regulating the RANKL/RANK/OPG pathway (31, 35).

CONCLUSION

Humans evolved on a diet low in saturated fat, carbohydrates, and sodium and much higher in calcium, vitamin C, fiber, and phytochemicals. Modern humans, however, consume high amounts of *n*-6 PUFA, about 10-15 higher than hominines. This elevates the ratio between *n*-6 to *n*-3 PUFA that stimulates pro-inflammatory processes and LGCI and promotes the pathogenesis of many chronic diseases, including obesity and osteoporosis. In contrast, *n*-3 PUFA and their derivatives, consumed by hominines in higher amounts, have been shown to promote anti-inflammatory processes and to have multiple beneficial health effects.

Obese individuals, who consume greater amounts of *n*-6 PUFA and exhibit higher circulating levels of pro-inflammatory cytokines (TNF-α, IL-6, C-RP), create the environment of a persistent LGCI, resulting in a perpetual feedback cycle. Furthermore, some cytokines (e.g. IL-6) stimulate osteoclastogenesis and

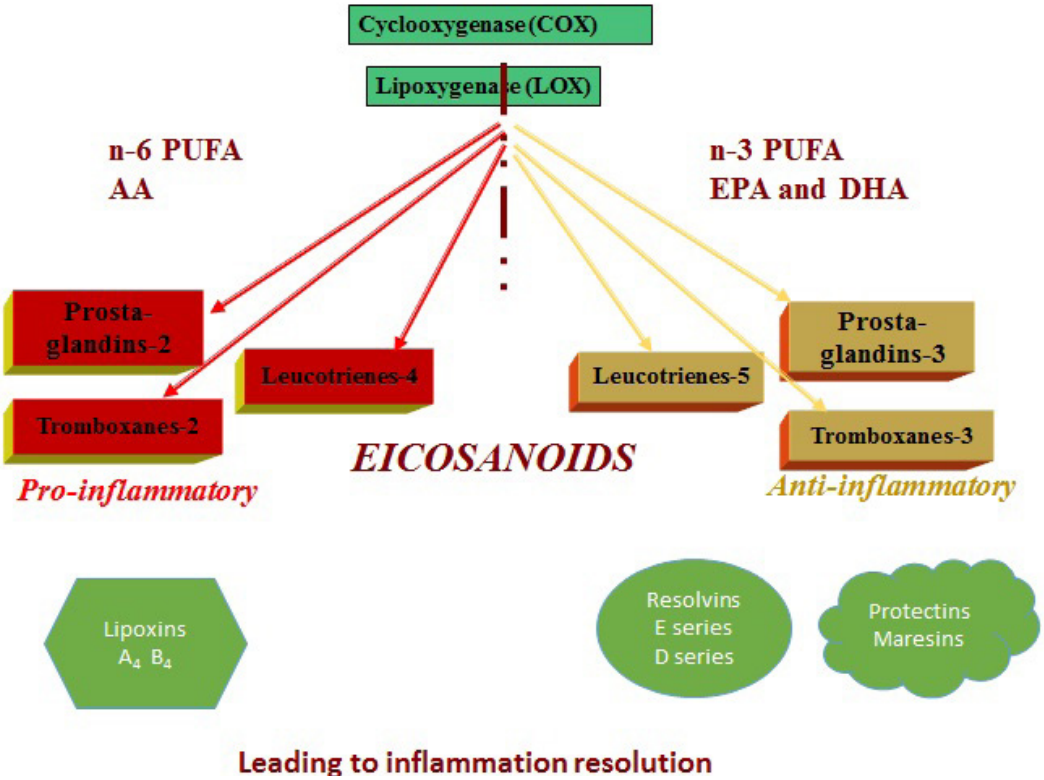

Figure 2 *Further breakdown of fatty acid metabolites and the conversion of eicosanoids to pro- and anti-inflammatory products and their roles in the resolution of inflammation. PUFA - polyunsaturated fatty acids; AA - arachidonic acid; EPA - eicosapentanoic acid; DHA - docosahexanoic acid*

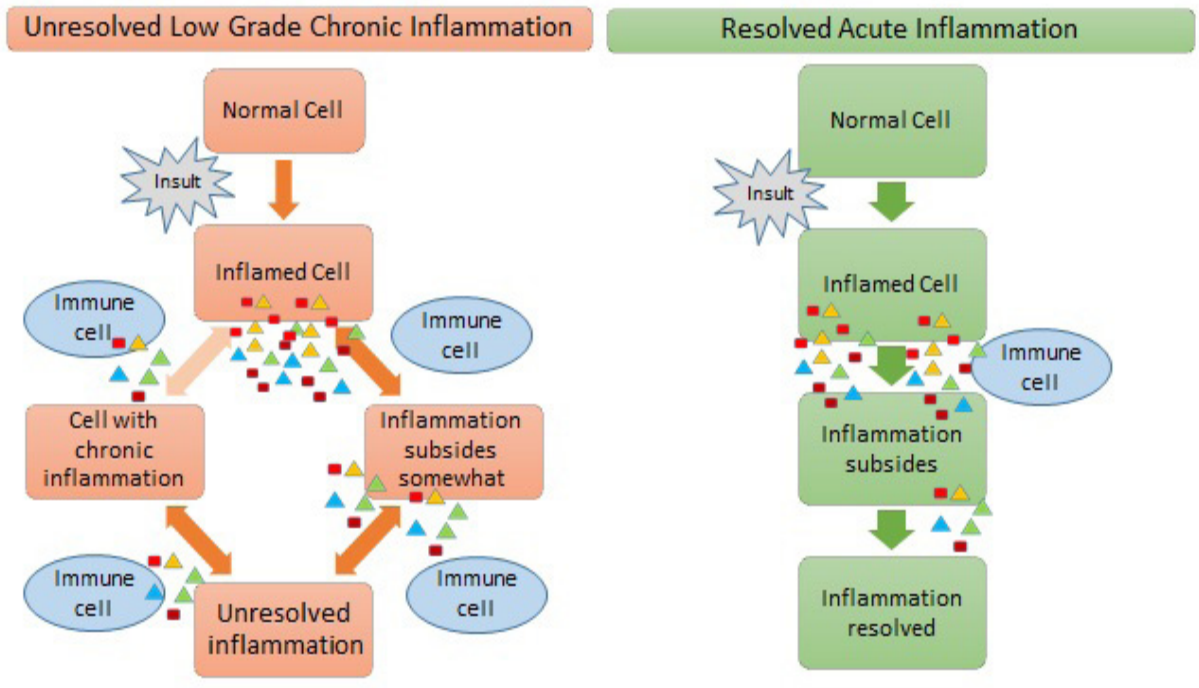

Figure 3 *Hypothetical representation of acute versus low-grade chronic inflammation. The acute process is linear, since the inflammation is resolved, whereas the chronic process is a constant cycle in which the inflammation is persistent and unresolved. Cytokines are represented by colored shapes. Adapted from (11)*

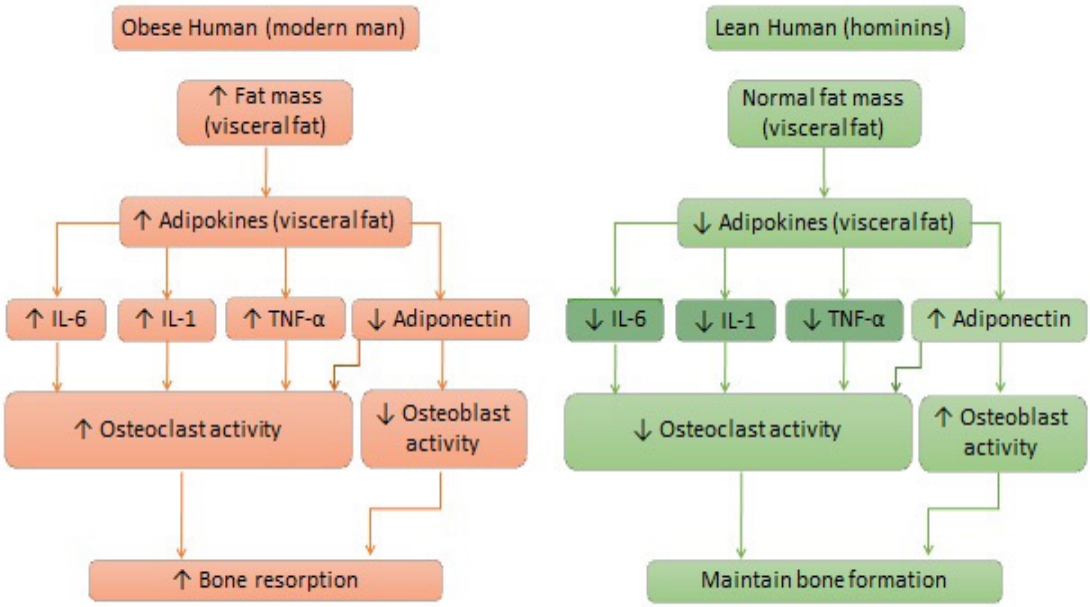

Figure 4 *The increase in fat mass leads to overproduction of interleukin-6 (IL-6), interleukin-1 (IL-1), and tumor necrosis factor alpha (TNF-α). These cytokines increase bone resorption by stimulating the osteoclasts and inhibiting the osteoblasts*

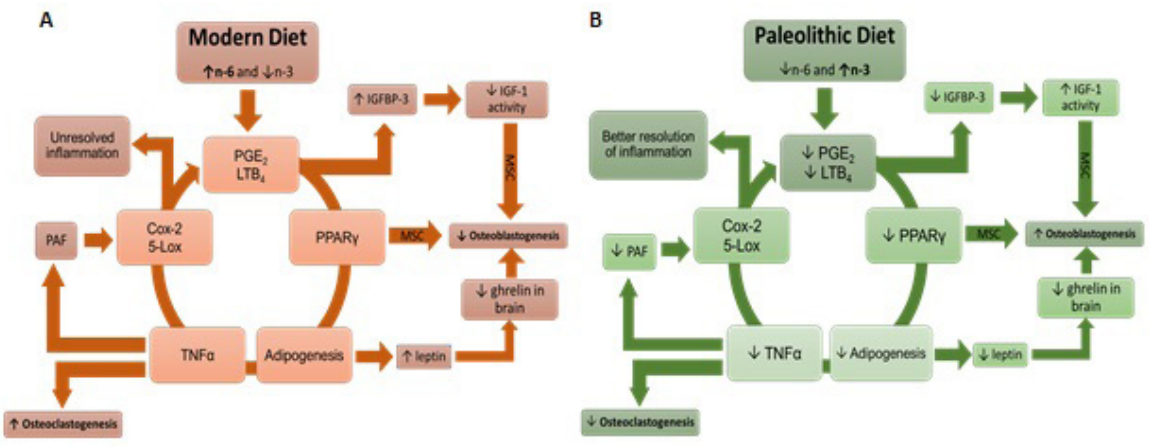

Figure 5 *The loop effect of modern (A) and Paleolithic (B) diet on adipogenesis, osteoblastogenesis, and osteoclastogenesis. Over-consumption of* n-*6 PUFA coupled with under-consumption of* n-*3 PUFA results in increased synthesis of pro-inflammatory lipid mediators PGE_2 and LTB_4 by Cox-2 and 5-Lox, leading to peroxisome proliferator-activated receptor gamma (PPARγ) signaling, which increases adipogenesis. This in turn produces more TNF-α, resulting in elevated osteoclastogenesis, and increases Cox-2 expression directly or indirectly via the platelet activating factor (PAF). Increased leptin production by adipose tissue can lower bone formation through its hypothalamic interactions. Furthermore, the elevated PGE_2 and LTB_4 result in an increase in the insulin-like growth factor-binding protein-3 (IGFBP-3), which inactivates the insulin-like growth factor-1 and promotes the differentiation of MSC to adipocytes. The net result of these events is an increased susceptibility to obesity and osteoporosis. For further review, see (11, 31)*

are considered osteoresorptive. Both osteoblasts and adipocytes share MSC as their common precursor in the bone microenvironment. In conditions of LGCI, pro-inflammatory mediators in the presence of a high *n*-6 to *n*-3 ratio and reactive oxygen species stimulate adipogenesis and suppress osteoblastogenesis, shifting MSC differentiation toward adipocytes. The presented evidence shows that the increased synthesis of pro-inflammatory cytokines, mediated by the high *n*-6 to *n*-3 ratios, propagate obesity and osteoporosis by increasing or maintaining LGCI. In view of the recognized changes in dietary habits of modern humans compared to our ancestors, it would be prudent to decrease the consumption of *n*-6 fatty acids toward a more beneficial *n*-6 to *n*-3 PUFA ratio of 4:1 (as opposed to the current 15:1) in order to reduce obesity and improve bone health.

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Sažetak

Stalna kronična upala niskoga stupnja zbog suvremenog načina prehrane potiče pretilost i osteoporozu

Pojedina univerzalna svojstva prehrane hominina prije pojave poljodjelstva izrazito se razlikuju od suvremene prehrane. Prehrambene navike hominina vjerojatno su bile ograničene na plodove divljeg bilja i lovinu; više od 70 % moderne prehrane odnosi se na konzumaciju rafiniranih šećera, biljnih ulja, žitarica i mliječnih prerađevina. Moderna je prehrana s višim unosom masti također dovela do nepovoljnijeg omjera omega-6 i omega-3 višestruko nezasićenih masnih kiselina (engl. krat. PUFA), koji pridonosi održavanju kronične upale niskoga stupnja, a time i nastanku mnogih kroničnih bolesti, uključujući pretilost i osteoporozu. U ovom se preglednom članku opisuju promjene uslijed modernog načina prehrane, s posebnim osvrtom na vrste i količine konzumirane masti. Također se objašnjavaju nedostatci moderne prehrane s obzirom na upalne procese te međusobna povezanost između pretilosti i upalnih procesa, koji su usto i poveznica između pretilosti i osteoporoze. U članku se iznose saznanja o tome da pretjerana konzumacija omega-6 masnih kiselina uz nedostatnu konzumaciju omega-3 masnih kiselina dovodi do kronične upale niskoga stupnja i povišenih vrijednosti reaktivnih kisikovih čestica (ROS), a time i do pomaka u mezenhimskih matičnih stanica (prekursora osteoblasta i adipocita) prema povećanoj adipogenezi i smanjenoj osteoblastogenezi. Uz povećanu sintezu upalnih citokina zbog pretilosti, moderna prehrana s nepovoljnim omjerom omega-6 i omega-3 kiselina u korist prvih nastavlja poticati pretilost i osteoporozu jer održava i pogoršava kroničnu upalu.

KLJUČNE RIJEČI: *adipociti; citokini; ikosanoidi; mezenhimske matične stanice; omega-3 masne kiseline; omega-6 masne kiseline; osteoblasti; osteoklasti; polinezasićene masne kiseline*

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