Omega-6 Polyunsaturated Fatty Acids (PUFA) and the Early Origins of Obesity

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Abstract

Purpose of review: The incidence of obesity and its related metabolic disorders has increased significantly over the past 3 decades, culminating in the current global epidemic of metabolic disease, leading to the search for contributing factors. Exposure of the developing fetus/neonate to a typical Western diet increases their risk of obesity and metabolic disorders throughout the life-course, creating an intergenerational cycle of metabolic disease. In Western countries, this epidemic of metabolic disease has coincided with a marked increase in the intake of omega-6 polyunsaturated fatty acids (omega-6 PUFA), leading to suggestions that the two may be causally related.

Recent findings: Recent studies have emphasised the pro-adipogenic properties of the omega-6 PUFA, and provided evidence that rodents fed on diets with omega-6 PUFA contents similar to the typical US diet (6-8%energy) increased fat mass. Importantly, recent studies have shown that perinatal exposure to a high omega-6 PUFA diet results in a progressive accumulation of body fat across generations.

Summary: This review highlights the recent evidence supporting the role of the omega-6 PUFA in the early life origins of obesity and metabolic disease, the need for more clinical studies and the potential need for health agencies to re-evaluate current recommendations to further increase omega-6 PUFA intakes.

Keywords*:* omega-6 PUFA, adipose tissue, biological programming, obesity, maternal nutrition

Introduction

The past decades have seen a substantial increase in the global incidence of obesity and its related metabolic disorders. In addition to the health and quality of life implications of these diseases, the direct and indirect costs of these conditions represent a significant economic burden to countries world-wide [1]. As a result, identifying the causes of this epidemic and strategies to overcome it has become a major public health priority, and numerous anti-obesity health campaigns have been launched. To date, however, these campaigns have done little to successfully combat the problem.

The importance of quantity and quality of nutritional intake for the regulation of body weight and fat mass in individuals is widely acknowledged, and has led to suggestions that changes in the nutritional quality of the typical Western diet is an important driver of the expanding waistlines of populations world-wide. Whilst good nutrition is important at all life stages, it is increasingly recognised that the nutritional environment an individual experiences before birth and in early infancy is of particular importance for their later metabolic health, and that exposure to an inappropriate nutritional supply during critical windows of development can predispose an individual to obesity and type 2 diabetes later in life [2, 3]. By extension, the diet consumed by pregnant and breast-feeding women is a key determinant of the metabolic health of future generations [4].

In this review, we will present the temporal and biological evidence underlying the hypothesis that excess intake of omega-6 PUFA is associated with increases in body fat mass, with a focus on existing evidence from animal and human studies that exposure to elevated intakes of omega-6 PUFA before birth or in early infancy can program an increased susceptibility to obesity throughout the life course. We will highlight the current paucity of human studies

which have examined the long-term consequences of perinatal exposure to high omega-6 PUFA intakes, and emphasise the need for increased research in order to establish conclusively whether there is a true causative association.

Setting the Scene: The Global Epidemic of Obesity and Metabolic Disease

The global incidence of overweight, obesity and metabolic disease nearly doubled in the period from 1980 to 2008 and continues to increase. In 2008, more than 1.4 billion adults (20 years and older) and 40 million children under the age of five were overweight and, of these, over 200 million men and nearly 300 million women were obese [1]. This increase in the number of overweight and obese individuals has been accompanied by a dramatic increase in the incidence of its associated co-morbidities, including type 2 diabetes and cardiovascular disease. The significant impact of obesity and its associated metabolic disorders on both the health and quality of life of sufferers and on the health budgets of economies world-wide has prompted extensive research to identify factors which have contributed to the epidemic and strategies for reversing the current trend.

Both genetic and environmental factors have been implicated in the aetiology of obesity and metabolic disease. There appears little doubt that genetics plays role in pre-disposing certain individuals to obesity and metabolic disease, and a there is an ever-growing list of single nucleotide polymorphisms that confer increased susceptibility to obesity and type 2 diabetes [5]. However, it is unlikely that there has been any substantial shift in the gene pool of humans over the relatively short time frame that the obesity epidemic has taken hold, suggesting that environmental, rather than genetic, factors are likely to play the more important role. Of these environmental factors, poor dietary habits play a significant role in promoting weight gain and the accumulation of body fat mass in individuals [6]. However, not all dietary components are

equal in this regard, and there are some which contribute more to fat accumulation than others, and there have been numerous attempts to identify those components of the diet which are the major contributors to weight gain on a population level.

Examining the Causes: Focus on Fat

It was initially postulated that excessive intake of saturated fat was a key driver of the obesity epidemic. However, it is now clear that the epidemic of obesity in the US, Australia and other Western countries has in fact coincided with a significant decline in the per capita intake of saturated fat, creating somewhat of a problem with this hypothesis. However, as saturated fatty acid intake has fallen, there has been a corresponding increase in the intake of omega-6 PUFA in Westernised nations around the world, leading to a significant increase in per capita omega-6 PUFA intake over this time [7]. This shift was initially prompted by the limited availability of animal-based fats during the Second World War, which led to their replacement with plant-based alternatives, and has since been reinforced by health recommendations which favour polyunsaturated over saturated fats [8]. In addition, changes in the lipid composition of formulated animal feeds have led to changes in the fatty acid composition of animal products, including meat and eggs [9].

There is growing concern that this increasing dominance of omega-6 PUFA may have negative consequences for metabolic health. These concerns are based on the biological actions of omega-6 (linoleic acid (LA); 18:2(n-6) and derivatives thereof), which are largely pro-inflammatory, pro-thrombotic and pro-adipogenic. It has been suggested that increases in omega-6 PUFA intake over the past few decades may be an important factor contributing to the current obesity epidemic; in particular there is evidence that exposure to excess omega-6 PUFA before birth or in early infancy may be responsible for promoting fat cell formation early

in life and thereby predisposing individuals to excess accumulation of body fat as children and adults [10].

The Early Life Origins of Obesity

Whilst good nutrition is important at all life stages, a number of critical periods in development have been identified during which exposure to a sub-optimal nutritional environment are particularly detrimental, since they can have lasting effects on an individual's propensity to develop obesity and metabolic disease later in life. Of these critical windows, the most important appear to be those that coincide with the major periods of development of the key metabolic systems, ie. before birth and during the first 2 years of life in humans, and during the fetal and suckling periods in rodents. Both human and experimental animal studies have shown that exposure to an inappropriate nutrient supply during these critical windows of development has life-long consequences for an individual's health [11]. The early studies of this 'biological programming of metabolic disease', focussed primarily on the effects of sub-optimal nutrition, either global caloric restriction or low protein, and showed that these exposures were associated with an increased accumulation of visceral adipose tissue in the offspring and, consequently, a predisposition to insulin resistance and type 2 diabetes [12]. More recently, attention has turned to the more common situation in most Western countries; that of maternal overnutrition, and these studies have demonstrated that exposure to a 'high-fat' and/or 'high-sugar' diet before birth or in the early neonatal period predisposes the offspring to obesity and metabolic disease after birth [2].

Numerous studies in both large and small animal models have explored the mechanisms underlying this association, and have demonstrated that altered nutrient supply to the developing fetus/neonate plays a predominant role. These studies demonstrate that exposure to

144 either excessive calories or an increased supply of fat and/or sugar during critical
145 developmental windows leads to altered development of key systems involved in the regulation
146 of energy balance and metabolism which permanently affects their structure and function [2,
147 13]. These systems include, but are not limited to, the central neural network for appetite
148 regulation, the fat cell or adipocyte, the mesolimbic reward system and insulin signalling
149 pathways in skeletal muscle [9, 13]. As a result of these programmed changes in development,
150 these offspring are hyperphagic, have an increased propensity to accumulate body fat, have a
151 preference for high-fat and high-sugar foods and are less insulin sensitive [14].
152
153 However, despite the extensive work which has been done in this area, fundamental questions
154 remain about which specific components of the diet are responsible for these programming
155 effect, and questions have been raised about the relevance of the common model of high-fat,
156 high-sugar feeding to typical human diets. In particular, the high-fat diets that are commonly
157 used in animal studies to induce maternal obesity are high in a number of fatty acid classes, but
158 there have been limited attempts to dissect out which of the individual fatty acids is responsible
159 for the programming effects. In the majority of these diets, saturated fat is the main fat
160 component of the high-fat mix which, from what we have seen in the previous section, may
161 not in fact be truly reflective of current trends in fatty acid intakes in humans. However, in our
162 hands, changes in dietary saturated fat content via the cafeteria diet approach was associated
163 with an increase in omega-6 PUFA in the maternal milk and offspring plasma (*Vithayathil &*
164 *Muhlhausler, unpublished observations*), and may be playing a central role in the adverse
165 outcomes of offspring born to mothers who consume high-fat diets during pregnancy and
166 lactation.
167
168 **Omega-6 PUFA and the Adipocyte**

The hypothesis that increased intake maternal intake of omega-6 PUFA could have consequences for fat deposition for the fetus or breast-fed offspring has a clear biological basis. A series of studies have demonstrated the capacity of LA and its long-chain derivative, arachidonic acid (AA; 20:4(n-6)) to promote the differentiation of pre-adipocytes *in vitro,* suggesting that increased exposure to omega-6 PUFA during critical windows in the development of the adipocyte could result in a permanent increase in the number of adipocytes in an individual, and thus their propensity to accumulate body fat [15, 16]. These *in vitro* studies are supported by experimental animal studies, in which rats provided with diets containing higher LA levels and/or higher ratios of LA/ALA exhibit an increased expression of lipogenic genes, increased fat mass and greater adipocyte size and adipocyte number compared with rats fed a diet containing lower LA levels [17, 18]. Thus, omega-6 PUFA promoted the expansion of fat depots by upregulating both hyperplasia and hypertrophy. In a study by Hibbeln and colleagues, mice were fed diets which contained either 1% energy LA or 8% energy LA, similar to the 7-8%en LA found in the typical US diet. Mice consuming the high LA diet exhibited increased food intake, increased body weight and higher fat mass compared to those on the 1% LA diet [19]. This provided new evidence that omega-6 PUFA could promote increases in fat deposition at levels of dietary LA which are commonly encountered in human diets.

Omega-6 PUFA and the Early Origins of Obesity

The major period of fat development in human infants occurs before birth and in the first year of life, with nutritional exposures during this time having permanent consequences for the regulation of body fat mass throughout life. The established pro-adipogenic role of the omega-6 PUFA forms the basis of the hypothesis that exposure to an increased supply of these fatty acids during the period of fat cell development could result in permanent programming of

194 increased body fat mass. The potential role of omega-6 PUFA in the programming of obesity
195 is supported by numerous animal studies. In one such study, the offspring of mice fed an LA-
196 rich diet during pregnancy were 40% heavier at weaning than offspring of dams fed on diets
197 with a balanced LA/ALA ratio [20]. Importantly, this occurred in conjunction with a significant
198 increase in body fat mass, and was still present in adult life [20]. The potential importance of
199 the omega-6 PUFA in the intergenerational cycle of obesity has been emphasised by a recent
200 study by Massiera and colleagues, which demonstrated that feeding rats a diet in which LA
201 made up 55% of the lipid fraction (19% of total energy) over four generations, led to a
202 progressive increase in body fat mass in each successive generation, in the absence of any
203 difference in the intake of saturated fat between the groups [21]. The accumulation of body fat
204 mass was due to an increase in both the hyperplastic and hypertrophic expansion of the adipose
205 depots, driven by the upregulation of genes implicated in the hyperplastic and hypertrophic
206 development of adipose tissue [21]. Importantly, in the guinea pig, which is considered as the
207 best animal model of adipose tissue growth, increasing the LA/ALA ratio from 2:1 to 30:1
208 during the pre-weaning period also resulted in increased fat mass in adulthood [22].
209

210 Since the period of fat cell development extends into the postnatal period in the majority of
211 species, including humans, the fatty acid composition of the infant diet is also likely to
212 contribute to the programming of the adipocyte and propensity to obesity. In lactating women,
213 the fatty acid composition of the maternal diet is reflected in the composition of the breast-
214 milk. Previous studies have demonstrated that women supplemented with omega-3 LCPUFA
215 accumulate EPA and DHA in their breast milk in proportion with their level of intake [23].
216 Consequently, the fatty acid composition of breast-milk in Western countries has undergone a
217 shift in line which that seen in the diet of the general population [7]. Infant formulas have also
218 undergone a marked evolution in their fatty acid composition over the past 3 decades. Those

formulas which are now manufactured provide an adequate content of ALA and have a more balanced LA/ALA ratio, generally ranging between 5 and 10 to 1 [24] *(Philippe Guesnet, personal communication)*. The Global Standard for the composition of infant formula by a coordinated group of international experts suggested that the minimum LA level of 2.7% energy would be adequate to meet requirements [24]. However due to the exclusive use of vegetable oils in the formulation of infant formulas, the contents of LA in many formulas are well above physiological requirements, and may be high enough to interfere with omega-3 PUFA metabolism *(Philippe Guesnet, personal communication)*. The International Society for the Study of Fatty Acids and Lipids (ISSFAL), in their 2008 Statement on Dietary Fats in Infant Nutrition, stated that the LA content of formulas ranged from between 6% and 25% of total fatty acids, however acknowledged that, given the potential negative effects of high omega-6 PUFA exposure, further research on high omega-6 formulas was needed [25].

Thus, Western infants, whether breast or formula-fed, are exposed to elevated levels of omega-6 PUFA not only before birth, but also during the early infant period, which could further exacerbate the effects of these fatty acids on the development of adipose tissue in these children.

Evidence from Humans

In humans, most studies have focussed on the effects of increasing omega-3 intake, and there are currently no clinical studies which have directly investigated the effects of increasing maternal omega-6 PUFA intake in a randomised controlled trial. In the Project Viva cohort, a higher omega-6:omega-3 PUFA ratio in umbilical cord blood phospholipids was associated with a high subscapular skin-fold thickness at 3 years of age [26]. In contrast, a recent intervention study involving supplementation with EPA and DHA and instruction to lower

arachidonic acid intake during pregnancy and lactation did not show any effect on infant fat mass and fat distribution during the first year of life [27]. Further studies should help to solve this issue.

Conclusion

The hypothesis that increased maternal intake of omega-6 PUFA could be associated with adverse metabolic outcomes in her offspring is certainly not new. A series of papers in the mid-2000s focussed on the potential role of the omega-6 PUFAs in the origins of childhood obesity, and raised several of the points outlined in this review [7, 28-30]. The increase in dietary intakes of omega-6 PUFA has been documented in several large studies, and has occurred over a time when the prevalence of obesity in the population has risen sharply, despite declines in the per capita intake of saturated fat. There is evidence supporting the hypothesis that omega-6 PUFA have pro-adipogeneic and pro-lipogenic properties, and recent work in animals has demonstrated that exposure to a high omega-6 PUFA diet during early life is sufficient to program an increased body fat mass in the offspring.

Thus far, the work implicating omega-6 PUFA in the programming of obesity appears to have been largely ignored by health agencies, which continue to advocate the health benefits of polyunsaturates without identifying the functional differences between omega-6 and omega-3 types [31]. In addition, the potential link between omega-6 PUFA and obesity does not appear to have challenged the popular belief that saturated fats are ‘bad’ and polyunsaturated fats are ‘good’. It is difficult, as scientists, to understand the reason for this. It is clear, however that there is an urgent need for human clinical studies, in particular randomized controlled trials, to conclusively demonstrate whether there is a causal link between maternal omega-6 PUFA

intakes and health outcomes in children, including obesity and insulin resistance. If causality is established, then it will be critical to use this as an evidence base for modifying existing dietary fat recommendations, particularly in light of the fact that the full impact of current high omega-6 PUFA intakes on future generations will not yet be apparent.

Word Count: 2838

Key points:

1. The omega-6 PUFA content of the typical Western diet has increased significantly in the past few decades
2. Omega-6 PUFA promote adipogenesis and increase expression of lipogeneic genes
3. Increased intake of omega-6 PUFA by pregnant and lactating women may be contributing to the intergenerational cycle of obesity

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