Review

Dietary supplements for lipedema

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Keywords

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Summary

Lipedema is a chronic disease that mostly manifests in females as the abnormal distribution of subcutaneous adipose connective tissue, usually coupled with bruising, pain, and edema. Lipedema molecular pathophysiology is currently not clear, but several studies suggest that genetics and hormonal imbalance participate in lipedema pathogenesis. Women with lipedema present in some cases with elevated body mass index, and the appearance of obesity in addition to lipedema, where the obesity can cause serious health issues as in lipedema-free individuals with obesity, such as diabetes and cardiovascular disorders. Unlike obesity, lipedema tissue does not respond well to diet or physical exercise alone. Therefore, in this review we discuss the effect of various dietary supplements that, along with diet and physical exercise, cause fat burning and weight loss, and which could potentially be important in the treatment of lipedema. Indeed, an effective fat burner should convert stored fats into energy, mobilize and break down triglycerides in adipocytes, boost metabolism and inhibit lipogenesis. Common ingredients of fat burning supplements are green tea, caffeine, chromium, carnitine, and conjugated linoleic acid. The use of fat burners could act synergistically with a healthy diet and physical exercise for decreasing adipose tissue deposition in patients with lipedema and resolve related health issues. The effects of fat burners in human studies are sometimes contradictory, and further studies should test their effectiveness in treating lipedema.

Introduction

Lipedema is a chronic and progressive disease that is characterized by the abnormal distribution of subcutaneous adipose connective tissue causing disproportionate and painful limbs [1]. Usually, it develops in females during their time of puberty or other times of hormonal, shape and weight change, including menopause or childbirth. Lipedema is characterized by the symmetrical enhancement of nodular subcutaneous adipose connective tissue on the lower body and arms, while leaving the upper trunk, hands, and feet unaffected. Lipedema tissue often affects the lower abdomen, thighs, buttocks, and calves. In about 80% of cases, lipedema can also affect the arms, whereas the hands and feet are not affected [2]. Although lipedema greatly affects women's health around the world, it remains either undiagnosed or misdiagnosed as other similar diseases, such as obesity or lymphedema [3]. Polygenic susceptibility along with lymphatic, hormonal and microvascular disorders might be at least partially responsible for the development of lipedema. Moreover, lipedema can progress to the point where lymphedema develops. The major causes for the onset of lymphedema include genetic susceptibility, lymphatic vessel malformations, surgery and trauma [4]. Lipedema does not respond well to restrictive diets, contrary to usual forms of obesity. Thus, lipedema leads to a disproportionate increase in lower body tissue that stubbornly retains its shape (waist to ankles) after diets or bariatric surgery. Lipedema is not restricted to just subcutaneous adipose connective tissue, in fact, women with lipedema had significantly lower muscle strength and a non-significant, but clinically relevant lower exercise-endurance capacity than women with obesity [5]. Excess subcutaneous adipose connective tissue and lower muscle function results in later stages, patients with lipedema with an elevated body mass index, increasing the risk of developing severe obesity with metabolic complications, which in turn worsens the symptoms of lipedema [1, 6-8]. The Mediterranean diet and ketogenic diet have been proposed for lipedema treatment, showing weight loss in both cases but failure to reduce pain with either intervention, and failure to reduce percent fat after the Mediterranean diet. [9, 10] The ketogenic diet trial was small; hence no evidence-based diet has been recommended for the treatment of lipedema. It is suggested that hypocaloric nutrition should be accompanied by suitable dietary supplements and exercise to overcome diet resistance and to manage weight gain in lipedema [8].

If a patient with lipedema develops obesity, it can cause similar serious health issues as in individuals with obesity but without lipedema. For example, it could trigger insulin resistance [2] resulting in hyperglycemia leading to the development of type 2 diabetes, which could further damage organs of the body as well as reduce quality of life. Moreover, obesity increases the risk of developing high blood pressure, hypercholesterolemia and increased blood clotting tendency that leads to higher risk of stroke and heart attacks [11-14].

In order to define an effective treatment option for lipedema, knowing the physiological process of subcutaneous adipose connective tissue deposition and reduction of muscle function and energy utilization is of outmost importance. Excess protein, fat and carbohydrates that are consumed daily can be converted into stored or ectopic fat though the process of lipogenesis in adipose tissue and the liver, and normally stored in adipose tissue as triacylglycerol [15-17]. When consumption of macronutrients, especially fat and carbohydrates, is in excess, fat can also be stored ectopically in muscle, liver, and other depots in the body [18]. Fat must be released from adipocytes through complex enzymatic/hormonal pathways in order to be utilized for energy production. When adipocytes are stimulated, they release triacylglycerol into the bloodstream as free fatty acids (FFA) via lipolysis. Then, FFA are transported by the blood stream to energy requiring tissues, especially muscles, and finally enter mitochondria where they are utilized for energy production [15, 19].

Dietary supplements that reduce adipose tissue and increase muscle (lean mass) could be an effective ally in the management of lipedema. Reduction of adipose tissue and increase in lean mass could improve body image, reduce pain, and improve mobility for patients with lipedema. The use of specific dietary supplements could help in reducing body fat and increasing lean mass thus preventing the invasive practice of microcannular tumescent lipedema reduction surgery including suction lipectomy, which is currently the most effective treatment for lipedema [20].

Fat-burning supplements

Fat-burning supplements are a specific type of dietary supplement that stimulates the fat burning process by several mechanisms. They can boost energy expenditure, increase fat metabolism, increase weight loss, increase oxidation of fats during exercise, as well as make long-term adjustments in metabolic pathways that enhance fat metabolism. Indeed, a good fat burner supplement should [15, 21, 22]:

- stimulate conversion of stored fats into energy;
- stimulate mobilization and break down of stored triacylglycerol from adipocytes;
- increase metabolism to burn stored fats;
- inhibit adipocyte enlargement via lipogenesis.

The efficacy of fat-burning supplements is supported by several studies. Indeed, weight loss induced by supplementation and diet together can be significantly higher than weight loss from diet alone [23]. In a study by Falcone et al., addition of thermogenic supplements containing caffeine, conjugated linoleic acid (CLA), multi-vitamins, and protein, to a hypocaloric diet with high-protein content for a period of 3 weeks resulted in 97% additional reduction in body weight and 35% additional fat loss when compared with the same diet alone. Thus, dietary supplements can increase overall weight loss, including fat loss [23].

Classes of fat-burning supplements

As described by El-Zayat et al., fat burners may be divided into several classes based on their mechanism of action: energy enhancers, protein and amino acids supplements, adrenergic enhancers, and lean mass enhancers [15]. Moreover, they can be comprised of several ingredients, each of which has its own mechanism of action. The main ingredients of fat burning supplements are green tea, caffeine, chromium, carnitine, and CLA. They can also include herbal stimulants such as ephedrine, pyruvate, yohimbine, and chitosan. Fat-burning supplements stimulate weight loss through several molecular mechanisms, mainly boosting metabolism and suppressing appetite [22, 24-26].

Energy enhancers

Fat-burning energy enhancers are usually caffeine or catechins. Caffeine is found in coffee, soft drinks, tea, cola nuts, and cocoa, and it can act as an energy enhancer and an exercise performance booster. Caffeine has the ability to increase stored fat release and the rate of calorie burn [15, 27-29]. Caffeine stimulates fat loss at the level of adipocytes and myocytes, mainly acting synergistically with beta-adrenergic drugs and neurotransmitters. Indeed, beta-adrenergic receptors stimulate fat loss and increase calorie burning, while alpha2-adrenergic receptors have the opposite function [30, 31].

Catechins are often derived from green tea. They have anti-obesity effects and their effect in weight loss is sustained by several human studies [32, 33]. Indeed, they stimulate fat oxidation and energy expenditure, decreasing dietary fat-induced weight gain. Their action is probably due to an increase in sympathetic neuronal activity, which in turn activates hepatic fat oxidation [34].

Protein and amino acids supplements

Protein supplements are utilized to create and maintain a positive nitrogen balance during the day without severely elevating caloric intake. They include whey protein and casein [15]. Whey protein is reported to help in building muscles, increasing strength, controlling appetite, improving endurance, aiding in weight loss, and boosting energy levels [35]. Casein provides all the essential amino acids required for exercise-induced growth of tissue. Casein also forms a gel within the stomach that causes it to slowly digest so that the amino acids/peptides are steadily absorbed over a longer period of time [36].

Adrenergic enhancers

Estrogens are thought to play a key role in the development of lipedema. Aromatase, produced by adipocytes, is an enzyme that converts androgens to estrogen. When mice had the aromatase gene knocked out, body weight gain and obesity-related metabolic complications occurred in both genders. This suggests that an optimal estrogen to testosterone ratio is important, and with increased lipedema tissue, this ratio may be high [37]; thus, dietary supplements that modify hormonal levels could be an effective strategy for lipedema treatment. Testosterone is a key molecule in the pathophysiology of weight gain and obesity. Indeed, it increases lean mass and decreases fat mass, where low testosterone levels are associated with energy imbalance, insulin resistance and dyslipidemia [38]. Supplementation of molecules that act on adrenergic receptors might help in increasing metabolic rate and fat burning, and in accelerating weight loss in women with lipedema. Adrenergic enhancers comprise 7-Keto dehydroepiandrosterone (DHEA) and yohimbine. 7-Keto-DHEA causes long-term changes in body levels of epitestosterone, testosterone, estradiol as well as other steroid hormones. It stimulates thermogenesis, diverting store fats in ATP and heat production [39, 40]. Yohimbe derives from the bark of *Pausinystalia yohimbe*. It is an alpha-2 receptor antagonist, and it accelerates weight loss, increasing testosterone levels, blood flow, thermogenesis, and fatty acid oxidation [15, 41-43].

Lean mass enhancers

The wide class of lean mass enhancers comprise several molecules that stimulate lean mass production through different molecular mechanisms. A non-exhaustive list, comprising their mechanism of action, is reported below in Table I [15]. Further studies will be needed to confirm their effects in humans, considering that a systematic review by Pittler & Ernst doubted the efficacy of several molecules, such as chitosan and pyruvate, in reducing body weight [41].

Fat-burning foods

Certain foods can help in the fat burning process by enhancing metabolism and suppressing appetite. Indeed, food consumption normally increases body weight, but certain foods stimulate lipolysis if coupled with regular exercise and sufficient water intake [15]. Fat-burning foods comprise good fats, medium chain triglycerides, and meat and dairy proteins. Good fats are lipids from several sources, among which are avocados, nuts, fish and vegetable oils [15]. These foods are rich in beta-sitosterol, oleic acids and omega-3 polyunsaturated fatty acids, and they accelerate fat burning and decrease triglycerides and LDL cholesterol levels [52, 53]. Medium chain triglycerides are found in cow butter, palm oil and coconut oil. They are easily digested and absorbed and are directly used for energy. Thus, foods rich in medium chain triglycerides suppress appetite and stimulate body fat loss [54]. Finally, meat and dairy proteins require a complex digestion and absorption processes, which burns energy. They stimulate satiety and use energy for their conversion and storage as fats, therefore meat and dairy they are excellent fat-burning foods [15, 55].

Conclusion

Lipedema is a chronic disease that results in the abnormal distribution of subcutaneous adipose tissue but also the loss of function of muscle. In some cases, obesity arises in later lipedema stages, leading to serious health issues. Lipedema adipose tissue is usually not responsive to diet and exercise, thus invasive techniques such as suction lipectomy are usually required. The use of fat-burning supplements and lean mass enhancers could improve the process of weight loss and but also increase muscle mass and possibly muscle function. Indeed, these supplements are known to increase fat mass loss boosting energy expenditure, increasing fat metabolism, and impairing fat absorption, which may in turn improve muscle function indirectly. Therefore, the use of dietary supplements could be a valid alternative to invasive techniques for the reduction of adipose tissue and related issues in lipedema patients. Human studies are needed to confirm their effectiveness in lipedema and to select the most effective dietary supplements.

Tab. I. Sources and mechanism of action of lean body enhancers.

Molecule	Source	Mechanism of action	References
Chitosan	Crustaceans	Reduces fat absorption	[40,41]
L-Carnitine	Chemical catalyst that is synthesized by human kidneys, brain, and liver	Participates in fatty acid transport into mitochondria during the breakdown of fats	[44,45]
Chromium	Trace mineral found in meat, grain, nuts	Reduces insulin resistance	[41,46]
Ephedrine	The plant *Ephedra sinica*	Stimulates sympathetic neuronal action	[47]
Synephrine	Citrus fruits	Stimulates thermogenesis	[48,49]
Pyruvate	Intermediate of glycolysis	Reduces appetite and fatigue, increases energy levels and muscle glycogen stores	[24,41]
Conjugated Linoleic Acid	Meat & dairy products	Transports dietary fats to cells for lipolysis	[50,51]

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Conflicts of interest statement

Authors declare no conflict of interest.

Author's contributions

Gabriele Bonetti, Karen L. Herbst: These authors contributed equally to this work. MB: study conception, editing and critical revision of the manuscript; GB, KLH, KD, AKK, Serena M, Silvia M, MRC, Sandro M, MR, Marina C, Michela C, TB, FB, PG: literature search, editing and critical revision of the manuscript. All authors have read and approved the final manuscript.

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