Glutamine diet supplementation prevents obesity through inhibiting inflammation

Ying Yang
Department of Molecular Biology and Biochemistry; School of Biological Sciences, University of California, Irvine, Irvine, CA 92697, USA **Correspondence**: yingy33@uci.edu

Abstract

Obesity has become a serious health concern worldwide because it is associated with a higher risk of heart diseases, diabetes, and even certain types of cancers. Since diet and lifestyle adjustments could be very challenging, there has been growing interest in dietary supplements to promote bodyweight loss and decrease the relapse rate. Therefore, many different kinds of food supplementations are now popular in the United States; however, the effects and mechanisms of most supplementations are still understudied. It has been established that obesity is characterized by chronic inflammation in white adipose tissue. Interestingly, glutamine, which is normally used to boost the immune system has shown the function of decreasing body weight and composition of fat tissues in humans and animals by reducing obesity-related inflammation. However, the underlying mechanism of dietary glutamine's effect on obesity is still far from clear. Here, in this review, we will discuss the current understanding of the use of glutamine supplementation as a treatment for obesity. The elucidation of the current dietary strategies using glutamine may highlight new approaches for obesity and diabetes treatment.
Keywords: Obesity, supplementations, glutamine, inflammation

Obesity has shown an unprecedented increase worldwide in the last several decades. According to recently published statistics, 39.8% of adults in the United States have obesity, which indicates more than 93 million people are suffering from it (1). Since obesity may increase the risks for other diseases such as cardiovascular disease, arthritis, hypertension, hyperlipidemia, non-alcoholic fatty liver disease, type 2 diabetes (T2D) and some types of cancers (2), it is considered a serious medical problem that affects the development of metabolic diseases (3). Specifically, obesity is the leading risk for T2D (4), which is evidenced by obese adults having three to seven times higher risk of developing T2D compared to those individuals with normal weight. Additionally, obesity is associated with up to 30% higher in medical costs than those with normal weight (5). Thus, obesity has attracted considerable attention to societies.

Besides surgery, the current medical treatments for obesity approved by the Food and Drug Administration (FDA) include Orlistat (Xenical), Lorcaserin (Belviq), Phentermine and topiramate (Qsymia), Bupropion/ naltrexone (Contrave), and Exenatide (Byetta). Unfortunately, the effects of these medicines may wane over time, and some may even have severe side effects. Meanwhile, it is common that people who lose weight regain the weight within a short time (6) no matter what treatment methods they try. This suggests that more effective and safe treatments are urgently needed for obese patients. This review mainly focuses on recently discovered diet supplementation interventions, with a specific focus on glutamine, and discusses the possible mechanisms of actions of glutamine supplementation on inflammation.

Dietary supplementation in treating obesity

According to the FDA, dietary supplements are products taken by mouth which contain a "dietary ingredient" such as vitamins, minerals, amino acids, herbs or some other substances in the diet. Usually, dietary supplements can be administered as tablets, capsules, powders, energy bars, and liquids. Compared to pharmacologic agents and surgery, dietary supplements represent alternatives to

traditional therapy because most of the ingredients have a low-toxicity profile and low cost. Since dietary supplements do not require premarket review or approval by the FDA, many ingredients are studied and have shown to promote weight loss and reduce body fat by different biological mechanisms (Table 1). So far, the data from scientific publications on each ingredient varies considerably and with limited information on the safety and efficacy. In addition, more studies tried to use supplement combinations partially due to the failures of a single dietary supplement.

Supplement	**Possible Mechanism**	**Reference**
Bitter orange	Promote lipolysis; inhibit cyclic adenosine monophosphate (cAMP)	(7)
β-glucans	Non-digestible fiber contains linear β-1,3, 1-4-linkages	(8)
Capsaicin	Increase peroxisome proliferator activated receptor gamma (PPAR-γ), uncoupling protein 1 (UCP-1), and peroxisome proliferator activated receptor gamma coactivator (PGC-1α)	(9)
Carnitine	Decrease the intramitochondrial acetyl-CoA/ CoA ratio and activate pyruvate dehydrogenase complex (PDHC)	(10)
Chitosan	An insoluble fiber	(11)
Forskolin	Stimulate cAMP	(12)
Fucoxanthin	Decrease the expression of acetyl-CoA carboxylase; decrease the expression of PPAR-γ, CCAAT enhancer binding proteins (C-EBPα), sterol regulatory element binding protein 1 (SREBP-1c) at the late stages of adipocyte differentiation; increase the expression of PPAR-γ, C-EBPα, SREBP-1c, fatty acid binding proteins (FABP), lipoprotein lipase, and glucose transporter4 (GLUT4) at the early stages of adipocyte differentiation	(13)
Garcinia cambogia	Inhibit citrate lyase	(14)
Glucomannan	Human salivary and pancreatic amylase cannot split β-1,4-linkages	(15)
Green coffee	Inhibit fatty acid synthase, hydroxymethylglutaryl-CoA reductase, and acyl-CoA-cholesterol acyltransferase; promote PPAR-γ expression	(16)
Guar gum	β-1,4-linkages	(17)
Hoodia gordonii	Increase hypothalamic ATP production	(18)
Irvingia gabonensis	Inhibit the expression of PPAR-γ and leptin; increase adiponectin expression	(19)
Raspberry ketone	Decrease the expression of PPAR-γ, C-EBPα, FABP2, acetyl-CoA carboxylase 1, fatty acid synthase, and stearoyl-CoA desaturase 1; increase adipose triglyceride lipase, hormone-sensitive lipase and carnitine palmitoyl transferase	(20, 21)
Pyruvate	Unclear	(22, 23)
Vitamin D	Reduce inflammation	(24)
White kidney bean	Inhibit pancreatic amylase	(25)

Table 1. Dietary supplementation in treating obesity

One possible mechanism of more than half of the ingredients in the most popular supplements is functioning through increasing peroxisome proliferator-activated receptor gamma (PPAR-γ) expression, which is a significant transcription factor regulating fatty acid storage and glucose metabolism. Interestingly, another possible mechanism is that some supplements have effectively inhibited pancreatic lipase activity, especially amylase, to stimulate the white and brown adipose (26). Alternatively, some ingredients are just soluble or insoluble fibers to inhibit fat absorption in the intestine.

Compared to supplements derived from food or product ingredients, there are limited studies on amino acid supplements except for branched-chain amino acids (leucine, isoleucine, and valine), which were shown to provide many physiological and metabolic benefits. Specifically, leucine is considered the main acting ingredient, in branched amino acid supplements, activating the mTOR signaling pathway and initiating protein synthesis (27). Amino acids are building blocks for proteins and are also essential factors in cellular development and repair, reactive oxygen species (ROS) homeostasis, the immune system, and the digestive system. Although amino acids dietary regimens have been comprehensively investigated for cancer therapies (28-30), their effect on obesity and diabetes remains understudied. Meanwhile, several groups consistently reported that the plasma amino acid profiles from obese people indicate a significant decrease in glutamine or its downstream intermediate glutamate (31-33). Therefore, the use of dietary glutamine supplementation to combat obesity has become an appealing approach for further studies in animal models and humans.

Glutamine metabolism

Glutamine, which occupies the central place in the biosynthesis of macromolecules, was considered a non-essential amino acid as the human body has the capability of synthesizing it. Theoretically, glutamine can be produced by glutamate dehydrogenase, which converts α-KG into glutamate, and glutamine synthetase which catalyzes glutamate into glutamine (34). During cell proliferation, glutamine, either from endogenous or exogenous, is an important intermediate to be used for producing amino acids, lipids and redox control molecules.

Four families of solute carrier (SLC)-type transporters are capable of transporting glutamine across the plasma membrane, which are SLC1, SLC6, SLC7 and SLC38. Generally, SLC38 is thought to be the major glutamine transporters (35). After entering cells, glutamine is deamidated to glutamate in mitochondria via glutaminase and then converted to α-KG which serves in replenishing the TCA cycle. During this process, $NADH_2$ or $NADPH_2$ are generated as high energy compounds and produce ATP through the electron transport chain (ETC) with oxidative phosphorylation (36). Then, during the conversion of glutamine to glutamate, the γ-nitrogen is provided for *de novo* synthesis of purine and pyrimidine through four rate-limiting enzymes including carbamoyl phosphate synthetase 2 (CAD), phosphoribosyl pyrophosphate amidotransferase (PPAT), and phosphoribosyl pyrophosphate synthetases 1 and 2 (PRPS1 and PRPS2) (37). Furthermore, mitochondrial glutamate is transported back to the cytosol where glutamate and cysteine are synthesized to gamma-glutamylcysteine by glutamate-cysteine ligase (GCL) followed by glycine binding to the C-terminal of gamma-glutamylcysteine which is catalyzed by glutathione synthetase. These adenosine triphosphate dependent steps are the main process of Glutathione biosynthesis (38).

Glutamine supplement decreases fat tissue inflammation

Obesity, which is defined by an excessive amount of body fat, results from a combination of genetics, overeating, psychological factors, personal diet, and exercise choices. Technically, not all body fat is closely linked to diseases (39), but fat accumulating around the central or

abdominal area has been associated with a statistically higher risk of disease including diabetes, heart disease, hypertension, and insulin resistance (40). Additionally, white adipose tissue (WAT) in the visceral fat was reported as a significant source of circulating free fatty acids (FFA) and a key factor for the occurrence of multiple risk changes (41). Recent discoveries suggest that there were increased inflammatory factors in the blood of obese subjects. Moreover, increased macrophages infiltration in WAT is often observed in patients and animals with obesity compared to their lean counterparts. These observations lead researchers to identify obesity as a low graded but chronic inflammatory state (42).

Physiologically, WAT contains not only adipocytes, but also macrophages, leukocytes, fibroblasts, cell progenitors, and endothelial cells (39). As new studies suggested, WAT is not just a passive energy reservoir but activates a chronic inflammatory response in obese humans and animals. The first observation linking obesity to inflammation was associated with increased secretion of pro-inflammatory mediators into the circulation system. Many cytokines and proteins are secreted to induce the inflammation in WAT, which include the interleukin family (such as IL-1β, IL-6, IL-8, and IL-10), inflammatory cytokines (such as TNFα, IFNγ, haptoglobin, and serum amyloid A (SAA)), chemokines (such as monocyte chemoattractant protein (MCP-1), angiopoietins, metallothioneins, and macrophage inflammatory protein-1α (MIP-1α)), and some other factors like transforming growth factor-β (TGF- β) and retinol-binding protein-4 (RBP4) (43).

The current understanding of the progress on the inflammation in WAT is that, after long term accumulation of excess lipids in WAT, nuclear factor-κB (NF- κB), c-Jun N-terminal kinase (JNK), p44/42 mitogen activated kinase (ERK), nuclear subunit p65, and TLR target genes expression are activated in immune cells (44). Due to the activation of these pro-inflammatory signaling pathways, the production of chemokines, leukotrienes, adhesion molecules, and chemoattractant molecules are increased and released into the circulation. Then multiple proteins favor the recruitment of monocytes and other inflammatory cells to infiltrate the WAT (45). For instance, in adipose tissue, endothelial cells can release ICAM-1, VCAM-1, E-selectin, and P-selectin in response to increased free fatty acids. These molecules promote the adhesion of inflammatory T cells and monocytes as well as leukocytes. These hypotheses were confirmed as macrophage infiltration was inhibited by weight loss (46, 47).

Recent studies showed that most cells depend on extracellular input of glutamine because the endogenous biosynthetic pathway is not sufficient to meet the normal demands. Under some severe catabolic states such as trauma, sepsis or severe cellular stress, the body needs much more exogenous glutamine to counteract its increased consumption (48, 49). Thus, clinical studies have explored the benefits of using a glutamine supplement in cases of critical illnesses (49-51). Although glutamine's effects on body weight, lipid synthesis, and glucose homeostasis have been investigated, how glutamine combats obesity is still unknown. Since glutamine level has been considered as a crucial factor for immune system functions, especially for neutrophils and macrophages (52, 53), researchers are trying to test the effect of glutamine supplementation on fat tissue inflammations, which was discovered commonly in obesity (Table 2).

Glutamine	**Samples**	**Method**	**Possible Mechanism**	**Reference**
30g per day (0.4g/kg per day)	Human	Oral	Decrease lipopolysaccharides (LPS)	(33)
30g per day	Human	Oral	Change gut microbiota	(54)

0.5g/kg per day	Female	Oral	-	(55)
30g per day	Human	Oral	-	(56)
2.4g/kg	Rat	Oral gavage and drinking water	Decrease LPS	(33)
-	Mice	Diet	Inhibit fatty acid oxidation	(57)

Table 2. Glutamine supplementation on fat tissue inflammations

Preventing obesity using glutamine suppleme -ntation through inhibiting inflammation

Excluding the possibility that glutamine stimulates the release of the glucagon-like peptide 1 (58), which might induce the reduction of appetite upon the use of glutamine dietary supplements, the benefits of glutamine supplementation in combating obesity was revealed by several studies, yet, the exact mechanisms are still unclear. Since the growing focus on immunometabolism, which is the interaction of immunity and metabolism, several mechanisms to explain the effect of glutamine by reducing the inflammation in WAT will be discussed here (Figure. 1).

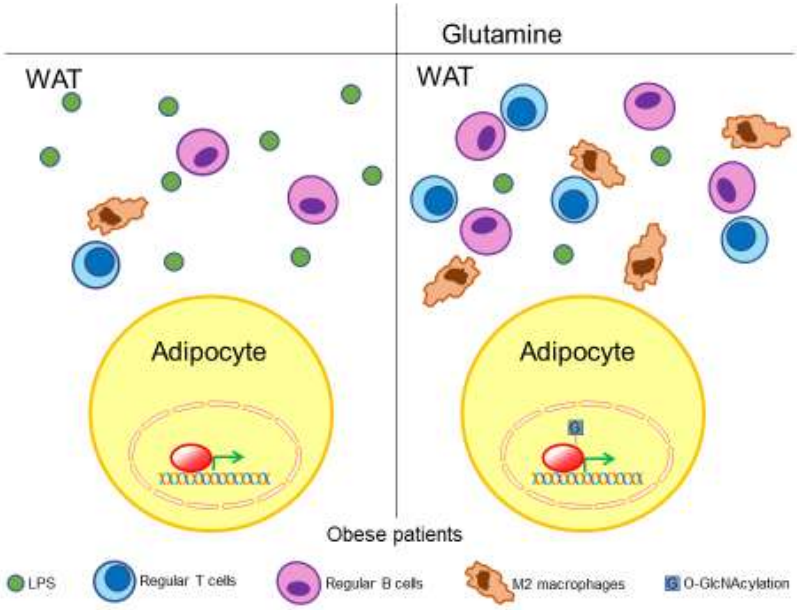

Figure 1. The model of glutamine mediated regulation of inflammatory

1. Glutamine reduces Lipopolysaccharides (LPS) induced inflammation

A high amount of fat in the diet can alter the gut microbial composition, which leads to increased intestinal permeability (59). Because of that, LPS, a gut-derived endotoxin, enters circulation and activates both macrophages and adipocytes to trigger the secretion of a large number of cytokines. Some studies used LPS as a significant parameter to explain the effect of glutamine supplementation (Table 2) as glutamine can repair gut barrier dysfunction by fueling enterocytes and colonocytes. Thus, glutamine can inhibit LPS induced hypoxia-inducible factor (HIF) pathway, reactive oxygen species (ROS) production, and NF-κB pathway activation in WAT.

2. Glutamine promotes M2 macrophage polarization

In response to the increased amount of FFA in the microenvironment of WAT, macrophages are activated by multiple different signals to secrete pro-inflammatory cytokines and molecules. Macrophages are divided into two groups: M1, classically activated macrophages, and M2, alternatively activated macrophages. Based on current evidence, M2 macrophages induce the resolution phase of inflammation. Glutamine was shown to modulate the polarization of M2 macrophages in two ways. First, α-ketoglutarate (α-KG), a downstream metabolite of glutamine, is essential for increasing oxidative phosphorylation (OXPHOS) and fatty acid oxidation (FAO) in M2 macrophages through histone modification regulated gene expression (60). The other pathway is mediated through the glutamine dependent UDP-N-acetylglucosamine (GlcNAc) pathway since the synthesis of UDP-GlcNAc is critical for the polarization of M2 macrophages. Therefore, glutamine may regulate the resolution phase of inflammation through M2 macrophages.

3. Glutamine promotes regulatory T and B cells activation

Emerging evidence suggested that regulatory T (Treg) (61) and B (Breg) cells (62) have significant roles in adipose tissue homeostasis. Compared to obese patients, Treg and Breg cells are predominant in the WAT in lean individuals (63), though the mechanisms of their contribution are still unclear.

Treg cells suppress the activation and functions of effector T cells and negatively regulate immune responses (64). Especially, in diet-induced obesity mice model, Treg cells are dramatically reduced, which is consistent with that expanding Treg cells in HFD-fed mice improves metabolism (63). Recently, dietary glutamine was observed to be critical for the proliferation and activation of Treg cells (65). The underlying mechanism might be glutaminolysis is critical for replenishing the TCA intermediates and support Treg cells' activation through mTORC1 signaling (66). Furthermore, due to elevated ERK signaling, Treg cells' activation induces a great increase in glutamine import by activating the expression of glutamine transporters, such as SLC38A1 and SLC38A2, and critical enzymes, such as glutaminase and α-KG conversion-related enzymes (67).

Similar to Treg cells, IL-10 secreting regulatory B cells were discovered to suppress the inflammatory response and improve glucose sensitivity in obese mice. Due to their function of inducing Treg cells, Breg cells inhibit Th1/Th17 cells activation (68). This observation was consistent with the reports that Breg cells deficiency increased the infiltration of CD8+ T cells and M1 macrophages into adipose tissue of obese mice, and deleting Breg cells in lean mice leads to insulin resistance and limited fasting glucose clearance (69). Glutamine is a critical immunomodulatory nutrient for the function of B cells. In stimulated Breg cells, rapidly increased expression of glutamine transporter genes suggested that extracellular glutamine induced the activation response (70). Thus, both animal and human studies indicated an increased level of glutamine enhanced the activation of Treg and Breg cells (71), though the underlying mechanisms need to be clarified.

4. Glutamine alter inflammation-related gene expression by O-GlcNAcylation

The O-linked β-N-acetylglucosamine (O-GlcNAc) glycosylation is a dynamic post-translational modification that regulates various signaling pathways. O-GlcNAc transferase (OGT) and O-GlcNAcase (OGA) are the only two enzymes that regulate O-Glc NAcylation. Diet-induced obesity increases the activity of OGT (72, 73) and a higher level of O-Glc NAcylation is considered to be significant in obesity statistically. Glutamine has been shown to lower the levels of O-Glc NAcylation in adipocytes through the inhibition of glycolysis and further decrease UDP-GlcNAc levels (74). Thus, the inflammation associated gene profile could be reversed by the supplementation of glutamine.

Conclusion

Obesity has become a serious consequence of the current fast life pace and the unhealthy western diet. Since dietary supplements are often easier to implement compared to strict dietary interventions and physical exercise, many studies focused on the development of new supplementations. Recently, new evidence demonstrated that glutamine dietary supplements can reduce body weight and fat mass and alleviate the inflammation in the adipose tissue associated with obesity. So far, some evidence showed that glutamine may reduce inflammation by reducing LPS, promoting M2 macrophage polarization, promoting regulatory T and B cells activation and regulating inflammation-related gene expression. But the mechanisms underlying dietary glutamine inhibits obesity is still unclear. Thus, it is imperative to study the signaling pathways affecting cell metabolism, especially in the adipose tissue upon the use of glutamine supplementation as a new avenue in the treatment of obesity.

Abbreviations list

T2D: type 2 diabetes; FDA: the Food and Drug Administration; cAMP: cyclic adenosine monophosphate; PPAR-γ: peroxisome proliferator activated receptor gamma; UCP-1: uncoupling protein 1; PGC-1α: peroxisome proliferator activated receptor gamma coactivator; PDHC: pyruvate dehydrogenase complex; C-EBPα: CCAAT enhancer binding proteins; SREBP-1c: sterol regulatory element binding protein 1; FABP: fatty acid binding proteins; GLUT4: glucose transporter type 4; mTOR: mammalian target of rapamycin; ROS: reactive oxygen species; WAT: white adipose tissue; FFA: free fatty acids; IL: interleukin; TNFα: tumor necrosis factor; IFNγ: type II interferon; SAA: serum amyloid; MCP-1: monocyte chemoattractant protein; MIP-1α: macrophage inflammatory protein-1α; TGF-β: transforming growth factor-β; RBP4: retinol-binding protein-4; NF- κB: nuclear factor-κB; JNK: c-Jun N-terminal kinase; ERK: p44/42 mitogen activated kinase; TLR: Toll-like receptor; SLC: solute carrier; α-KG: α-ketoglutarate; TCA: tricarboxylic acid cycle; NADH: nicotinamide adenine dinucleotide; NADPH: nicotinamide adenine dinucleotide phosphate; ETC: electron transport chain; CAD: carbamoylphosphate synthetase 2; PPAT: phosphoribosyl pyrophosphate amidotransferase; PRPS1 and 2: phosphoribosyl pyrophosphate synthetases 1 and 2; GCL: glutamate cysteine ligase; ICAM-1: intercellular adhesion molecule 1; VCAM-1: vascular cell adhesion protein 1; LPS: lipopolysaccharides; HIF: hypoxia induced factor; OXPHOS: oxidative phosphorylation; FAO: fatty acid oxidation; GlcNAc: N-acetylglucosamine; Treg: regulatory T cells; Breg: regulatory B cells; O-GlcNAc: O-linked β-N-acetylglucosamine; OGT: O-GlcNAc transferase; OGA: O-GlcNAcase.

References

1. Hales CM, Carroll MD, Fryar CD, Ogden CL. Prevalence of Obesity Among Adults and Youth: United States, 2015-2016. NCHS data brief. 2017(288):1-8. Epub 2017/11/21. PubMed PMID: 29155689.

2. Guidelines (2013) for managing overweight and obesity in adults. Preface to the Expert Panel Report (comprehensive version which includes systematic evidence review, evidence statements, and recommendations). Obesity (Silver Spring, Md). 2014;22 Suppl 2:S40. Epub 2014/06/26. doi: 10.1002/oby.20822. PubMed PMID: 24961824.

3. Burhans MS, Hagman DK, Kuzma JN, Schmidt KA, Kratz M. Contribution of Adipose Tissue Inflammation to the Development of Type 2 Diabetes Mellitus. Comprehensive Physiology. 2018;9(1):1-58. Epub 2018/12/15. doi: 10.1002/cphy.c170040. PubMed PMID: 30549014; PMCID: PMC6557583.

4. Barnes AS. The epidemic of obesity and diabetes: trends and treatments. Texas Heart Institute journal. 2011;38(2):142-4. Epub

2011/04/16. PubMed PMID: 21494521; PMCID: PMC3066828.
5. Biener A, Cawley J, Meyerhoefer C. The High and Rising Costs of Obesity to the US Health Care System. Journal of general internal medicine. 2017;32(Suppl 1):6-8. Epub 2017/03/09. doi: 10.1007/s11606-016-3968-8. PubMed PMID: 28271429; PMCID: PMC5359159.
6. Montesi L, El Ghoch M, Brodosi L, Calugi S, Marchesini G, Dalle Grave R. Long-term weight loss maintenance for obesity: a multidisciplinary approach. Diabetes, metabolic syndrome and obesity : targets and therapy. 2016;9:37-46. Epub 2016/03/26. doi: 10.2147/dmso.s89836. PubMed PMID: 27013897; PMCID: PMC4777230.
7. Haaz S, Fontaine KR, Cutter G, Limdi N, Perumean-Chaney S, Allison DB. Citrus aurantium and synephrine alkaloids in the treatment of overweight and obesity: an update. Obesity reviews : an official journal of the International Association for the Study of Obesity. 2006;7(1):79-88. Epub 2006/01/27. doi: 10.1111/j.1467-789X.2006.00195.x. PubMed PMID: 16436104.
8. El Khoury D, Cuda C, Luhovyy BL, Anderson GH. Beta glucan: health benefits in obesity and metabolic syndrome. Journal of nutrition and metabolism. 2012;2012:851362. Epub 2011/12/22. doi: 10.1155/2012/851362. PubMed PMID: 22187640; PMCID: PMC3236515.
9. Kang JH, Goto T, Han IS, Kawada T, Kim YM, Yu R. Dietary capsaicin reduces obesity-induced insulin resistance and hepatic steatosis in obese mice fed a high-fat diet. Obesity (Silver Spring, Md). 2010;18(4):780-7. Epub 2009/10/03. doi: 10.1038/oby.2009.301. PubMed PMID: 19798065.
10. Uziel G, Garavaglia B, Di Donato S. Carnitine stimulation of pyruvate dehydrogenase complex (PDHC) in isolated human skeletal muscle mitochondria. Muscle & nerve. 1988;11(7):720-4. Epub 1988/07/01. doi: 10.1002/mus.880110708. PubMed PMID: 3405240.
11. Mhurchu CN, Poppitt SD, McGill AT, Leahy FE, Bennett DA, Lin RB, Ormrod D, Ward L, Strik C, Rodgers A. The effect of the dietary supplement, Chitosan, on body weight: a randomised controlled trial in 250 overweight and obese adults. International journal of obesity and related metabolic disorders : journal of the International Association for the Study of Obesity. 2004;28(9):1149-56. Epub 2004/08/18. doi: 10.1038/sj.ijo.0802693. PubMed PMID: 15311218.
12. Henderson S, Magu B, Rasmussen C, Lancaster S, Kerksick C, Smith P, Melton C, Cowan P, Greenwood M, Earnest C, Almada A, Milnor P, Magrans T, Bowden R, Ounpraseuth S, Thomas A, Kreider RB. Effects of coleus forskohlii supplementation on body composition and hematological profiles in mildly overweight women. Journal of the International Society of Sports Nutrition. 2005;2:54-62. Epub 2008/05/27. doi: 10.1186/1550-2783-2-2-54. PubMed PMID: 18500958; PMCID: PMC2129145.
13. Maeda H, Kanno S, Kodate M, Hosokawa M, Miyashita K. Fucoxanthinol, Metabolite of Fucoxanthin, Improves Obesity-Induced Inflammation in Adipocyte Cells. Marine drugs. 2015;13(8):4799-813. Epub 2015/08/08. doi: 10.3390/md13084799. PubMed PMID: 26248075; PMCID: PMC4557005.
14. Onakpoya I, Hung SK, Perry R, Wider B, Ernst E. The Use of Garcinia Extract (Hydroxycitric Acid) as a Weight loss Supplement: A Systematic Review and Meta-Analysis of Randomised Clinical Trials. Journal of obesity. 2011;2011:509038. Epub 2011/01/05. doi: 10.1155/2011/509038. PubMed PMID: 21197150; PMCID: PMC3010674.
15. Keithley JK, Swanson B, Mikolaitis SL, DeMeo M, Zeller JM, Fogg L, Adamji J. Safety and efficacy of glucomannan for weight loss in overweight and moderately obese adults. Journal of obesity. 2013;2013:610908. Epub 2014/02/04. doi: 10.1155/2013/610908. PubMed PMID: 24490058; PMCID: PMC3892933.
16. Prabhakar PK, Doble M. Synergistic effect of phytochemicals in combination with hypoglycemic drugs on glucose uptake in myotubes. Phytomedicine : international journal of phytotherapy and phytopharmacology. 2009;16(12):1119-26. Epub 2009/08/08. doi: 10.1016/j.phymed.2009.05.021. PubMed PMID: 19660925.

17. Papathanasopoulos A, Camilleri M. Dietary fiber supplements: effects in obesity and metabolic syndrome and relationship to gastrointestinal functions. Gastroenterology. 2010;138(1):65-72.e1-2. Epub 2009/11/26. doi: 10.1053/j.gastro.2009.11.045. PubMed PMID: 19931537; PMCID: PMC2903728.
18. MacLean DB, Luo LG. Increased ATP content/production in the hypothalamus may be a signal for energy-sensing of satiety: studies of the anorectic mechanism of a plant steroidal glycoside. Brain research. 2004;1020(1-2):1-11. Epub 2004/08/18. doi: 10.1016/j.brainres.2004.04.041. PubMed PMID: 15312781.
19. Oben JE, Ngondi JL, Blum K. Inhibition of Irvingia gabonensis seed extract (OB131) on adipogenesis as mediated via down regulation of the PPARgamma and leptin genes and up-regulation of the adiponectin gene. Lipids in health and disease. 2008;7:44. Epub 2008/11/19. doi: 10.1186/1476-511x-7-44. PubMed PMID: 19014517; PMCID: PMC2588592.
20. Leu SY, Chen YC, Tsai YC, Hung YW, Hsu CH, Lee YM, Cheng PY. Raspberry Ketone Reduced Lipid Accumulation in 3T3-L1 Cells and Ovariectomy-Induced Obesity in Wistar Rats by Regulating Autophagy Mechanisms. Journal of agricultural and food chemistry. 2017;65(50):10907-14. Epub 2017/11/23. doi: 10.1021/acs.jafc.7b03831. PubMed PMID: 29164883.
21. Lopez HL, Ziegenfuss TN, Hofheins JE, Habowski SM, Arent SM, Weir JP, Ferrando AA. Eight weeks of supplementation with a multi-ingredient weight loss product enhances body composition, reduces hip and waist girth, and increases energy levels in overweight men and women. Journal of the International Society of Sports Nutrition. 2013;10(1):22. Epub 2013/04/23. doi: 10.1186/1550-2783-10-22. PubMed PMID: 23601452; PMCID: PMC3639826.
22. Kalman D, Colker CM, Wilets I, Roufs JB, Antonio J. The effects of pyruvate supplementation on body composition in overweight individuals. Nutrition (Burbank, Los Angeles County, Calif). 1999;15(5):337-40. Epub 1999/06/04. doi: 10.1016/s0899-9007(99)00034-9. PubMed PMID: 10355844.
23. Koh-Banerjee PK, Ferreira MP, Greenwood M, Bowden RG, Cowan PN, Almada AL, Kreider RB. Effects of calcium pyruvate supplementation during training on body composition, exercise capacity, and metabolic responses to exercise. Nutrition (Burbank, Los Angeles County, Calif). 2005;21(3):312-9. Epub 2005/03/31. doi: 10.1016/j.nut.2004.06.026. PubMed PMID: 15797672.
24. Foroughi M, Maghsoudi Z, Ghiasvand R, Iraj B, Askari G. Effect of Vitamin D Supplementation on C-reactive Protein in Patients with Nonalcoholic Fatty Liver. International journal of preventive medicine. 2014;5(8):969-75. Epub 2014/12/10. PubMed PMID: 25489444; PMCID: PMC4258669.
25. Santimone M, Koukiekolo R, Moreau Y, Le Berre V, Rouge P, Marchis-Mouren G, Desseaux V. Porcine pancreatic alpha-amylase inhibition by the kidney bean (Phaseolus vulgaris) inhibitor (alpha-AI1) and structural changes in the alpha-amylase inhibitor complex. Biochimica et biophysica acta. 2004;1696(2):181-90. Epub 2004/02/12. doi: 10.1016/j.bbapap.2003.11.001. PubMed PMID: 14871659.
26. Rios-Hoyo A, Gutierrez-Salmean G. New Dietary Supplements for Obesity: What We Currently Know. Current obesity reports. 2016;5(2):262-70. Epub 2016/04/08. doi: 10.1007/s13679-016-0214-y. PubMed PMID: 27053066.
27. Qin LQ, Xun P, Bujnowski D, Daviglus ML, Van Horn L, Stamler J, He K. Higher branched-chain amino acid intake is associated with a lower prevalence of being overweight or obese in middle-aged East Asian and Western adults. The Journal of nutrition. 2011;141(2):249-54. Epub 2010/12/21. doi: 10.3945/jn.110.128520. PubMed PMID: 21169225; PMCID: PMC3021443.
28. Maddocks ODK, Athineos D, Cheung EC, Lee P, Zhang T, van den Broek NJF, Mackay GM, Labuschagne CF, Gay D, Kruiswijk F, Blagih J, Vincent DF, Campbell KJ, Ceteci F, Sansom OJ, Blyth K, Vousden KH. Modulating the therapeutic response of tumours to dietary serine and glycine starvation. Nature. 2017;544(7650):372-

6. Epub 2017/04/21. doi: 10.1038/nature22056. PubMed PMID: 28425994.
29. Maddocks OD, Berkers CR, Mason SM, Zheng L, Blyth K, Gottlieb E, Vousden KH. Serine starvation induces stress and p53-dependent metabolic remodelling in cancer cells. Nature. 2013;493(7433):542-6. Epub 2012/12/18. doi: 10.1038/nature11743. PubMed PMID: 23242140; PMCID: PMC6485472.
30. Hoffman RM. Clinical Studies of Methionine-Restricted Diets for Cancer Patients. Methods in molecular biology (Clifton, NJ). 2019;1866:95-105. Epub 2019/02/07. doi: 10.1007/978-1-4939-8796-2_9. PubMed PMID: 30725411.
31. Takashina C, Tsujino I, Watanabe T, Sakaue S, Ikeda D, Yamada A, Sato T, Ohira H, Otsuka Y, Oyama-Manabe N, Ito YM, Nishimura M. Associations among the plasma amino acid profile, obesity, and glucose metabolism in Japanese adults with normal glucose tolerance. Nutrition & metabolism. 2016;13:5. Epub 2016/01/21. doi: 10.1186/s12986-015-0059-5. PubMed PMID: 26788116; PMCID: PMC4717594.
32. Bagheri M, Djazayery A, Farzadfar F, Qi L, Yekaninejad MS, Aslibekyan S, Chamari M, Hassani H, Koletzko B, Uhl O. Plasma metabolomic profiling of amino acids and polar lipids in Iranian obese adults. Lipids in health and disease. 2019;18(1):94. Epub 2019/04/11. doi: 10.1186/s12944-019-1037-0. PubMed PMID: 30967146; PMCID: PMC6456979.
33. Abboud KY, Reis SK, Martelli ME, Zordao OP, Tannihao F, de Souza AZZ, Assalin HB, Guadagnini D, Rocha GZ, Saad MJA, Prada PO. Oral Glutamine Supplementation Reduces Obesity, Pro-Inflammatory Markers, and Improves Insulin Sensitivity in DIO Wistar Rats and Reduces Waist Circumference in Overweight and Obese Humans. Nutrients. 2019;11(3). Epub 2019/03/06. doi: 10.3390/nu11030536. PubMed PMID: 30832230; PMCID: PMC6471297.
34. Gustavo Blanco AB. Medical Biochemistry: Academic Press; 2017. 795 p.
35. Bhutia YD, Ganapathy V. Glutamine transporters in mammalian cells and their functions in physiology and cancer. Biochimica et biophysica acta. 2016;1863(10):2531-9. Epub 2016/01/03. doi: 10.1016/j.bbamcr.2015.12.017. PubMed PMID: 26724577; PMCID: PMC4919214.
36. Fan J, Kamphorst JJ, Mathew R, Chung MK, White E, Shlomi T, Rabinowitz JD. Glutamine-driven oxidative phosphorylation is a major ATP source in transformed mammalian cells in both normoxia and hypoxia. Molecular systems biology. 2013;9:712. Epub 2013/12/05. doi: 10.1038/msb.2013.65. PubMed PMID: 24301801; PMCID: PMC3882799.
37. Zhu Y, Li T, Ramos da Silva S, Lee JJ, Lu C, Eoh H, Jung JU, Gao SJ. A Critical Role of Glutamine and Asparagine gamma-Nitrogen in Nucleotide Biosynthesis in Cancer Cells Hijacked by an Oncogenic Virus. mBio. 2017;8(4). Epub 2017/08/16. doi: 10.1128/mBio.01179-17. PubMed PMID: 28811348; PMCID: PMC5559638.
38. Lu SC. Glutathione synthesis. Biochimica et biophysica acta. 2013;1830(5):3143-53. Epub 2012/09/22. doi: 10.1016/j.bbagen.2012.09.008. PubMed PMID: 22995213; PMCID: PMC3549305.
39. Gomez-Hernandez A, Beneit N, Diaz-Castroverde S, Escribano O. Differential Role of Adipose Tissues in Obesity and Related Metabolic and Vascular Complications. International journal of endocrinology. 2016;2016:1216783. Epub 2016/10/22. doi: 10.1155/2016/1216783. PubMed PMID: 27766104; PMCID: PMC5059561.
40. Westphal SA. Obesity, abdominal obesity, and insulin resistance. Clinical cornerstone. 2008;9(1):23-9; discussion 30-1. Epub 2008/12/03. doi: 10.1016/s1098-3597(08)60025-3. PubMed PMID: 19046737.
41. Coelho M, Oliveira T, Fernandes R. Biochemistry of adipose tissue: an endocrine organ. Archives of medical science : AMS. 2013;9(2):191-200. Epub 2013/05/15. doi: 10.5114/aoms.2013.33181. PubMed PMID: 23671428; PMCID: PMC3648822.
42. Tordjman J, Guerre-Millo M, Clement K. Adipose tissue inflammation and liver pathology in human obesity. Diabetes & metabolism. 2008;34(6 Pt 2):658-63. Epub 2009/02/07. doi: 10.1016/s1262-3636(08)74601-9. PubMed PMID: 19195627.
43. Cancello R, Clement K. Is obesity an inflammatory illness? Role of low-grade

inflammation and macrophage infiltration in human white adipose tissue. BJOG : an international journal of obstetrics and gynaecology. 2006;113(10):1141-7. Epub 2006/08/15. doi: 10.1111/j.1471-0528.2006.01004.x. PubMed PMID: 16903845.

44. Huang S, Rutkowsky JM, Snodgrass RG, Ono-Moore KD, Schneider DA, Newman JW, Adams SH, Hwang DH. Saturated fatty acids activate TLR-mediated proinflammatory signaling pathways. Journal of lipid research. 2012;53(9):2002-13. Epub 2012/07/07. doi: 10.1194/jlr.D029546. PubMed PMID: 22766885; PMCID: PMC3413240.

45. Arango Duque G, Descoteaux A. Macrophage cytokines: involvement in immunity and infectious diseases. Frontiers in immunology. 2014;5:491. Epub 2014/10/24. doi: 10.3389/fimmu.2014.00491. PubMed PMID: 25339958; PMCID: PMC4188125.

46. Cancello R, Henegar C, Viguerie N, Taleb S, Poitou C, Rouault C, Coupaye M, Pelloux V, Hugol D, Bouillot JL, Bouloumie A, Barbatelli G, Cinti S, Svensson PA, Barsh GS, Zucker JD, Basdevant A, Langin D, Clement K. Reduction of macrophage infiltration and chemoattractant gene expression changes in white adipose tissue of morbidly obese subjects after surgery-induced weight loss. Diabetes. 2005;54(8):2277-86. Epub 2005/07/28. doi: 10.2337/diabetes.54.8.2277. PubMed PMID: 16046292.

47. Clement K, Viguerie N, Poitou C, Carette C, Pelloux V, Curat CA, Sicard A, Rome S, Benis A, Zucker JD, Vidal H, Laville M, Barsh GS, Basdevant A, Stich V, Cancello R, Langin D. Weight loss regulates inflammation-related genes in white adipose tissue of obese subjects. FASEB journal : official publication of the Federation of American Societies for Experimental Biology. 2004;18(14):1657-69. Epub 2004/11/04. doi: 10.1096/fj.04-2204com. PubMed PMID: 15522911.

48. Yang Y, Ishak Gabra MB, Hanse EA, Lowman XH, Tran TQ, Li H, Milman N, Liu J, Reid MA, Locasale JW, Gil Z, Kong M. MiR-135 suppresses glycolysis and promotes pancreatic cancer cell adaptation to metabolic stress by targeting phosphofructokinase-1. Nature communications. 2019;10(1):809. Epub 2019/02/20. doi: 10.1038/s41467-019-08759-0. PubMed PMID: 30778058; PMCID: PMC6379428.

49. Ying Yang MBIG, Mei Kong. Metabolic adaptations to glutamine deprivation in pancreatic cancer. Journal of Life Sciences. 2019;1(2):26-32.

50. Simsek T, Simsek HU, Canturk NZ. Response to trauma and metabolic changes: posttraumatic metabolism. Ulusal cerrahi dergisi. 2014;30(3):153-9. Epub 2014/01/01. doi: 10.5152/ucd.2014.2653. PubMed PMID: 25931917; PMCID: PMC4379844.

51. Cruzat V, Macedo Rogero M, Noel Keane K, Curi R, Newsholme P. Glutamine: Metabolism and Immune Function, Supplementation and Clinical Translation. Nutrients. 2018;10(11). Epub 2018/10/27. doi: 10.3390/nu10111564. PubMed PMID: 30360490; PMCID: PMC6266414.

52. Ardawi MS, Newsholme EA. Glutamine metabolism in lymphocytes of the rat. The Biochemical journal. 1983;212(3):835-42. Epub 1983/06/15. doi: 10.1042/bj2120835. PubMed PMID: 6882397; PMCID: PMC1153161.

53. Newsholme P, Curi R, Pithon Curi TC, Murphy CJ, Garcia C, Pires de Melo M. Glutamine metabolism by lymphocytes, macrophages, and neutrophils: its importance in health and disease. The Journal of nutritional biochemistry. 1999;10(6):316-24. Epub 2004/11/13. doi: 10.1016/s0955-2863(99)00022-4. PubMed PMID: 15539305.

54. de Souza AZ, Zambom AZ, Abboud KY, Reis SK, Tannihao F, Guadagnini D, Saad MJ, Prada PO. Oral supplementation with L-glutamine alters gut microbiota of obese and overweight adults: A pilot study. Nutrition (Burbank, Los Angeles County, Calif). 2015;31(6):884-9. Epub 2015/05/03. doi: 10.1016/j.nut.2015.01.004. PubMed PMID: 25933498.

55. Laviano A, Molfino A, Lacaria MT, Canelli A, De Leo S, Preziosa I, Rossi Fanelli F. Glutamine supplementation favors weight loss in nondieting obese female patients. A pilot study. European journal of clinical nutrition. 2014;68(11):1264-6. Epub 2014/09/18. doi:

10.1038/ejcn.2014.184. PubMed PMID: 25226827.
56. Mansour A, Mohajeri-Tehrani MR, Qorbani M, Heshmat R, Larijani B, Hosseini S. Effect of glutamine supplementation on cardiovascular risk factors in patients with type 2 diabetes. Nutrition (Burbank, Los Angeles County, Calif). 2015;31(1):119-26. Epub 2014/12/04. doi: 10.1016/j.nut.2014.05.014. PubMed PMID: 25466655.
57. Opara EC, Petro A, Tevrizian A, Feinglos MN, Surwit RS. L-glutamine supplementation of a high fat diet reduces body weight and attenuates hyperglycemia and hyperinsulinemia in C57BL/6J mice. The Journal of nutrition. 1996;126(1):273-9. Epub 1996/01/01. doi: 10.1093/jn/126.1.273. PubMed PMID: 8558312.
58. Tolhurst G, Zheng Y, Parker HE, Habib AM, Reimann F, Gribble FM. Glutamine triggers and potentiates glucagon-like peptide-1 secretion by raising cytosolic Ca2+ and cAMP. Endocrinology. 2011;152(2):405-13. Epub 2011/01/07. doi: 10.1210/en.2010-0956. PubMed PMID: 21209017; PMCID: PMC3140224.
59. Murphy EA, Velazquez KT, Herbert KM. Influence of high-fat diet on gut microbiota: a driving force for chronic disease risk. Current opinion in clinical nutrition and metabolic care. 2015;18(5):515-20. Epub 2015/07/15. doi: 10.1097/mco.0000000000000209. PubMed PMID: 26154278; PMCID: PMC4578152.
60. Ren W, Xia Y, Chen S, Wu G, Bazer FW, Zhou B, Tan B, Zhu G, Deng J, Yin Y. Glutamine Metabolism in Macrophages: A Novel Target for Obesity/Type 2 Diabetes. Advances in nutrition (Bethesda, Md). 2019;10(2):321-30. Epub 2019/02/13. doi: 10.1093/advances/nmy084. PubMed PMID: 30753258; PMCID: PMC6416106.
61. Wang Q, Wu H. T Cells in Adipose Tissue: Critical Players in Immunometabolism. Frontiers in immunology. 2018;9:2509. Epub 2018/11/22. doi: 10.3389/fimmu.2018.02509. PubMed PMID: 30459770; PMCID: PMC6232870.
62. Shaikh SR, Haas KM, Beck MA, Teague H. The effects of diet-induced obesity on B cell function. Clinical and experimental immunology. 2015;179(1):90-9. Epub 2014/08/30. doi: 10.1111/cei.12444. PubMed PMID: 25169121; PMCID: PMC4260901.
63. Feuerer M, Herrero L, Cipolletta D, Naaz A, Wong J, Nayer A, Lee J, Goldfine AB, Benoist C, Shoelson S, Mathis D. Lean, but not obese, fat is enriched for a unique population of regulatory T cells that affect metabolic parameters. Nature medicine. 2009;15(8):930-9. Epub 2009/07/28. doi: 10.1038/nm.2002. PubMed PMID: 19633656; PMCID: PMC3115752.
64. Abul Abbas AHL, Shiv Pillai. Cellular and Molecular Immunology2014.
65. Hsiung YC, Liu JJ, Hou YC, Yeh CL, Yeh SL. Effects of dietary glutamine on the homeostasis of CD4+ T cells in mice with dextran sulfate sodium-induced acute colitis. PloS one. 2014;9(1):e84410. Epub 2014/01/15. doi: 10.1371/journal.pone.0084410. PubMed PMID: 24416230; PMCID: PMC3887000.
66. Wei J, Raynor J, Nguyen TL, Chi H. Nutrient and Metabolic Sensing in T Cell Responses. Frontiers in immunology. 2017;8:247. Epub 2017/03/25. doi: 10.3389/fimmu.2017.00247. PubMed PMID: 28337199; PMCID: PMC5343023.
67. Carr EL, Kelman A, Wu GS, Gopaul R, Senkevitch E, Aghvanyan A, Turay AM, Frauwirth KA. Glutamine uptake and metabolism are coordinately regulated by ERK/MAPK during T lymphocyte activation. Journal of immunology (Baltimore, Md : 1950). 2010;185(2):1037-44. Epub 2010/06/18. doi: 10.4049/jimmunol.0903586. PubMed PMID: 20554958; PMCID: PMC2897897.
68. Nishimura S, Manabe I, Takaki S, Nagasaki M, Otsu M, Yamashita H, Sugita J, Yoshimura K, Eto K, Komuro I, Kadowaki T, Nagai R. Adipose Natural Regulatory B Cells Negatively Control Adipose Tissue Inflammation. Cell metabolism. 2013;18(5):759-66. Epub 2013/11/12. doi: 10.1016/j.cmet.2013.09.017. PubMed PMID: 24209772.
69. Wang RX, Yu CR, Dambuza IM, Mahdi RM, Dolinska MB, Sergeev YV, Wingfield PT, Kim SH, Egwuagu CE. Interleukin-35 induces regulatory B cells that suppress autoimmune disease. Nature medicine. 2014;20(6):633-41.

Epub 2014/04/20. doi: 10.1038/nm.3554. PubMed PMID: 24743305; PMCID: PMC4048323.
70. Shannon Heyse TC, Cheryl Doughty and Thomas Chiles. The regulation and role of L-glutamine in B-lymphocyte activation. The journal of immunology. 2015;194(1).
71. Coeffier M, Marion R, Ducrotte P, Dechelotte P. Modulating effect of glutamine on IL-1beta-induced cytokine production by human gut. Clinical nutrition (Edinburgh, Scotland). 2003;22(4):407-13. Epub 2003/07/26. doi: 10.1016/s0261-5614(03)00040-2. PubMed PMID: 12880609.
72. Yang Y, Fu M, Li MD, Zhang K, Zhang B, Wang S, Liu Y, Ni W, Ong Q, Mi J, Yang X. O-GlcNAc transferase inhibits visceral fat lipolysis and promotes diet-induced obesity. Nature communications. 2020;11(1):181. Epub 2020/01/12. doi: 10.1038/s41467-019-13914-8. PubMed PMID: 31924761; PMCID: PMC6954210.
73. Li MD, Vera NB, Yang Y, Zhang B, Ni W, Ziso-Qejvanaj E, Ding S, Zhang K, Yin R, Wang S, Zhou X, Fang EX, Xu T, Erion DM, Yang X. Adipocyte OGT governs diet-induced hyperphagia and obesity. Nature communications. 2018;9(1):5103. Epub 2018/12/07. doi: 10.1038/s41467-018-07461-x. PubMed PMID: 30504766; PMCID: PMC6269424.
74. Petrus P, Lecoutre S, Dollet L, Wiel C, Sulen A, Gao H, Tavira B, Laurencikiene J, Rooyackers O, Checa A, Douagi I, Wheelock CE, Arner P, McCarthy M, Bergo MO, Edgar L, Choudhury RP, Aouadi M, Krook A, Ryden M. Glutamine Links Obesity to Inflammation in Human White Adipose Tissue. Cell metabolism. 2019. Epub 2019/12/24. doi: 10.1016/j.cmet.2019.11.019. PubMed PMID: 31866443.