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An Evidence-Based Review of Dietary Supplements on Inflammatory Biomarkers in Obesity

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Abstract

Obesity is a multifactorial chronic disease characterized by the hypertrophy and hyperplasia of the adipose tissue accompanied by low-grade chronic inflammation, which is in turn related to cardiometabolic diseases. The main treatment for obesity involves lifestyle changes, however, there are several factors that can prevent or impact successful weight loss in obese subjects. Recently, dietary supplements have been considered for their potential anti-inflammatory effect in obesity. Relevant literature sought in PubMed database focuses on human randomized placebo controlled trials to analyze the effect of dietary supplements on inflammatory biomarkers in obesity. However, there is a lack of existing evidence that the supplements are safe to use, and thus unfit for recommendation. Therefore, the objective of this evidence-based review is to analyze the current body of literature for evidence of the anti-inflammatory effects of dietary supplements, especially in regards to treating obesity.



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Cytokines,
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Introduction

Currently, obesity is a serious public health problem due to the fact that it is associated with various diseases, among which are diabetes mellitus type 2, metabolic syndrome¹, cardiovascular diseases, hypertension, dyslipidemia and some

types of cancer². Obesity (body mass index [BMI] equal to or greater than 30 kg/m²) is a chronic disease that has increased dramatically in recent years, mainly in developing countries. It is currently considered the epidemic of the 21st century, since more than 1.9 billion people are overweight or

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obese^{3, 4}. In this context, it is estimated that, by the year 2030, there will be at least half of the adult population with overweight or obesity worldwide⁵.

Obesity is a complex disease that is influenced by several factors and is characterized by hypertrophy and hyperplasia of the adipose tissue which is caused by the positive energy balance. In addition, this increase in the plasticity of the white adipose tissue is accompanied by chronic low-grade inflammation, also called "subclinical inflammation", which leads to metabolic changes such as insulin resistance⁶.

One of the main treatments for obesity is the change in lifestyle that includes a healthy diet and exercise. However, since weight loss is a very complex process that encompasses environmental, biological, and behavioral factors, adhering to this treatment can be difficult⁷. Dietary supplements have been used as adjuvants in the promotion of weight loss in people with obesity. However, to date there is little scientific information that evidences a relationship between different dietary supplements and the the inflammatory process derived from obesity. The aim of this evidence-based review is to summarize the studies that have been conducted so far in regards to the effects of dietary supplements on the inflammatory profile in adult subjects with obesity.

Obesity-Induced Inflammation

Obesity is characterized by induced, chronic low-grade inflammation due to the expansion of adipocytes (hypertrophy), and by adipogenesis (hyperplasia) of visceral adipose tissue⁸. In the past, adipose tissue was known to be the main site of energy storage, organ protection, and cold insulation⁹⁻¹¹. However, in recent decades this context has changed due to the identification and comprehension of the different functions from the adipose tissue. Adipose tissue is currently known as a metabolically active endocrine organ that secretes mediators and adipokines, contributes in cellular and tissue communication, and plays a role in the inflammatory processes at the local and systemic levels¹¹. Adipose tissue is a heterogeneous tissue and is composed mainly of adipocytes, preadipocytes, but other cell types are also present, such as fibroblasts, pericytes, macrophages, lymphocytes,

neutrophils and T cells¹². The cells of the immune system, in conjunction with the adipocytes, are indispensable for the maintenance of the physiology and metabolism of adipose tissue¹³.

During obesity, the number of infiltrated macrophages in the adipose tissue increases. In fact, there is a high correlation between the amounts of macrophages with the size and number of the adipocytes¹⁴. Evidence derived from murine models indicates that macrophages in lean mice constitute approximately 5% of the total adipose tissue cells, whereas in obese mice, macrophages represent up to 50% of all adipose tissue¹⁵. The macrophages of adipose tissue show different phenotypes depending on various conditions. In this sense, macrophages can be classified into classically-activated macrophages (M2) or anti-inflammatory phenotype, and alternatively activated macrophages (M1) or pro-inflammatory phenotype¹⁴.

The polarization of macrophages M0 (precursor) to M1 occurs through the activation of the classical pathway in which pro-inflammatory cytokines of type 1 T-helper cells such as interferon-gamma (IFN- γ) and tumor necrosis factor alpha (TNF- α) along with bacterial components such as lipopolysaccharide (LPS) promote the expression of pro-inflammatory cytokines such as TNF- α (cytokine that causes lipolysis in the adipose tissue), interleukin (IL) 6, IL-1, IL-12, Monocyte Chemoattractant Protein-1 (MCP-1), CXC chemokine ligand (CXCL) 1-3, CXCL-5 and CXCL8-10¹⁶⁻¹⁸.

The M1 macrophages are found mostly during periods of obesity, and they are associated with the development of insulin resistance and type 2 diabetes mellitus. On the other hand, M2 macrophages are activated by cytokines such as IL-4 and IL-13 and secreted by type 2 T-helper cells that promote the expression of anti-inflammatory cytokines such as IL-1 receptor agonist (IL-RA), IL-10, IL-12 and arginase-1¹⁹. M2 macrophages unlike M1 macrophages are found mostly in lean adipose tissue¹⁴.

Several mechanisms are involved in the development of obesity-induced inflammation, among which are: hypoxia²⁰, increased concentrations of free fatty acids (FFA)²¹, LPS²², reactive oxygen species

(ROS)²³ and pro-inflammatory cytokines²⁴. However, to date, it is not known with certainty what triggers this inflammatory process. The combination of the mentioned factors on adipose tissue (hypoxia, FFA, ROS, pro-inflammatory cytokines and LPS) culminates with the transcription of genes that code for pro-inflammatory cytokines such as TNF- α and IL-1 β via activation of transcription factors such as (NF- κ B), hypoxia-inducible factor 1 (HIF-1), interferon regulatory factor 3 (IRF-3) and activator protein 1 (AP-1)¹⁴. Hypoxia and TNF- α inhibit the production of adiponectin (adipocyte-derived adipokine) which, in lean subjects, is found in high concentrations, has anti-inflammatory actions, and is related to anti-atherosclerotic properties²⁵.

Methodology

A PubMed search for human randomized placebo controlled trials was conducted using the following key words: "dietary supplements", "obesity", "inflammation" and "biomarkers". Studies that included single dietary supplements were selected. Only studies published in English and from 2012 to 2017 were included. There were no restrictions on the type of randomized placebo controlled trials (parallel or crossover). Studies involving children or adolescents, diet therapy, medication and exercise were excluded.

Results and Discussion

Vitamins and Trace Elements

Vitamin D

Vitamin D is a steroid hormone whose main function is to maintain bone mineral homeostasis²⁶. It is mainly synthesized by the skin tissue (90%) via exposure to sunlight, and the remaining 10% is obtained from dietary sources^{27,28}. Vitamin D is hydroxylated and converted to 25-hydroxyvitamin D [(25(OH)D)] in the liver and then to the hormonal form 1,25-dihydroxyvitamin D [(1,25(OH)₂D)] in kidney. Then, 1,25(OH)₂D is mediated and sent to different tissues whose cells contain vitamin D receptor (VDR) (intestinal epithelium, renal tubules, parathyroid gland cells, skin, mammary epithelium, pancreas, skeleton, monocytes, macrophages, T-lymphocytes^{29,30}). In recent years, it has been observed that the prevalence of vitamin D deficiency (hypovitaminosis D) has increased. Currently, about 1000 million people of all age groups suffer from this deficiency³¹. In its 2011 report, the

Institute of Medicine has proposed that the cut-off point for identifying hypovitaminosis D at serum concentrations below 50 nmol/L or 20 ng/mL³². One of the main strategies in combating vitamin D deficiency has been the fortification of foods with this micronutrient, but these efforts have only been possible in some countries³³.

Observational studies have shown that decreased serum levels of 25(OH)D are independently related with obesity and insulin resistance. As an example, in the REGARDS cohort of USA, low serum levels of 25(OH)D were associated negatively with high levels of serum IL-6 and insulin resistance which was evaluated with the homeostasis model assessment of insulin resistance (HOMA-IR) tool, and lower serum concentration of adiponectin. Regarding anthropometric parameters, low serum levels of this vitamin were associated with greater WC and BMI³⁴.

To date, there have been few randomized controlled trials evaluating the effect of vitamin D supplementation on inflammatory profiles in obese adults. As an example, Von Hurst *et al.*, performed a small randomized controlled trial with 42 adult overweight women (18 – 68 years) with insulin resistance and hypovitaminosis D (≤ 25 nmol/L), that were supplemented with 100 μ g (4000 IU) of Vitamin D3 (cholecalciferol) daily for 6 months. At the end of the study, the women who were supplemented with vitamin D3 showed improvement in insulin sensitivity, but not in high-sensitivity C-reactive protein (hs-CRP) levels, compared to the placebo group³⁵. On the other hand, in 2012, *Beilfuss et al.*, performed a randomized controlled trial with 332 overweight and obese subjects (men and women) (BMI= 28.0 - 47.9 kg/m²), who were assigned into three groups that underwent two different treatments. One group was supplemented with 40,000 IU of cholecalciferol per week, the second group was supplemented with 20,000 IU of cholecalciferol, and the third group was supplemented with a placebo. All groups followed the treatment for one year. At the end of the experimental period, the groups supplemented with cholecalciferol showed an increase in serum levels of 25(OH)D when compared with the placebo group. In addition, supplementation with cholecalciferol decreased serum levels of IL-6 and elevated serum levels of hs-CRP. Supplementation with cholecalciferol had

no effect on TNF- α levels or on insulin resistance³⁶. In this sense, it can be observed that there are still opportunities for promising results in these studies, since controversial and varied results have been reported between different studies.

Several meta-analyses of randomized controlled trials have focused on identifying the role of vitamin D supplementation on the inflammatory profile in overweight or obese adults. In 2016, Zuk *et al.*, conducted a systematic review and meta-analysis that included 11 randomized controlled trials that evaluated the anti-inflammatory effects of vitamin D3 supplementation in overweight or obese adults. The results showed no benefits of supplementing with vitamin D3 on inflammatory markers (CRP and TNF- α)³⁷. Another meta-analysis by Jamka *et al.*, which included overweight and obese subjects with vitamin D deficiency at the beginning of the study reported that vitamin D supplementation did not improve plasma CRP concentrations (MD -0.13 95% CI: -0.38 - 0.12, P = 0.15), TNF- α (MD -0.13, 95% CI: -0.38 - 0.12, P = 0.31) and IL-6 (MD 0.1; 95% CI: -0.43 - 0.63, P = 0.71)³⁸. Finally, Dinca *et al.*, focused on evaluating the effects of vitamin D supplementation on adiponectin and leptin serum levels. Regarding the results, they did not find significant changes after supplementation in both adiponectin (MD: 4.45%, 95% CI: -3.04 - 11.93, P = 0.244) and leptin (MD -4.51%; 95% CI -25.13 - 16.11; P = 0.668) serum levels³⁹. It is important to consider the limitations and risk of bias in the studies, and the heterogeneity of the results. For example, variables such as population, age, time of follow-up, dose and quality of supplementation could have impacted the results. It is necessary to conduct studies with greater methodological rigor in order to reach strong, evidence-backed conclusions involving supplementation of vitamin D in this population.

Studies suggest that a low concentration of 25(OH)D during obesity may be attributable to an arrest of 25(OH)D (from diet or skin tissue) by adipocytes⁴⁰. It has been reported that the increase of 1 kg/m² of BMI is associated with a decrease of 1.15% (95% CI 0.94% - 1.36%) of 25(OH)D concentrations levels in plasma⁴¹. Conversely, other studies suggest that the decrease in body fat could increase 25(OH)D levels in patients with obesity⁴²⁻⁴⁵. Although current evidence from observational studies showed

a relationship between obesity and vitamin D deficiency, the direction of this association is still unknown.

Zinc

Zinc is a trace element of the human body, the second most abundant after iron⁴⁶. The adult human body contains approximately 2-3 g of zinc. Zinc is ubiquitous; however, the largest amount of this trace element is stored in skeletal muscle tissue, approximately 60%. Zinc serum levels represent approximately 0.1% of the body's total zinc^{47,48}. Zinc plays an important role in several important biological processes, such as structural component, catalytic factor, and signaling mediator⁴⁸. Zinc requirements are mediated by different factors such as sex, age, pregnancy and lactation⁴⁹. Zinc deficiency is a serious problem that affects a third of the world's population⁵⁰. Developing countries are the most affected with this condition, mainly because their diet is rich in foods with high phytate content, such as beans and bread, and low in protein, preventing the proper absorption of this trace element^{50,51}. This micronutrient deficiency contributes to the 1.4% of all deaths worldwide⁵².

Several randomized controlled trials have studied the effects of zinc supplementation on anthropometric, biochemical and inflammatory parameters within obese subjects. However, the results differ significantly between studies. For example, in 2012, Kim & Lee conducted a quasi-experimental study to evaluate zinc supplementation (30 mg zinc gluconate) in 40 obese adult Korean women with a follow-up time of 8 weeks. The conclusion of this study was that zinc supplementation increased zinc serum (15%) and urinary (65%) levels (P < 0.05 in both cases), but had no positive effects on anthropometric parameters (BMI, WC) or improved insulin sensitivity. However, the risk of bias in this study (lack of randomization of groups and control in confounding variables) cannot be ignored⁵³. Likewise, the same group of researchers conducted a double-blind randomized controlled trial to analyze the effects of this same dose and time of zinc supplementation in 40 overweight or obese young Korean women (19 - 28 years). The results showed that serum inflammatory markers (hs-CRP, IL-6 and TNF- α) and leptin levels were increased, whereas serum adiponectin concentrations were decreased

in obese women compared with the placebo group at baseline. Moreover, after 8 weeks of zinc gluconate supplementation, obese women showed a decrease in serum hs-CRP and TNF- α levels⁵⁴. In another double-blind randomized controlled trial with zinc supplementation (30 mg of zinc gluconate in tablet per day for 4 weeks) evaluated in 60 obese adults (BMI = 30 - 40 kg/m²) showed that zinc serum levels increased significantly, while the BMI decreased significantly in the group supplemented with zinc⁵⁵.

The anti-inflammatory effects of zinc supplementation may be attributable to the fact that it inhibits the transcription factor NF- κ B. In vitro studies have shown that hs-CRP has the ability to inhibit the expression and synthesis of adiponectin via the PI-3 kinase pathway⁵⁶.

Amino Acids

Histidine

Histidine is a conditionally essential amino acid because only adults can synthesize it endogenously⁵⁷. It is a precursor for the synthesis of histamine and is also an agent that acts as a defense against oxidative stress⁵⁸ by removing free radicals from cellular respiration. It also defends against oxidation of polyunsaturated fatty acids and chelate divalent metal ions⁵⁹. Studies have shown that histidine serum levels are decreased in obesity and therefore low histidine serum concentrations are related to inflammatory markers (IL-6, CRP) and oxidative stress (SOD, MDA)^{58,60}.

A randomized controlled trial performed by Feng *et al.*, included 92 overweight or obese adult women, who were supplemented with either 4 g/day of histidine (n=47) or a placebo (n=45) for 3 months. Histidine supplementation showed favorable results in this study. Compared to the placebo group, the supplemented group showed a significant increase in histidine and adiponectin serum levels, as well as a significant decrease in HOMA-IR, BMI, WC, non-esterified fatty acids (NEFAs) and pro-inflammatory cytokines (TNF- α and IL-6)⁶¹.

Studies in animals suggest that exogenous histidine inhibits the production of pro-inflammatory cytokines (IL-6 and TNF- α) by suppressing NF- κ B activation in macrophages. In addition, histidine inhibits the expression of genes that encode for TNF- α

and IL-6 independently in rat peritoneal tissue macrophages⁶².

Taurine

Taurine is a non-essential sulfuric amino acid and represents approximately 0.1% of total body weight, which translates into the most abundant amino acid in the human body⁶³. It is synthesized endogenously from precursors such as methionine and cysteine⁶⁴ in white adipose tissue, the liver, and kidneys^{17,65}. Furthermore, it can also be consumed exogenously from the diet, especially in fish and seafood. The biological functions of taurine have been well-described, such as the conjugation of bile salts, osmoregulation, stabilization of the cell membrane, calcium modulation, agent against oxidative stress, and immunomodulatory functions⁶⁶. Taurine has anti-obesity properties that can be attributed through the regulation of glucose and lipid metabolism, inhibiting appetite and decreasing inflammation in adipose tissue¹⁷. In 2004, Zhang *et al.*, conducted a small randomized double-blind controlled trial with 30 college students supplemented with 3 g/day of taurine for 7 weeks. The results of this study showed that there was a significant reduction in body weight and triglyceride concentrations in the taurine supplemented group at 7 weeks of follow-up⁶⁷.

Studies in humans and animals have shown that taurine serum levels are decreased during obesity, but there is little evidence in humans to demonstrate the anti-inflammatory and anti-obesity effects of taurine supplementation in subjects with obesity. As an example, Rosa *et al.*, conducted a small randomized controlled trial in obese subjects supplemented with 3 g/day of taurine orally for eight weeks. The results showed that taurine plasma levels were decreased in obese subjects at baseline. Moreover, the supplemented group showed a significant increase in taurine (97%) and adiponectin (12%) plasma levels, and a significant reduction in hs-CRP (29%) compared to the placebo group. However, no changes were observed in TNF- α , IL-6 and IL-8 plasma levels after the supplementation period in comparison to the placebo group⁶⁴.

The anti-inflammatory properties of taurine seem to be related to its ability as an antioxidant to neutralize hypochlorous acid, forming the complex

taurine-chloramide, a relatively more stable and less toxic compound. The taurine-chloramide can be regulate the expression and secretion of nitric oxide and cytokines such as IL-6, IL-8 and TNF- α ⁶⁸. The mechanism involves the inhibition of NF- κ B activation through the oxidation of the inhibitor protein I κ B α ⁶⁹.

Coenzyme Q10

Coenzyme Q10 (CoQ10) is an endogenous fat-soluble component synthesized by the mevalonate pathway, and it is present in cell membranes⁷⁰. CoQ10 is an essential cofactor in the chain of electron transport in the mitochondria^{71,72} and plays an important role in oxidative phosphorylation, cellular respiration, energy production, and antioxidant defense^{70,72}. CoQ10 can also be found in dietary sources, and studies have reported that the daily intake of beef, chicken, and fish are the sources that contain the highest amount of CoQ10. The daily intake of these foods contributes approximately 3 to 5 mg of CoQ10^{73,74}. CoQ10 supplements can be found in presentations such as soft gel capsules, oral sprays, hard cover capsules, and tablets⁷⁵. However, the bioavailability of CoQ10 varies between brands and formulations⁷⁶. CoQ10 deficiencies have been associated with various diseases, such as hypertension, Parkinson's disease, and obesity⁷¹. Studies in humans have shown that CoQ10 plasma levels are decreased in obese subjects; however, other studies have reported results do not support these findings⁷⁷.

Human studies evidenced the benefits of coenzyme Q10 supplementation in cardiovascular and neurodegenerative diseases⁷⁸, but few clinical studies have shown the beneficial effects of CoQ10 supplementation in obesity-induced inflammation. For example, a small double-blind randomized controlled trial conducted by Lee *et al.*, evaluated oral CoQ10 supplementation (200 mg/day) for 12 weeks of follow-up in obese subjects. The results showed that there was a significant increase in CoQ10 serum levels in the supplemented group compared to the placebo group; however, supplementation with CoQ10 did not have significant effects on inflammatory or anthropometric parameters⁷⁸. Another double-blind randomized controlled trial

conducted in obese subjects with non-alcoholic fatty liver disease showed that supplementation with 100 mg/day of CoQ10 for 4 weeks significantly reduced WC but not BMI⁷⁹. Raygan *et al.*, conducted a randomized double-blind controlled trial to evaluate the supplementation of CoQ10 (100 mg/day) for 8 weeks in subjects with metabolic syndrome. At the end of the study, those who were supplemented showed decreased levels of serum insulin, HOMA-IR and HOMA- β (beta-cell function), in comparison with the placebo group. However, no changes were observed in hs-CRP levels⁸⁰. A meta-analysis conducted by Zhai *et al.* evaluated the effects of CoQ10 supplementation on inflammatory markers. They found that supplementation with CoQ10 decreased TNF- α but not IL-6 and CRP serum levels. It is necessary to mention that most of the studies included in this meta-analysis came from Asian countries (Iran, Korea, China), so these results could potentially only apply to this population⁸¹. In a more recent meta-analysis, it was found that supplementation with CoQ10 significantly reduced the circulating levels of TNF- α , IL-6 and CRP; however, this meta-analysis included subjects with various diseases such as cardio-cerebral vascular disease, rheumatoid arthritis, multiple sclerosis, type 2 diabetes mellitus, obesity, fatty liver disease, and renal diseases⁸².

Conclusion

Currently, the potential anti-inflammatory effects of various dietary supplements on obesity-induced inflammation have been investigated. However, the results of the studies remain controversial and should be considered with caution. In this sense, studies with greater scientific rigor are needed to provide definitive conclusions.

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