



ABSTRACT

Nutrients against adipogenesis : aim to cheating age or weight reduction

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Received: 17 October 2022
Accepted: 20 October 2022
Published: 31 October 2022

Abstract : Nutrition Virtual Symposium 2022 - Speaker

Link to DOI:
[10.25220/WNJ.V06.S1.0006](https://doi.org/10.25220/WNJ.V06.S1.0006)

Citation: Herrero S. Nutrients against adipogenesis : aim to cheating age or weight reduction. World Nutrition Journal. 2022 October 31, 6(S1): 8-10.



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Obesity is associated with increased risk of conditions such as type 2 diabetes, CHD, hypertension, dyslipidaemia (which are often included in the so-called metabolic syndrome), gall stones, certain types of cancer (breast and colon), osteoarthritis, non-alcoholic steatohepatitis, sleep apnoea, infertility, and many psychological conditions. Moreover, there is a marked reduction in life expectancy of the order of several years. With an increasing amount of body fat there is an increasing risk of developing type 2 diabetes in particular; the likelihood of developing this disease increases 10-fold at a BMI of 30 kg/m².

Alterations in adipose derived factors, elevated levels of fatty acids (FAs) and proinflammatory cytokines along with low level of adiponectin from higher mass of dysfunctional adipose tissues, are thought to cause or exacerbate cardiometabolic diseases in obesity¹.

Adipogenesis is regulated by a combination of signals including insulin and cyclic AMP. In response to adipogenic signals, preadipocytes both in vitro and in vivo exit quiescence and reenter the cell cycle to regenerate preadipocytes and generate daughter cells that differentiate into adipocytes^{2,3}.

Specifically, WAT can expand by both generating more adipocytes (hyperplasia) and by storing more fat in existing adipocytes (hypertrophy)⁴.

Excessive hypertrophy is linked to increased tissue hypoxia, fibrosis, and inflammation, leading to insulin resistance and metabolic dysfunction⁵.

Adult mesenchymal stem cells, including preadipocytes, possess a cellular sensory organelle called the primary cilium. Ciliated preadipocytes abundantly populate perivascular compartments in fat and are activated by high fat diet.

Omega-3 fatty acids to control adipogenesis

FFAR4: This gene encodes a G protein-coupled receptor (GPR) which belongs to the rhodopsin family of GPRs. The encoded protein functions as a receptor for free fatty acids, including omega 3, and participates in suppressing anti-inflammatory

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responses and insulin sensitizing. Multiple transcript variants encoding different isoforms have been found for this gene.

TULP3 (TUB Like Protein 3) is a protein coding gene. This gene encodes a member of the tubby gene family of bipartite transcription factors. TULP3 has been characterized as an adaptor protein that traffics membrane proteins into cilia.

Hilgendorf KI, et al⁶ discover that TULP3-dependent ciliary localization of the omega-3 fatty acid receptor FFAR4/GPR120 promotes adipogenesis. FFAR4 agonists and ω -3 fatty acids, but not saturated fatty acids, trigger mitosis and adipogenesis by rapidly activating cAMP production inside cilia.

Pro-resolving of mediators (SPMs)

Among the mechanisms that facilitate resolution, the biosynthesis of SPMs, a class of endogenous lipid mediators which includes, among others, resolvins, protectins and maresins generated from the omega-3 fatty acids EPA and docosahexaenoic acid (DHA), has been described to efficiently resolve inflammation with minimal damage to the surrounding tissue.

In particular, receptor of the pro-resolving mediator RvE1 is formed from EPA during the resolution phase of acute inflammation via cell-cell interactions such as endothelial cell-leukocyte interactions.

Vitamin A have a profound impact on all stages of adipogenesis.

Retinoic acid, an active metabolite of vitamin A, activates both retinoic acid receptors (RAR) and retinoid X receptors (RXR), inducing epigenetic changes in key regulatory genes governing adipogenesis.

Moreover, disease progression within the NAFLD spectrum to NASH, cirrhosis, and cancer is associated with declining circulating and hepatic retinol levels.

PPAR α / γ ligands: Potential for treatment of fatty liver diseases.

In humans, there are three, closely related, PPAR genes: *PPAR α* , *PPAR δ* and *PPAR γ* ⁷. PPARs are involved in a number of metabolic, inflammatory and bone disorders in addition to type 2 Diabetes (T2D) and fatty liver disorders.

Beyond cosmetics

A structural analog of coenzyme Q₁₀ (idebenone) that elicits spatially restricted partial agonist activity for both PPAR α and PPAR γ was identified.

Coenzyme Q₁₀ was also found to bind and activate both PPARs in a similar fashion, suggesting an endogenous role in relaying the states of mitochondria, peroxisomes and cellular redox to the two receptors. Testing idebenone in a mouse model of type 2 diabetes revealed the ability to reverse fatty liver development.

These findings indicate new mechanisms of action for both PPAR α and PPAR γ , and new potential treatment options for nonalcoholic fatty liver disease (NAFLD) and steatosis and presumably CoQ₁₀ and idebenone could be used to treat some of these disorders. However, CoQ₁₀ lacks sufficient solubility to be used effectively either orally or topically for any of these indications at the moment.

Keywords: adipogenesis, omega 3 fatty acid, vitamin A, vitamin D and coenzyme Q10

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