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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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Keywords

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 syndrome[1], cardiovascular diseases, hypertension, dyslipidemia and some types of cancer[2]. Obesity (body mass index [BMI] equal to or greater than 30 kg/m^2) 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 worldwide[5].

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 resistance[6].

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 difficult[7]. 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 tissue[8]. In the past, adipose tissue was known to be the main site of energy storage, organ protection, and cold insulation[9-11]. 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 levels[11]. 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 cells[12]. The cells of the immune system, in conjunction with the adipocytes, are indispensable for the maintenance of the physiology and metabolism of adipose tissue[13].

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 adipocytes[14]. 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 tissue[15]. 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 phenotype[14].

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 CXCL8-10[16-18].

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-1[19]. M2 macrophages unlike M1 macrophages are found mostly in lean adipose tissue[14].

Several mechanisms are involved in the development of obesity-induced inflammation, among which are: hypoxia[20], increased concentrations of free fatty acids (FFA)[21], LPS[22], reactive oxygen species

(ROS)[23] and pro-inflammatory cytokines[24]. 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-1β via activation of transcription factors such as (NF-κB), 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 properties[25].

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 homeostasis[26]. 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$(OH)_2$D)] in kidney. Then, 1,25$(OH)_2$D 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 deficiency[31]. 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/mL[32]. 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 countries[33].

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 BMI[34].

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 mmol/L), that were supplemented with 100 ug (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 group[35]. On the other hand, in 2012, *Beilfulss et al.,* performed a randomized controlled trial with 332 overweight and obese subjects (men and women) (BMI= 28.0 - 47.9 kg/m^2), 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 resistance[36]. 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-analyzes 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 levels[39]. 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 adipocytes[40]. 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 plasma[41]. Conversely, other studies suggest that the decrease in body fat could increase 25(OH)D levels in patients with obesity[42-45]. 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 iron[46]. 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 mediator[48]. Zinc requirements are mediated by different factors such as sex, age, pregnancy and lactation[49]. Zinc deficiency is a serious problem that affects a third of the world's population[50]. 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 worldwide[52].

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 ignored[53]. 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 levels[54]. 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/m^2) showed that zinc serum levels increased significantly, while the BMI decreased significantly in the group supplemented with zinc[55].

The anti-inflammatory effects of zinc supplementation may be attributable to the fact that it inhibits the transcription factor NF-κB. In vitro studies have shown that hs-CRP has the ability to inhibit the expression and synthesis of adiponectin via the PI-3 kinase pathway[56].

Amino Acids

Histidine

Histidine is a conditionally essential amino acid because only adults can synthesize it endogenously[57]. It is a precursor for the synthesis of histamine and is also an agent that acts as a defense against oxidative stress[58] by removing free radicals from cellular respiration. It also defends against oxidation of polyunsaturated fatty acids and chelate divalent metal ions[59]. 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-κB activation in macrophages. In addition, histidine inhibits the expression of genes that encode for TNF-α and IL-6 independently in rat peritoneal tissue macrophages[62].

Taurine

Taurine is a non-essential sulfuric amino acid and represents approximately 0.1% of total body weight, wich translates into the most abundant amino acid in the human body[63]. It is synthesized endogenously from precursors such as methionine and cysteine[64] 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 functions[66]. Taurine has anti-obesity properties that can be attributed through the regulation of glucose and lipid metabolism, inhibiting appetite and decreasing inflammation in adipose tissue[17]. 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-up[67].

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 group[64].

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-κB activation through the oxidation of the inhibitor protein IκBα[69].

Coenzyme Q10

Coenzyme Q10 (CoQ10) is an endogenous fat-soluble component synthesized by the mevalonate pathway, and it is present in cell membranes[70]. 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 tablets[75]. However, the bioavailability of CoQ10 varies between brands and formulations[76]. CoQ10 deficiencies have been associated with various diseases, such as hypertension, Parkinson's disease, and obesity[71]. Studies in humans have shown that CoQ10 plasma levels are decreased in obese subjects; however, other studies have reported results do not support these findings[77].

Human studies evidenced the benefits of coenzyme Q10 supplementation in cardiovascular and neurodegenerative diseases[78], 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 parameters[78]. 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 BMI[79]. *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 levels[80]. 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 population[81]. 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 diseases[82].

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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References

1. Jensen, M.D., *et al.,* 2013 AHA/ACC/TOS guideline for the management of overweight and obesity in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and The Obesity Society. *Circulation*.2014. 129(25 Suppl 2): p. S102-38.
2. Maldonado-Ruiz, R., *et al.,* Microglia activation due to obesity programs metabolic failure leading to type two diabetes. *Nutr Diabetes*.2017;***7***(3): p. e254.
3. Collaboration, N.R.F., Trends in adult body-mass index in 200 countries from 1975 to 2014: a pooled analysis of 1698 population-based measurement studies with 19·2 million participants. *The Lancet*.2016;***387***(10026): p. 1377-1396.
4. Saltiel, A.R. and J.M. Olefsky, Inflammatory mechanisms linking obesity and metabolic disease. *J Clin Invest*.2017;***127***(1): p. 1-4.
5. Tremmel, M., et al., Economic Burden of Obesity: A Systematic Literature Review. *Int J Environ Res Public Health*.2017;***14***(4).
6. Kunath, A. and N. Klöting, Adipocyte biology and obesity-mediated adipose tissue remodeling. *Obesity Medicine*.2016;***4***: p. 15-20.
7. Montesi, L., *et al.,* Long-term weight loss maintenance for obesity: a multidisciplinary approach. *Diabetes Metab Syndr Obes*.2016;***9***: p. 37-46.
8. Jo, J., *et al.,* Hypertrophy and/or Hyperplasia: Dynamics of Adipose Tissue Growth. *PLoS Comput Biol*.2009;***5***(3): p. e1000324.
9. Coelho, M., T. Oliveira, and R. Fernandes, Biochemistry of adipose tissue: an endocrine organ. *Arch Med Sci*.2013;***9***(2):p. 191-200.
10. Matafome, P. and R. Seica, Function and Dysfunction of Adipose Tissue. *Adv Neurobiol*. 2017;***19***: p. 3-31.
11. Boutens, L. and R. Stienstra, Adipose tissue macrophages: going off track during obesity. *Diabetologia*.2016;***59***(5):p. 879-94.
12. Lee, M.J., Y. Wu, and S.K. Fried, Adipose tissue heterogeneity: implication of depot differences in adipose tissue for obesity complications. *Mol Aspects Med*.2013;***34***(1): p. 1-11.
13. Macdougall, C.E., *et al.,* Visceral Adipose Tissue Immune Homeostasis Is Regulated by the Crosstalk between Adipocytes and Dendritic Cell Subsets. *Cell Metab*.2018: ***27***(3):p. 588-601 e4.
14. Johnson, A.R., J.J. Milner, and L. Makowski, The inflammation highway: metabolism accelerates inflammatory traffic in obesity. *Immunol Rev*.2012:***249***(1):p. 218-38.
15. Weisberg, S.P., *et al.,* Obesity is associated with macrophage accumulation in adipose tissue. *J Clin Invest*.2003;***112***(12): p.1796-808.
16. Martinez, F.O. and S. Gordon, The M1 and M2 paradigm of macrophage activation: time for reassessment. *F1000 Prime Rep*.2014;***6***: p. 13.
17. Murakami, S., The physiological and pathophysiological roles of taurine in adipose tissue in relation to obesity. *Life Sci*.2017;***186***: p. 80-86.
18. Wang, N., H. Liang, and K. Zen, Molecular mechanisms that influence the macrophage m1-m2 polarization balance. *Front Immunol*. 2014;***5***:p. 614.
19. Castoldi, A., *et al.,* The Macrophage Switch in Obesity Development. *Front Immunol*.2015; ***6***:p. 637.
20. Trayhurn, P., Hypoxia and adipose tissue function and dysfunction in obesity. *Physiol Rev*.2013;***93***(1):p. 1-21.
21. Makki, K., P. Froguel, and I. Wolowczuk, Adipose tissue in obesity-related inflammation and insulin resistance: cells, cytokines, and chemokines. *ISRN Inflamm*.2013;***2013***: p. 139239.
22. Hersoug, L.G., P. Moller, and S. Loft, Role of microbiota-derived lipopolysaccharide in adipose tissue inflammation, adipocyte size and pyroptosis during obesity. *Nutr Res Rev*. 2018;p. 1-11.
23. Marseglia, L., *et al.,* Oxidative stress in obesity: a critical component in human

diseases. *Int J Mol Sci*.2014.***16***(1): p. 378-400.

24. Kang, Y.E., *et al.,* The Roles of Adipokines, Proinflammatory Cytokines, and Adipose Tissue Macrophages in Obesity-Associated Insulin Resistance in Modest Obesity and Early Metabolic Dysfunction. *PLoS One*. 2016;***11***(4):p. e0154003.
25. Zappala, G. and M.M. Rechler, IGFBP-3, hypoxia and TNF-alpha inhibit adiponectin transcription. *Biochem Biophys Res Commun*.2009;***382***(4):p. 785-9.
26. Holick, M.F., *et al.,* Vitamin D and skin physiology: a D-lightful story. *J Bone Miner Res*.2007;***22*** Suppl 2:p. V28-33.
27. Hossein-nezhad, A. and M.F. Holick, Vitamin D for health: a global perspective. *Mayo Clin Proc*.2013;***88***(7):p. 720-55.
28. Kuwabara, A., *et al.,* High prevalence of vitamin D deficiency in patients with xeroderma pigmetosum-A under strict sun protection. *Eur J Clin Nutr*.2015;***69***(6): p. 693-6.
29. Achakzai, H., *et al.,* Hypovitaminosis-D: Frequency and association of clinical disease with biochemical levels in adult patients of RMI Medical OPD. *Pak J Med Sci*. 2016; ***32***(2):p. 394-8.
30. Wang, Y., J. Zhu, and H.F. DeLuca, Where is the vitamin D receptor? *Arch Biochem Biophys*.2012;***523***(1):p. 123-33.
31. Nair, R. and A. Maseeh, Vitamin D: The "sunshine" vitamin. *J Pharmacol Pharmacother*.2012;***3***(2):p. 118-26.
32. Ross, A.C., *et al.,* The 2011 report on dietary reference intakes for calcium and vitamin D from the Institute of Medicine: what clinicians need to know. *J Clin Endocrinol Metab*.2011;***96***(1):p. 53-8.
33. Holick, M.F. and T.C. Chen, Vitamin D deficiency: a worldwide problem with health consequences. *Am J Clin Nutr*.2008;***87***(4): p. 1080S-6S.
34. Jackson, J.L., *et al.,* Associations of 25-hydroxyvitamin D with markers of inflammation, insulin resistance and obesity in black and white community-dwelling adults. *J Clin Transl Endocrinol*.2016;***5***:p. 21-25.
35. von Hurst, P.R., W. Stonehouse, and J. Coad, Vitamin D supplementation reduces insulin resistance in South Asian women living in New Zealand who are insulin resistant and vitamin D deficient - a randomised, placebo-controlled trial. *Br J Nutr*.2010;***103***(4): p. 549-55.
36. Beilfuss, J., *et al.,* Effects of a 1-year supplementation with cholecalciferol on interleukin-6, tumor necrosis factor-alpha and insulin resistance in overweight and obese subjects. *Cytokine*.2012;***60***(3):p. 870-4.
37. Zuk, A., T. Fitzpatrick, and L.C. Rosella, Effect of Vitamin D3 Supplementation on Inflammatory Markers and Glycemic Measures among Overweight or Obese Adults: A Systematic Review of Randomized Controlled Trials. *PLoS One*.2016;***11***(4): p. e0154215.
38. Jamka, M., *et al.,* The effect of vitamin D supplementation on selected inflammatory biomarkers in obese and overweight subjects: a systematic review with meta-analysis. *Eur J Nutr*.2016;***55***(6):p. 2163-76.
39. Dinca, M., *et al.,* Does vitamin D supplementation alter plasma adipokines concentrations? A systematic review and meta-analysis of randomized controlled trials. *Pharmacol Res*.2016;***107***:p. 360-71.
40. Dura-Trave, T., *et al.,* Prevalence of hypovitaminosis D and associated factors in obese Spanish children. *Nutr Diabetes*.2017; ***7***(3):p. e248.
41. Vimaleswaran, K.S., *et al.,* Causal relationship between obesity and vitamin D status: bi-directional Mendelian randomization analysis of multiple cohorts. *PLoS Med*.2013;***10***(2): p. e1001383
42. Rock, C.L., *et al.,* Weight loss is associated with increased serum 25-hydroxyvitamin D in overweight or obese women. *Obesity (Silver Spring)*.2012;***20***(11):p. 2296-301.
43. Mallard, S.R., A.S. Howe, and L.A. Houghton, Vitamin D status and weight loss: a systematic review and meta-analysis of randomized and nonrandomized controlled weight-loss trials. *Am J Clin Nutr*.2016;***104***(4):p. 1151-1159.
44. Gangloff, A., *et al.,* Effect of adipose tissue volume loss on circulating 25-hydroxyvitamin D levels: results from a 1-year lifestyle intervention in viscerally obese men. *Int J Obes (Lond)*.2015;***39***(11):p. 1638-43.

45. Ceglia, L., *et al.,* Association between body weight and composition and plasma 25-hydroxyvitamin D level in the Diabetes Prevention Program. *Eur J Nutr.*2017;***56***(1): p. 161-170.
46. Gammoh, N.Z. and L. Rink, *Zinc in Infection and Inflammation. Nutrients.*2017;***9***(6).
47. Jackson, M.J., Physiology of Zinc: *General Aspects.*1989;p. 1-14.
48. Kambe, T., *et al.,* The Physiological, Biochemical, and Molecular Roles of Zinc Transporters in Zinc Homeostasis and Metabolism. *Physiol Rev*. 2015;***95***(3): p. 749-84.
49. Roohani, N., *et al.,* Zinc and its importance for human health: An integrative review. *J Res Med Sci.*2013;***18***(2):p. 144-57.
50. Tapiero, H. and K.D. Tew, Trace elements in human physiology and pathology: zinc and metallothioneins. *Biomed Pharmacother.*2003; ***57***(9):p. 399-411.
51. Jurowski, K., *et al.,* Biological consequences of zinc deficiency in the pathomechanisms of selected diseases. *J Biol Inorg Chem.*2014;***19***(7):p. 1069-79.
52. Ranasinghe, P., *et al.,* Effects of Zinc supplementation on serum lipids: a systematic review and meta-analysis. *Nutr Metab (Lond)*. 2015;***12***:p. 26.
53. Kim, J. and S. Lee, Effect of zinc supplementation on insulin resistance and metabolic risk factors in obese Korean women. *Nutr Res Pract.*2012;***6***(3):p. 221-5.
54. Kim, J. and J. Ahn, Effect of zinc supplementation on inflammatory markers and adipokines in young obese women. *Biol Trace Elem Res.*2014;***157***(2):p. 101-6.
55. Payahoo, L., *et al.,* Effects of zinc supplementation on the anthropometric measurements, lipid profiles and fasting blood glucose in the healthy obese adults. *Adv Pharm Bull.*2013;***3***(1):p. 161-5.
56. Yuan, G., *et al.,* C-reactive protein inhibits adiponectin gene expression and secretion in 3T3-L1 adipocytes. *J Endocrinol*.2007; ***194***(2):p. 275-81.
57. Tessari, P., *et al.,* Essential amino acids: master regulators of nutrition and environmental footprint? *Sci. Rep.*2016;***6***;26074.
58. Li, Y.C., *et al.,* Relationships of Dietary Histidine and Obesity in Northern Chinese Adults, an Internet-Based Cross-Sectional Study. *Nutrients.*2016;***8***(7).
59. Lee, J.W., et al., Improved functional recovery of ischemic rat hearts due to singlet oxygen scavengers histidine and carnosine. *J Mol Cell Cardiol.*1999;***31***(1):p. 113-21.
60. Niu, Y.C., et al., Histidine and arginine are associated with inflammation and oxidative stress in obese women. *Br J Nutr.*2012; ***108***(1):p. 57-61.
61. Feng, R.N., *et al.,* Histidine supplementation improves insulin resistance through suppressed inflammation in obese women with the metabolic syndrome: a randomised controlled trial. *Diabetologia.*2013;***56***(5): p. 985-94.
62. Andou, A., *et al.,* Dietary histidine ameliorates murine colitis by inhibition of proinflammatory cytokine production from macrophages. *Gastroenterology.*2009;***136***(2):p. 564-74 e2.
63. Murakami, S., Role of taurine in the pathogenesis of obesity. *Mol Nutr Food Res*. 2015;***59***(7):p. 1353-63
64. Rosa, F.T., *et al.,* Oxidative stress and inflammation in obesity after taurine supplementation: a double-blind, placebo-controlled study. *Eur J Nutr.*2014;***53***(3): p. 823-30.
65. Ide, T., *et al.,* mRNA expression of enzymes involved in taurine biosynthesis in rat adipose tissues. *Metabolism.*2002;***51***(9):p. 1191-7.
66. Jeevanandam, M., L. Ramias, and W.R. Schiller, Altered plasma free amino acid levels in obese traumatized man. *Metabolism.*1991; ***40***(4):p. 385-90.
67. Zhang, M., *et al.,* Beneficial effects of taurine on serum lipids in overweight or obese non-diabetic subjects. *Amino Acids.*2004;***26***(3): p. 267-71.
68. Marcinkiewicz, J., *et al.,* Taurine chloramine, a product of activated neutrophils, inhibits in vitro the generation of nitric oxide and other macrophage inflammatory mediators. *J Leukoc Biol.*1995;***58***(6):p. 667-74.
69. Barua, M., Y. Liu, and M.R. Quinn, Taurine chloramine inhibits inducible nitric oxide synthase and TNF-alpha gene expression in activated alveolar macrophages: decreased NF-kappaB activation and IkappaB kinase

activity. *J Immunol*.2001;***167***(4):p. 2275-81.

70. Mehrdadi, P., ***et al.,*** The Effect of Coenzyme Q10 Supplementation on Circulating Levels of Novel Adipokine Adipolin/CTRP12 in Overweight and Obese Patients with Type 2 Diabetes. *Exp Clin Endocrinol Diabetes.* 2017; ***125***(3):p. 156-162.
71. Alam, M.A. and M.M. Rahman, Mitochondrial dysfunction in obesity: potential benefit and mechanism of Co-enzyme Q10 supplementation in metabolic syndrome. *J Diabetes Metab Disord*.2014;***13***: p. 60.
72. Marcoff, L. and P.D. Thompson, The role of coenzyme Q10 in statin-associated myopathy: a systematic review. *J Am Coll Cardiol*. 2007; ***49***(23):p. 2231-7.
73. Pravst, I., K. Zmitek, and J. Zmitek, Coenzyme Q10 contents in foods and fortification strategies. *Crit Rev Food Sci Nutr.*2010; ***50***(4): p. 269-80.
74. Weber, C., A. Bysted, and G. Holmer, Coenzyme Q10 in the diet--daily intake and relative bioavailability. *Mol Aspects Med.*1997; ***18*** Suppl: p. S251-4.
75. Saini, R., Coenzyme Q10: The essential nutrient. *J Pharm Bioallied Sci*.2011;***3***(3): p. 466-7.
76. Molyneux, S., *et al.,* The bioavailability of coenzyme Q10 supplements available in New Zealand differs markedly. *N Z Med J*.2004; ***117***(1203):p. U1108.
77. Menke, T., *et al.,* Comparison of coenzyme Q10 plasma levels in obese and normal weight children. *Clin Chim Acta*.2004; ***349***(1-2): p. 121-7.
78. Lee, Y.-J., *et al.,* Effects of Coenzyme Q10on Arterial Stiffness, Metabolic Parameters, and Fatigue in Obese Subjects: A Double-Blind Randomized Controlled Study. *Journal of Medicinal Food*.2011;***14***(4):p. 386-390.
79. Jafarvand, E., *et al.,* Effects of coenzyme Q10 supplementation on the anthropometric variables, lipid profiles and liver enzymes in patients with non-alcoholic fatty liver disease. *Bangladesh Journal of Pharmacology*.2015; ***11***(1):p. 35.
80. Raygan, F., *et al.,* The effects of coenzyme Q10 administration on glucose homeostasis parameters, lipid profiles, biomarkers of inflammation and oxidative stress in patients with metabolic syndrome. *Eur J Nutr.*2016; ***55***(8):p. 2357-2364.
81. Zhai, J., *et al.,* Effects of Coenzyme Q10 on Markers of Inflammation: A Systematic Review and Meta-Analysis. *PLoS One*.2017; ***12***(1):p. e0170172.
82. Fan, L., *et al.,* Effects of coenzyme Q10 supplementation on inflammatory markers: A systematic review and meta-analysis of randomized controlled trials. *Pharmacol Res*. 2017;***119***:p. 128-136.