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REVIEW ARTICLE

The effect of polyunsaturated fatty acids on obesity through epigenetic modifications☆

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KEYWORDS
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Abstract
Background and purpose: In recent years it has been demonstrated that polyunsaturated fatty acids (PUFA) have anti-inflammatory and as regulators of lipid metabolism. However, the epigenomic mechanisms involved in these processes are not known in depth. The aim of this review was to describe the scientific evidence supports that regular consumption of PUFA may reduce obesity and overweight by altering epigenetic marks.
Material and methods: A search of recent publications was carried out in human clinical trials, as well as animal model and *in vitro* experiments.
Results: Exist a possible therapeutic effect of PUFAs on the prevention and development of obesity due to their ability to reversively modify the methylation of the promoters of genes associated with lipid metabolism and to modulate the activity of certain microRNAs.
Conclusions: A better knowledge and understanding of the PUFAs role in epigenetic regulation of obesity is possible with the current published results. The PUFAs may modulate the promotor epigenetic marks in several adipogenic genes and regulate the expression of several miRNAs.

PALABRAS CLAVE
Ácidos grasos poliinsaturados;
MicroARN;
Epigenética;
Obesidad

Efecto de los ácidos grasos poliinsaturados en la prevención de la obesidad a través de modificaciones epigenéticas

Resumen
Antecedentes y objetivo: En los últimos años se ha demostrado que los ácidos grasos poliinsaturados (AGPI) tienen efectos antiinflamatorios y como reguladores del metabolismo lipídico. No obstante, no se conocen en profundidad los mecanismos epigenómicos implicados en estos

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procesos. El objetivo de esta revisión fue describir las evidencias científicas que apoyan que el consumo regular de AGPI puede reducir la obesidad mediante modificaciones de las marcas epigenéticas.
Material y métodos: Se realizó una búsqueda de publicaciones recientes llevadas a cabo en ensayos clínicos en humanos, modelos animales o ensayos *in vitro*.
Resultados: Existe un posible efecto terapéutico de los AGPI sobre la prevención y desarrollo de la obesidad gracias a su capacidad de modificar reversiblemente la metilación de los promotores de genes asociados con el metabolismo lipídico y de modular la actividad de determinados microARN.
Conclusiones: Los resultados publicados hasta la fecha referentes al rol de los AGPI en la prevención de la obesidad contribuyen al mejor conocimiento y entendimiento de las modificaciones epigenéticas de la obesidad. Los AGPI han demostrado poder modificar epigenéticamente diferentes genes adipogénicos mediante la metilación de sus promotores o mediante la regulación de su interacción con diversos microARN.

Introduction

Overweight and obesity are defined as an abnormal or excess fat accumulation that may impair health.[1] This is a complex multifactorial disorder where both genetic and environmental factors interact. The body mass index (BMI) is the most commonly used tool for classifying overweight and obesity, and may be defined as the ratio between weight in kilograms and the square of height in meters (kg/m^2).[1] BMI values of 25 or higher represent overweight, while values of 30 or higher represent obesity.[1] This measure correlates well with body adiposity. Excess weight is associated with increased morbidity and mortality, including an increased risk of type 2 diabetes mellitus, atherosclerosis, high blood pressure, hyperlipidemia, osteoarthritis, sleep apnea syndrome, and some types of cancer.[2]

There is currently a pandemic of overweight and obesity which has been increasing for decades[2] and continues to increase.[3] A study of the worldwide population published in 2008 estimated that 23.2% of the adult population had overweight, and 9.8% obesity, which represents some 937 million and 396 million people with overweight and obesity respectively.[3] This study also predicted for 2030 an adult population of up to 2160 million people with overweight and 1120 million with obesity if the secular trends seen to date continue.[3] The situation is Spain is also worrying. A study published in 2011[4] reported a 34.2% prevalence of overweight in adults, with higher values in males (43.9%) as compared to females (25.7%). Obesity was reported in 13.6%, with no sex difference.[4] This growing prevalence of obesity is related to an increased prevalence of metabolic syndrome.[5] The definition of this syndrome, which is closely related to abdominal fat, usually refers to glucose intolerance, abdominal obesity, hypertension, and dyslipidemia that severely impair the health of those who suffer from it.[5,6] Obesity is therefore a significant public health problem, and involves high financial costs because of its associated comorbidities.[2] The worldwide financial burden of obesity has been estimated to range from 0.7% to 2.8% of all healthcare expenses, with a financial impact of 9.1% for overweight and obesity.[2] The most commonly accepted model for explaining human obesity is based on the interaction between genetic predisposition, metabolic abnormalities, and environmental factors such as sedentary lifestyles and unhealthy nutrition. Specifically, it has been estimated from twin, adoption, and familial studies that the genetic component causes approximately 40% of interindividual variability in obesity values.[7,8] More specifically, comparisons of twin studies with familial and adoption studies show that 60–90% of the BMI variance in the population may be explained by genetic effects.[9] Linkage and association studies have located multiple obesity *loci* along the genome.[10] The central role of lipid metabolism in obesity and overweight has led to extensive analysis of the genetic varieties of genes encoding for the proteins involved in the metabolic pathways of adipogenesis, energy intake, lipolysis, and energy expenditure. Thus, for example, polymorphisms in the apolipoprotein B[11] and A5,[11] CD36 (cluster of differentiation 36),[12] USF1 (upstream transcription factor 1),[13,14] FADS3 (fatty acid desaturase 3),[14] GCKR (glucokinase regulatory protein),[15] INSIG2 (insulin-induced gene 2),[16] NPP1 (ectonucleotide pyrophosphatase/phosphodiesterase 1),[17] FTO (fat mass and obesity-associated protein),[18] and CTNNBL1 (catenin beta like 1)[19] genes have been studied. More than 40 genetic variants associated with obesity and body fat distribution are currently known[20] (Table 1). However, these studies with genetic markers cannot fully account for the heritability of obesity. This may partly be due to the polygenetic nature of obesity, in which different variants of the DNA sequence have only a small effect. For this reason, a very large analysis population is required for detection.[10]

Another potential explanation is the existence of other forms of variation, such as epigenetic modifications and alterations.[20] Epigenetics may currently be defined as the heredity of DNA activity that does not depend on the sequence itself, but on chemical modifications in DNA and adjacent regulatory proteins.[21] The best known epigenetic marks include the addition of a methyl group to DNA in cytosine of the CpG dinucleotide.[21] These dinucleotides are abundant in the promoter regions of many genes. Hypermethylation is usually associated with decreased gene