Review

Omega-3 and Omega-6 Fatty Acids: Role in Body Fat Gain and Development of Obesity

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The ratio of ω6 to ω3 polyunsaturated fatty acid (PUFA) in western diet has remarkably increased over the past decades. This change in dietary fatty acid (FA) composition, independent of the total caloric intake and total fat intake, may contribute to the obesity epidemic in many populations. Experimental studies show that ω3 and ω6 FAs play different role in adipogenesis, lipid homeostasis, brain-gut-adipose axis signaling, and systemic inflammation, resulting in divergent effects on body fat growth. Evidence from human studies remains limited and inconclusive. Very few observational studies and clinical trials have examined the association between composition of PUFA, particularly ω6 FA and ω6/ω3 ratio, with obesity-specific parameters. A consensus on the optimal intake of ω3 and ω6 subtype FAs and ω6/ω3 ratio in diet is lacking. We reviewed the temporal change in dietary PUFA composition in US, experimental studies that examine the effects of ω3 and ω6 FAs on body fat, and epidemiologic studies that assess the association between dietary PUFAs and the development of obesity. Future studies need to further evaluate dietary FAs and their biomarkers in association with objective and longitudinal measurements of body fat and elucidate the potential role of diet with a balanced ω3 and ω6 FA composition in the primary prevention of obesity.

INTRODUCTION

The ongoing obesity epidemic is a major public health issue in the US and worldwide. High fat intake has been implicated in the development of obesity,[1,2] whereas evidence from prospective cohort studies [3-6] and randomized trials [7-10] linking total fat intake to body weight gain remains weak and inconsistent. In recent decades, total fat and saturated fat intake (as % of calories) in typical western diet has fallen [11,12] but the ratio of ω6 to ω3 fatty acids (FAs) increased remarkably,[13] in parallel with an alarming increase in the prevalence of overweight and obesity. Intake of ω3 FAs, particularly long-chain ω3 FAs that are mainly supplied by marine products, has shown benefits on multiple obesity-related disorders. ω6 FAs, more broadly available from vegetable oils to meat products, demonstrate less clear effect, with evidence suggesting possible harm.[14] ω3 and ω6 FAs compete for common metabolic enzymes[15] and incorporation to tissues.[16] ω3 and ω6 FAs also may elicit opposing effects on adipogenesis,[17] lipid homeostasis,[18,19] brain-gut-adipose axis signaling,[20] and systemic inflammation.[21] Albeit strong laboratory evidence, epidemiologic data on the association between an imbalanced ω3 and ω6 FA intake with weight gain and obesity development is limited. With the lack of consensus on the optimal intake of ω3 and ω6 subtype polyunsaturated FA (PUFA) and the ω6/ω3 ratio, we reviewed experimental, population, and clinical study evidence regarding the effect of dietary PUFA composition (i.e. proportion of ω3 and ω6 FAs in total fat and the ω6/ω3 ratio) on the gain of body fat and development of obesity, independent of total caloric and total fat intake.

SIGNIFICANCE OF OBESITY EPIDEMIC AND OBESITY PREVENTION

Over the last few decades, the prevalence of overweight (defined as body mass index or BMI 25 to < 30 kg/m^2) and obesity (BMI ≥ 30 kg/m^2) has dramatically increased in developed as well as developing countries.[22-25] According to data from the National Center of Health Statistics (www.cdc.gov/nchs/data/factsheets), the prevalence of obesity has more than doubled since the 1970s among US adults aged ≥ 20 years. Although recent estimates suggest that the overall rates of obesity have plateaued or even declined in some groups, the widespread obesity epidemic continues to be a leading public health problem in the US.[26,27] Worldwide, nearly 500 million people 20 years and older were considered obese and 1.4 billion overweight in 2008.[28] Obesity is a well-recognized modifiable risk factor for many adult-onset chronic diseases, such as cardiovascular disease (CVD),[29] diabetes,[30] hypertension,[31] and cancer.[32] The estimated total costs of health care for obesity-related conditions are as high as $139 billion annually.[33,34] Effective strategies to control the obesity epidemic are urgently needed. Because the formation of adipose tissue appears to be an

irreversible process,[35] maintenance of normal body fat will have more efficient and sustainable health benefits than the treatment of established obesity,[6,36] highlighting the importance of obesity primary prevention.

TEMPORAL CHANGE IN CONSUMPTION OF ω3 AND ω6 FA IN THE UNITED STATES

Since dietary fat represents a major source of energy, high fat intake has been considered a possible cause of obesity.[11,37,38] However, evidence from prospective cohort studies[3-6] and randomized trials[7-10] linking total fat intake with gain of body weight or body fat is weak and inconsistent. This discrepancy may be explained by dietary fat composition.[13,39] In the past half-century, the total fat and saturated fat intake (as % of calories) in industrial countries has continuously fallen,[11,12] while the indiscriminate diet recommendations to substitute vegetable fats, which is high in ω6 and low in ω3 FAs, for animal fats have led to a substantial rise in intake of ω6 FAs.[13] These changes are accompanied by a significant increase in the supply of arachidonic acid (AA, 20:4ω6, broadly available from vegetable oil to meat products) but no parallel increase in supply of long-chain ω3 FAs (mainly from marine products) (**Table 1**).[40] Moreover, substantial changes in animal feeds and food chain have been introduced.[13] As a result, the ratio of ω6 to ω3 FAs in common Western diet has increased from the range of 1 to 4[41] to 10 to 40 (**Table 2**).[13,40] This remarkable change in the balance of ω3 and ω6 FA intake may have contributed to the increasing prevalence of overweight and obesity in children and adults of many populations. In support of the recommendation by some research groups on reducing ω6 FA intake to lower ω6/ω3 ratio,[42,43] there is emerging evidence suggesting possible harm of excess ω6 FA intake.[14] However, the American Heart Association Scientific Advisory published in 2009 recommended ω6 FA intake of at least 5-10% of energy, based on evidence that the consumption of ω6 FAs (particularly linoleic acid, LA 18:2 ω6) is associated with reduced risk of coronary heart disease.[44] At the meantime, guidelines on specific intake of LA (18:2ω6), α-linolenic acid (ALA, 18:3ω3), and longer-chain PUFAs are formulated in several European countries by health authorities, but the recommended levels vary substantially.[13] The optimal intake of ω3 and ω6 subtype PUFAs and ω6/ω3 ratio remains unresolved.

Table 1. Main Food Sources of ω3 and ω6 Fatty Acids in the United States in Year 1909 and 1999*.

ω6 FA	Food Category	% of contribution		ω3 FA	Food Category	% of contribution	
		1909	1999			1909	1999
LA, 18: 2ω6				ALA, 18: 3ω3			
	Soybean Oil	0.076	43.1		Soybean Oil	0.041	44.6
	Fats	19.8	11.3		Dairy	24.7	10.7
	Shortening	9.0	9.1		Fats	27.6	8.2
AA, 20: 4ω6				EPA, 20: 5ω3			
	Poultry	11.1	34.4		Finfish	79.4	50.6
	Eggs	29.9	23.2		Shellfish	5.1	30.4
	Pork	21.5	17.7		Poultry	2.23	13.7
DPA, 22: 5ω6				DHA, 22: 6ω3			
	Poultry	10.6	63.7		Finfish	60.0	43.4
	Finfish	29.0	15.4		Poultry	6.6	25.4
	Shellfish	53.1	13.9		Shellfish	8.1	12.5

* Originally from Blasbalg TL, Hibbeln JR, Ramsden CE, Majchrzak SF, Rawlings RR. Changes in consumption of omega-3 and omega-6 fatty acids in the United States during the 20th century. Am J Clin Nutr. 2011;93:950-962. Data was obtained from the US Department of Agriculture (USDA).
Abbreviations: FA: fatty acid; AA: arachidonic acid (20:4ω6); LA: linoleic acid (18:2ω6); ALA: α-linolenic acid (18:3 ω3); EPA: eicosapentaenoic acid (20:5ω3); DHA: docosahexaenoic acid (22:6ω3); DPA: docosapentaenoic acid (22:5ω3)

DIVERGENT EFFECTS OF ω3 AND ω6 FA ON DEVELOPMENT OF OBESITY

Advice to substitute PUFAs for saturated FAs (SFAs) is a cornerstone of worldwide dietary guideline since 1960s.[45] By the time this guideline was initiated, PUFA was considered a uniform molecular category with beneficial effect of lowering blood lipids.[46] Later research recognizes that PUFAs comprise of ω3 and ω6 subspecies, each having unique biochemical properties and playing different roles in metabolic outcomes including obesity. ω3 and ω6 FAs are distinguished based on the location of the first double bond. Both ω3 and ω6 FAs are essential for human because they

cannot be synthesized and must be obtained from diet. Precursor FAs in both classes, ALA (18:3ω3) and LA (18:2ω6) respectively, can be desaturated and elongated to longer-chain FAs of the same class, albeit to a very low extent (**Figure 1**). In contrast, the two classes cannot be converted, and they are metabolically and physiologically distinct. In cultured cells, ω3 FAs inhibited,[47] while ω6 FAs increased,[48] cellular triglyceride content. In animal models,

feeding mother rats with a high-fat diet rich in LA (18:2ω6) resulted in hyperplasia or hypertrophy of white adipose tissue in suckling pups,[49] whereas intake of fish oil rich in eicosapentaenoic acid (EPA, 20:5ω3) and docosahexaenoic acid (DHA, 22:6ω3) prevented the enhancement of fat mass.[50,51] Thus, ω3 and ω6 FAs in diet potentially have divergent effects on the gain of body fat and the development of obesity.

Table 2. ω6/ω3 Fatty Acid Ratio in Usual Diet of Industrial Countries.

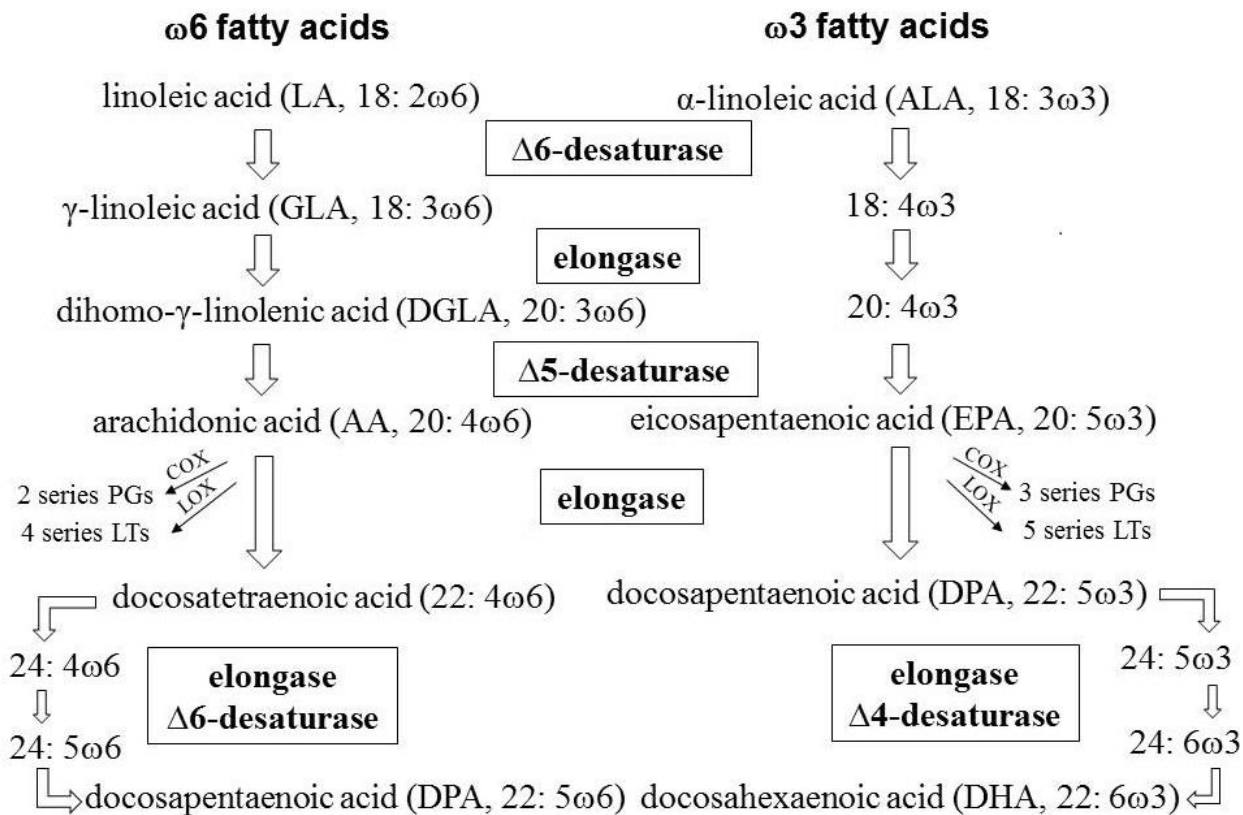| Populations	Years	ω6/ω3 Ratio
Paleolithic		0.79[41]
Greece	1960	1.0-2.0[41]
Japan	2000	4.0[41]
US	1909	5.4[40]
	1999	9.6[40]
France	1960	4.1[13]
	2000	12[13]
UK	2000	15[41]
India, rural	2003	5-6[41]
India, urban	2003	38-50[41]

Figure 1. Elongation and desaturation of ω3 and ω6 fatty acids.

POSSIBLE MECHANISMS OF DIVERGENT EFFECTS OF ω3 AND ω6 FA ON OBESITY DEVELOPMENT

Due to the similarity in chemical structure, ω3 and ω6 FAs compete for common metabolic enzymes, both in the process of elongation and desaturation of precursor PUFAs and in the synthesis of downstream metabolites such as prostacycline and thromboxane.[15] They also compete for incorporation into plasma lipid fractions and cell membranes.[16] In addition to the competitions in metabolism, ω3 and ω6 FAs may have divergent effects on the development of obesity via several other mechanisms (**Figure 2**, **Table 3**).[17-19]

ω3 AND ω6 FA REGULATE GENE EXPRESSION IN ADIPOGENESIS AND LIPID METABOLISM

During the development of obesity, pluripotent stem cell precursors give rise to multipotent preadipocytes, and preadipocytes differentiate into mature adipocytes; lipid then fills in to cope with the high exogenous levels of fats.[35] Because mature adipocytes do not divide in vivo or undergo significant turnover under physiological conditions, the proliferation of precursor cells and their differentiation into adipocytes are critical events in adipose tissue development.[49] ω3 and ω6 FAs could serve as transcriptional factors to regulate the expression of genes involved in preadipocyte differentiation.[17] ω6 FAs such as AA (20:4ω6) are potent adipogenic FA that up-regulates the expression of multiple adipogenic genes. In the early steps of preadipocyte differentiation, the metabolite of AA (20:4ω6) by cyclooxygenase (COX) - prostacyclin - binds to its receptor (IP-R) on cell surface of preadipocytes, activates the protein kinase A (PKA) pathway,[52] which ultimately up-regulates the expression of peroxisome proliferators-activated receptor (PPAR) family and leads to adipogenesis.[53-57] The long-term adipogenic effect of AA is impaired by COX inhibitors.[58] In IP-R knockout mice, no activation of PKA pathway occurs through IP-R, and thereafter the adipogenic effect of ω6 FAs is similar to ω3 FAs.[58] In the later steps of preadipocyte differentiation, metabolites of AA (20:4ω6) by lipoxygenases (LOX) also activate PPARs expression and promote adipogenesis.[59]

Table 3. Possible Mechanisms of Divergent Effects of ω3 and ω6 Fatty Acids on Obesity Development.

ω6 FA	ω3 FA
Adipogenesis	
PG metabolite by COX activates the PKA pathway, up-regulates the expression of PPAR family and leads to adipogenesis.[52-57] Metabolites by LOX also activate PPARs expression and promote adipogenesis.[59]	Decrease the expression of COX-2 mRNA and production of COX-2 protein.[60] Inhibit the activities of COX.[61] Directly inhibit the effect of ω6 FA derived PGs.[62] Down-regulate the production of cAMP or the catalytic subunit of PKA.[49,63]
Lipid homeostasis	
Increase cellular triglyceride content by increasing membrane permeability.[48]	Suppress the expression of genes involved in lipogenesis.[18-19] Increase the expression of genes involved in β-oxidation.[18-19]
Brain-Gut-Adipose Axis	
Metabolites endocannabinoids can stimulate food intake and lipogenesis in liver.[66] Increase leptin production.[71] Decrease adiponectin production and release.[87]	Reduce the endogeneous endocannabinoids production or lower the receptor sensitivity.[67,68] Induce neuropeptide proopiomelanocortin, which curb appetite and lead to weight loss.[20] Decrease the gene expression of leptin[72] and leptin receptor.[73] Increase adiponectin production and release.[81,82]
Systemic Inflammation	
Metabolites are pro-inflammatory compounds.	Metabolites are less pro-inflammatory or anti-inflammatory.

Abbreviations: COX: cyclooxygenase; PKA: protein kinase A; PPAR: peroxisome proliferators-activated receptor; LOX: lipoxygenases; PG: prostaglandins.

ω3 FAs could inhibit the adipogenic effect of ω6 FAs at multiple steps. First, ω3 FAs such as DHA (22:6ω3) have been shown to decrease the expression of COX-2 mRNA and production of COX-2 protein.[60] Second, some ω3 FAs, with potency of EPA(20:5ω3) > DHA(22:6ω3) > ALA(18:3ω3), could inhibit the activities of COX-1 and COX-2.[61] Third, long-chain ω3 FAs could also directly inhibit the effect of prostaglandins arising from AA (20:4ω6).[62] Finally, ω3 FAs [EPA(20:5ω3) > DHA(22:6ω3)] could down-regulate the production of cAMP[49] or the catalytic subunit of PKA [63] in the prostacyclin-IP-R signaling pathway. In addition to these inhibitory effects on adipogenesis, ω3 FAs also modulate lipid homeostasis by suppressing the expression of genes involved in lipogenesis including fatty acid synthase (FAS), lipoprotein lipase (LPL) and stearoyl-CoA desaturase-I (SCD-I) while increasing the expression of genes involved in β-oxidation such as acetyl-CoA oxidase (ACOX).[18,19] The net result is a reduction in body fat deposition, mainly in liver and also in skeletal muscle and adipose tissue.

ω3 AND ω6 FAs AND BRAIN-GUT-ADIPOSE AXIS SIGNALING

Another putative mechanism through which ω3 and ω6 FAs may affect body fat gain differently is the brain-gut-adipose axis. First, ω6 FAs derived metabolites endocannabinoids can mediate central control of appetite and energy balance. Endocannabinoids can be produced from the hydrolysis of AA-containing membranes.[64] Receptors of endocanna-binoids are present in all tissues involved in energy homeostasis.[65] Activation of endocannabinoids receptors will stimulate food intake and lipogenesis in liver.[66] ω3 FAs can reduce the endogeneous endocannabinoids production or lower the receptor sensitivity.[67,68] Moreover, long-chain ω3 FA DHA (22:6ω3) can induce another anorexigenic neuropeptide proopiomelanocortin in the hypothalamus, which curbs appetite and leads to weight loss.[20]
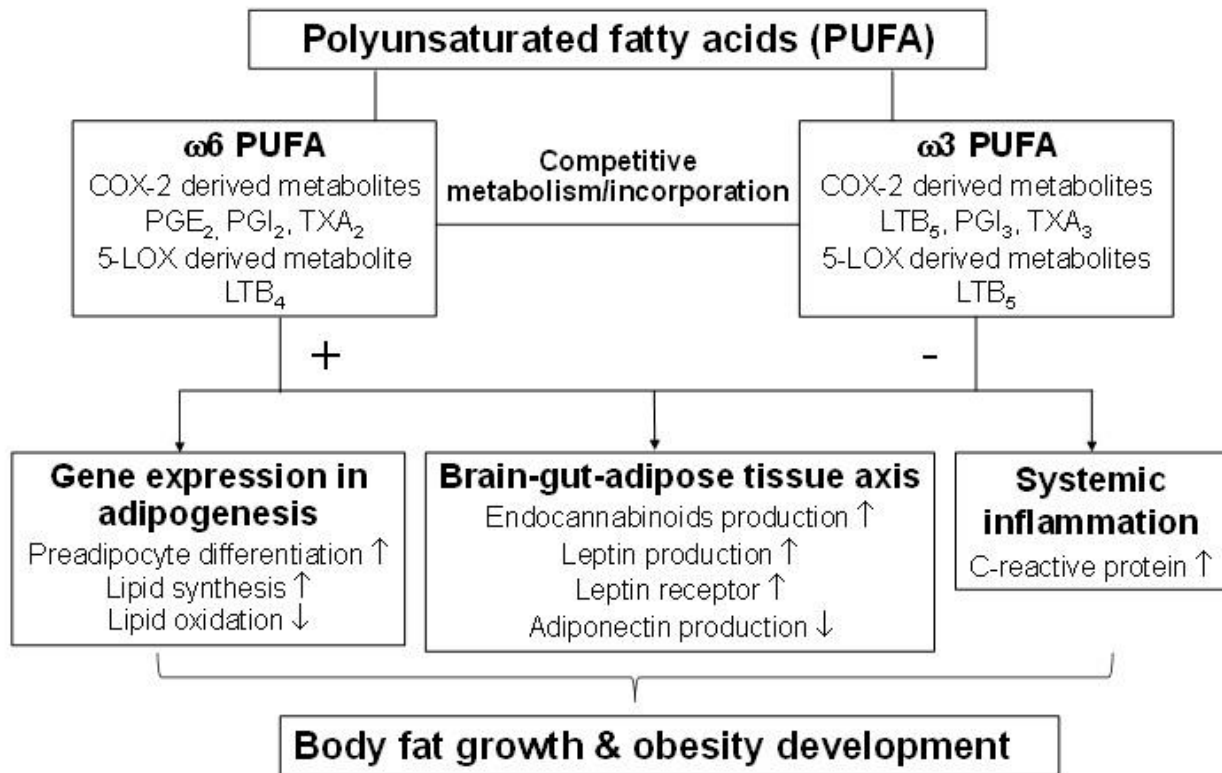

Figure 2. Potential effects of ω3 and ω6 PUFA on body fat growth and development of obesity. LOX: lipoxygenases; PG: prostaglandins; LT: leukotrienes; TX: thromboxane.

Second, ω3 and ω6 FAs may affect leptin signaling pathway differently. Leptin is a peptide hormone encoded by ob gene and is primarily produced and secreted by adipose tissue. The main function of leptin is the regulation of body weight by affecting appetite and energy expenditure.[69] It has been postulated that human obesity might represent a state of leptin resistance.[70] Dietary FA composition can affect leptin signaling. In rats, a diet rich in ω3 and ω6 FAs led to higher serum leptin levels than a diet rich in SFAs and monounsaturated FAs (MUFAs).[71] When ω3 FAs were studied specifically, however, a high intake of ω3 FAs decreased the gene expression of leptin[72] and leptin receptor[73] both in vitro and in vivo. It is therefore possible that ω3 and ω6 FAs have divergent effects on leptin production, secretion as well as receptor signaling. In a small trial of healthy non-obese men (n = 30) and women (n = 25), the serum leptin concentration markedly decreased in women but not in men who received diet rich in MUFAs and ALA (18:3ω3), despite only minor change in body weight and food intake. Serum leptin did not change in subjects who received diet rich in MUFAs only or ω6 FAs.[74]

Third, ω3 and ω6 FAs could modulate expression and secretion of adiponectin differently.[75] Adiponectin is a plasma protein that is produced and secreted exclusively by adipocytes.[76] Adiponectin suppresses a number of pathological processes linked with obesity. Experimental studies have shown that adiponectin activates 5'-AMP-activated protein kinase (AMPK),[77] which stimulates FA oxidation and glucose utilization.[78,79] These favorable effects ultimately lead to reduced lipid stores and improved insulin sensitivity in tissues.[80] In mice model, diet rich in long-chain ω3 FAs EPA (20:5ω3) and DHA (22:6ω3) significantly increased the production and release of adiponectin in

adipose tissue.[81,82] One possible mechanism is that EPA (20:5ω3) and DHA (22:6ω3) activate PPARγ, which in turn up-regulates the expression of adiponectin gene.[82,83] In human studies, positive associations were found between circulating adiponectin and ω3 FAs in plasma and adipose tissue.[84,85] Diet intervention studies further demonstrated that long-chain ω3 FA supplement raised plasma adiponectin concentration in human subjects.[86] Few studies had examined the associations of ω6 FAs with adiponectin. In a recent study of 44 end-stage renal disease patients, plasma adiponectin was positively associated with erythrocyte ω3 FAs (r = 0.58) while inversely associated with ω6 FAs (r = -0.64) (both $p < 0.01$).[87]

ω3 AND ω6 FAs METABOLISM AND SYSTEMIC INFLAMMATION

The potential effects of ω3 and ω6 FAs are also related to the synthesis of specific eicosanoids through their downstream metabolism. The 2-series prostaglandins (PGE2, PGI2, and TXA2) and 4-series leukotrienes (LTB4) derived from ω6 FAs by COX-2 and 5-LOX, respectively, are potent pro-inflammatory compounds. In contrast, 3-series prostaglandins (PGE3, PGI3, and TXA3) and 5-series leukotrienes (LTB5) derived from ω3 FAs by the same enzymes are less pro-inflammatory. Since ω3 and ω6 FAs directly compete for access to the same converting enzymes, the balance in inflammatory status depends on the ω6/ω3 ratio. If ω3 FA intake is high, ω6 FA derived pro-inflammatory eicosanoids are inhibited, the risk of inflammatory conditions decreases. Additionally, the E series resolving (resolving E1 and E2, both formed by 5-LOX) derived from EPA (20:5ω3) and the resolvins, protectins, and maresins derived from DHA (22:6ω6) are all potent molecules that resolve inflammation, further enhancing the anti-inflammatory properties of ω3 FAs. In animal models, ω3 FAs, regardless provided in low-fat or high-fat diet, significantly lowered the expression of inflammatory markers such as monocyte chemoattractant protein-1 (MCP-1),[88] interleukin-6 (IL-6),[88] interferon-γ (IFN-γ),[88] and plasminogen activator inhibitor type 1(PAI-1).[89] In adipoctye-derived stem cells from the ob/ob mouse, EPA (20:5ω3) and other ω3 FAs significantly reduced IL-6 mRNA expression and secretion compared with AA (20:4ω6) or LA (18:2ω6).[90] In human studies, ω3 FAs rich diet or ω3 FA supplementation significantly lowered ω6/ω3 ratio in plasma,[91] circulating levels of C-reactive protein (CRP),[92] IL-6,[91,92] tumor necrosis factor-α (TNF-α),[93] MCP-1,[94] and adipose tissue macrophage number.[94] Laboratory and clinical studies specifically on ω6 FAs or ω6/ω3 ratio with systemic inflammation are little. The direction of relation between obesity and inflammation has yet to be elucidated. It is well-accepted that accumulating adipose tissues promote the production of inflammatory cytokines and lead to an elevated chronic inflammation status. Alternatively, it is also possible that early stage of excess fat mass causes the change in growth factor environment over time, and results in a shift toward preadipocyte differentiation.[95]

EPIDEMIOLOGIC STUDIES OF PUFA INTAKE AND OBESITY

Distinctive associations of ω3 and ω6 FA intake with the development of several obesity-related disorders, such as hyperlipidemia and atherosclerotic disease, have been observed in population studies.[41] Associations of ω3 and ω6 FA intake with the risk of type 2 diabetes, which is characterized by obesity and insulin resistance, are less clear. In prospective studies, the association between fish or EPA(20:5ω3) + DHA(22:6ω3) intake and incident type 2 diabetes has been mixed, with some studies in the US showing positive relations.[96-98] There are fewer studies on ω6 FAs: in cross-sectional studies, higher long-chain ω6 FAs in skeletal muscle or erythrocyte phospholipids was associated with higher insulin sensitivity in healthy individuals,[99] obese Pima Indians,[100] and non-obese type 2 diabetic patients;[101] while in prospective studies, higher γ-linolenic acid (GLA, 18:3ω6), eicosatrienoic acid (20:3ω6), and AA (20:4ω6) in serum cholesterol ester were associated with increased risk of type 2 diabetes.[102,103]

The associations of dietary PUFAs with the development of obesity per se have been rarely studied in human populations. We are aware of only two prospective cohort studies that examined dietary FAs in relation to longitudinal anthropometric change. Among 41,518 women in the Nurses' Health Study, the intake of SFAs, MUFAs, PUFAs, and *trans* FAs was each weakly associated with weight gain during 8 years follow-up: the regression coefficients (β) on weight change (lbs) for each 1% difference in baseline FA intake (as % of calories) were 0.40, -0.31, 0.42, and 0.54, respectively (all $P > 0.05$).[104] Among 16,587 men in the Health Professionals' Follow-up Study, a 2% increment in energy intake from *trans* FAs that was isocalorically substituted for PUFAs was significantly associated with a 0.77 cm gain in abdominal circumference during 9 years follow-up ($P < 0.001$), and this association remained significant after controlling for concurrent change in BMI.[105] These two studies have several limitations. First, both studies used self-administered semi-quantitative food frequency questionnaires (FFQ) to estimate dietary fat intake; second, both studies did not investigate ω3 and ω6 subtype PUFAs separately; third, both studies relied on self-reports to assess changes in anthropometry.

Our group recently conducted a prospective study in 534 participants of the Women's Health Study (WHS) who had baseline measurement of erythrocyte FAs and a baseline BMI of 18.5 to < 25 kg/m². Body weight was updated at a total of 6 time points during an average of 10.4 years follow-up. After multivariable adjustment for lifestyle and dietary factors including total energy intake and physical activity, the weight gain (kg) during follow-up in the highest versus the lowest quartile of baseline erythrocyte FAs was 3.08 vs. 2.32 for *cis* ω6 FA (p trend: 0.04), 2.07 vs. 2.92 for *cis* ω3 FA (p trend: 0.08), 2.93 vs. 2.05 for ω6/ω3 ratio (p trend: 0.046), and 3.03 vs. 2.27 for *trans* FA (p trend: 0.06).[106] The

Erythrocyte ω6/ω3 ratio was also positively associated with the risk of becoming overweight or obese (n = 186). To our knowledge, this is the first study that examined biomarkers of dietary PUFAs in association with longitudinal weight gain and newly developed obesity. However, the nature of this observational study did not allow investigation of the effect of fat composition change on adiposity measurement.

Several interventional studies have found that ω3 FA supplementation can have beneficial effects on measurements of body weight and body fat in lean,[107] overweight,[108,109] and obese [110] individuals. Comparable study on ω6 FA is lacking. We identified one diet intervention trial conducted in France that aimed to investigate the effect of an increased ω3 FA combined with a reduced ω6 FA consumption, with no change in total energy and other macronutrient intake.[111] A total of 17 (10 men and 7 women) healthy, normal weight subjects with a low usual intake of ω3 FAs were studied. After 10-week intervention via dietary recommendations focusing on ω6/ω3 ratio, intake of ALA (18:3ω3) increased and LA (18:2ω6) decreased, in erythrocyte membrane ω3 FA increased while ω6 FA did not change. The measurement of anthropometry including body weight, BMI, waist/hip ratio, fat mass, and plasma leptin concentration did not change significantly during the trial, but plasma adiponectin significantly increased (6.50 vs. 7.63 μg/ml at baseline and post-intervention, respectively) and plasma TNF-α (2.18 vs. 1.50 pg/ml), IL-6 (1.28 vs. 1.00 pg/ml), and CRP (0.23 vs. 0.17 mg/l) decreased. Major limitations of this trial include the small sample size, short-term intervention, and lack of a control group. There is clear need for more studies to further investigate the long-term effect of dietary ω6/ω3 ratio change and the optimal ω6/ω3 ratio for overall health.

CONCLUSION

ω3 and ω6 FAs are metabolically and physiologically distinct PUFA subclasses. Experimental studies suggest that ω3 and ω6 FAs may have divergent effect on body fat gain and development of obesity, though evidence on ω6/ω3 ratio specifically is little. Epidemiologic study of dietary PUFAs with the development of human obesity remains limited; there is currently no consensus on the optimal intake of ω3 and ω6 FAs and ω6/ω3 ratio. More studies are needed to examine the association of dietary ω3 and ω6 FAs, ω6/ω3 ratio, and their biomarkers with objective and longitudinal measures of obesity. These studies will provide insights regarding the long-term effects of dietary fat composition and whether a limit on ω6 FA intake and maintenance of a balance between ω3 and ω6 FAs will promote a favorable change in body fat mass, curb epidemic of obesity, and prevent obesity-related health problems.

CONFLICT OF INTEREST
None.

ABBREVIATIONS
FA: fatty acid; SFA: saturated fatty acid; MUFA: monounsaturated fatty acid; PUFA: polyunsaturated fatty acid; AA: arachidonic acid (20:4ω6); LA: linoleic acid (18:2ω6); ALA: α-linolenic acid (18:3ω3); EPA: eicosapentaenoic acid (20:5ω3); DHA: docosahexaenoic acid (22:6ω3); DPA: docosapentaenoic acid (22:5ω3); BMI: body mass index; CVD: cardiovascular disease; COX: cyclooxygenase; PKA: protein kinase A; PPAR: peroxisome proliferators-activated receptor; LOX: lipoxygenases; PG: prostaglandins; LT: leukotrienes; TX: thromboxane

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