Medical Hypotheses xxx (xxxx) xxx

Contents lists available at ScienceDirect

Medical Hypotheses

journal homepage: www.elsevier.com/locate/mehy

Ketogenic diet as a potential intervention for lipedema

L. Keith [a,b,*], C.A. Seo [a,b], C. Rowsemitt [b,c,d], M. Pfeffer [b,d,e], M. Wahi [f], M. Staggs [b], J. Dudek [d,g], B. Gower [h], M. Carmody [i]

[a] The Lipedema Project, Boston, MA, USA
[b] Lipedema Simplified, Boston, MA, USA
[c] Comprehensive Weight Management, Templeton, CA and Providence, RI, USA
[d] The Lipedema Project: Medical Advisory Board, Boston, MA, USA
[e] I Choose Health, Metung, Australia
[f] DethWench Professional Services, Boston, MA, USA
[g] SWPS University of Social Sciences and Humanities, Warsaw, Poland
[h] University of Alabama at Birmingham, Department of Nutrition Sciences, Birmingham, AL, USA
[i] Harvard Medical School, Boston, MA, USA

ARTICLE INFO

Keywords:
Lipedema
Ketogenic diet
Obesity
Lymph
Ketosis
Hypothyroid

ABSTRACT

Lipedema (LI) is a common yet misdiagnosed condition, often misconstrued with obesity. LI affects women almost exclusively, and its painful and life-changing symptoms have long been thought to be resistant to the lifestyle interventions such as diet and exercise. In this paper, we discuss possible mechanisms by which patients adopting a ketogenic diet (KD) can alleviate many of the unwanted clinical features of LI. This paper is also an effort to provide evidence for the hypothesis of the potency of this dietary intervention for addressing the symptoms of LI. Specifically, we examine the scientific evidence of effectiveness of adopting a KD by patients to alleviate clinical features associated with LI, including excessive and disproportionate lower body adipose tissue (AT) deposition, pain, and reduction in quality of life (QoL). We also explore several clinical features of LI currently under debate, including the potential existence and nature of edema, metabolic and hormonal dysfunction, inflammation, and fibrosis. The effectiveness of a KD on addressing clinical features of LI has been demonstrated in human studies, and shows promise as an intervention for LI. We hope this paper leads to an improved understanding of optimal nutritional management for patients with LI and stimulates future research in this area of study.

Introduction

The disease entity lipedema (LI) was first clinically recognized in 1940 at the Mayo Clinic in the United States [1,2]. According to a monograph published by Dayan and colleagues, "the diagnosis of LI is made clinically and is typically defined by the disproportionate and symmetrical accumulation of adipose tissue (AT) in the lower extremities accompanied by complaints of orthostatic edema" [3]. LI is further distinguished by lower body hypersensitivity and pain, bruising with minimal trauma, firm nodules in subcutaneous fat, and apparent resistance to traditional diet and exercise regimens [4].

Although LI was initially identified in 1940, to date, little is known about its clinical features, natural history, causes, and therapies. This paper is divided into two parts. In the first part, we summarize what is known about the epidemiology, diagnosis, clinical manifestations, and conventional treatment for LI. In the second part, we hypothesize how patients adopting a ketogenic diet (KD) could directly and positively impact the clinical course of their LI and propose mechanisms for these effects.

Abbreviations: AA, African American; AT, adipose tissue; BHB, beta hydroxybutyrate; BMI, body mass index; CHO, carbohydrate; hsCRP, C-reactive protein; K+, potassium; KD/KDs, ketogenic diet(s); LAT, lipedema adipose tissue; LC, low carbohydrate; LE, lymphedema; LF, low fat; LI, lipedema; NAFLD, nonalcoholic fatty liver disease; NLRP3, nucleotide-binding domain-like receptor protein 3; NO, nitrous oxide; QoL, quality of life; ROS, reactive oxygen species; rT_3, reverse T_3; T_3, liothyronine; T_4, free levothyroxine; TSH, thyroid stimulating hormone.

* Corresponding author at: The Lipedema Project, 60 Boston Ave, Boston, MA 02144, USA. 60 Boston Avenue, Somerville, MA 02144, USA.
E-mail address: leslyn@lipedemaproject.org (L. Keith).

https://doi.org/10.1016/j.mehy.2020.110435
Received 5 August 2020; Received in revised form 6 November 2020; Accepted 24 November 2020
Available online 27 November 2020

Epidemiology

LI is an underdiagnosed AT disorder that is thought to be relatively common, especially in women [5,6]. Currently, it is estimated that LI impacts approximately 11% of women, occurring only rarely in men with hormonal dysfunction [3,7], and has a profoundly negative impact on quality of life (QoL) [8]. Of patients with LI, more than 50% are obese, with secondary lymphedema (LE) often being the direct consequence of obesity, rather than the LI [9]. Additional research studies have shown obesity to co-occur with LI in 85% to 88% of the sample studied [10,11], which demonstrates the necessity for an effective intervention that will address both conditions. Recent literature also suggests LI has genetic underpinnings [11,12] with hormonal changes, stress and/or surgery playing important roles in its onset [13].

Stigma and lack of awareness

Most medical professionals are unaware of LI, often misdiagnosing LI as obesity because signs and symptoms of LI are not recognized [6,14]. Culturally, LI is caught in the same social stigmatization as obesity "even to the point of abhorrence" [15]. While weight stigma influences many aspects of the lives of people with obesity and LI, it is most impactful in the area of healthcare, where understanding, acceptance, and support are critical for accurate diagnosis, effective treatment, and ongoing health maintenance [16].

Diagnosis

Though the diagnosis of LI is generally done in the clinical setting, there is no formal medical training on how to diagnose LI. There are also few resources to guide clinicians with respect to LI, and no standard-of-care for LI treatment. In fact, the term *lipedema* is often confused with the terms *lipidemia* or *lipemia* which apply to alterations of serum lipid levels, adding further confusion during patients' attempts to attain a diagnosis of an AT disorder [4].

LI is first suspected by the clinical observation of unusual AT distribution, generally with disproportionate AT below the waist. Often, it is understood by the patient as a family trait. Since neither the public nor most professionals recognize this as a diagnosis distinct from obesity, both patients and providers assume it to be a normal variant of obesity. LI is classified into five types based on the distribution of AT [14] (see Fig. 1).

In addition to being classified by type, diagnosis of LI also includes staging. As seen in Fig. 2 [3], early LI usually consists of an unusual but unremarkable distribution of AT in the legs. Left untreated, the disease progresses through four stages where AT is increased in the legs, largely sparing the feet and hands unless LE develops. The dramatic increase in AT in the legs in later stages can be both physically and emotionally debilitating.

Differential diagnosis

The triad of the diagnoses LI, obesity, and LE occurring together is a dominating factor that challenges the identification and treatment of LI. Table 1 compares and contrasts diagnostic features of these three conditions. The salient features of LE that distinguish it from LI include limb asymmetry and pitting edema with a positive Stemmer sign, while LI will typically display limb symmetry and non-pitting edema with a negative Stemmer sign.

Clinical manifestations

Clinical manifestations of LI most salient to this paper are discussed below. First, we discuss the most widely accepted features of LI of abnormal AT deposition, pain and compromised QoL. This is followed by a description of several disputed characteristics including the existence and nature of metabolic and hormonal dysfunction, edema, inflammation, and fibrosis in LI.

Abnormal adipose tissue deposition

As stated above, the classic presentation of LI is an idiopathic excessive and disproportionate gynoid distribution of AT to the hips, buttocks, thighs, and lower legs. Suga et al. [17] saw histological changes in lipedema adipose tissue (LAT) not unlike those found in subjects with obesity, including macrophage infiltration encircling dying adipocytes and a significant buildup of adipose-derived stem cells. However, more recent research has shown decreased differentiation potential in stem cells in LI compared to obesity [18,19]. Excessive expansion of AT in the lower body may have genetic [11] and/or female sex hormone influences [13]. Although the gynoid distribution of AT seems to be metabolically protective due to its negative correlation with cardiovascular risk factors [20], the pathophysiology of AT likely has metabolic underpinnings [21].

Pain

LI has been described in medical literature as a "painful fat disorder" [22]. A recent study of the signs and symptoms of patients with LI found that 89.7% reported daily pain in LAT [23]. LI-associated pain can be severe, and a factor in worsening QoL and loss of mobility [24]. In an internet survey of 120 women with LI, all but seven reported that pain was a daily concern, and 66% described their pain as moderate or severe [8]. Further, women with LI may have a high incidence of joint pain in part due to co-occurring gait issues and osteoarthritis in addition to pain in regions of LAT [25,26].

The mechanism behind pain in LI is unclear, making it difficult to treat and control. Heightened sensitivity to palpation may be labeled nociceptive pain, neuropathic pain, or central sensitization [27]. Pain associated with LI may be caused by increased inflammation and/or compression of peripheral nerves from AT and fluid accumulation in the affected tissue [28,29].

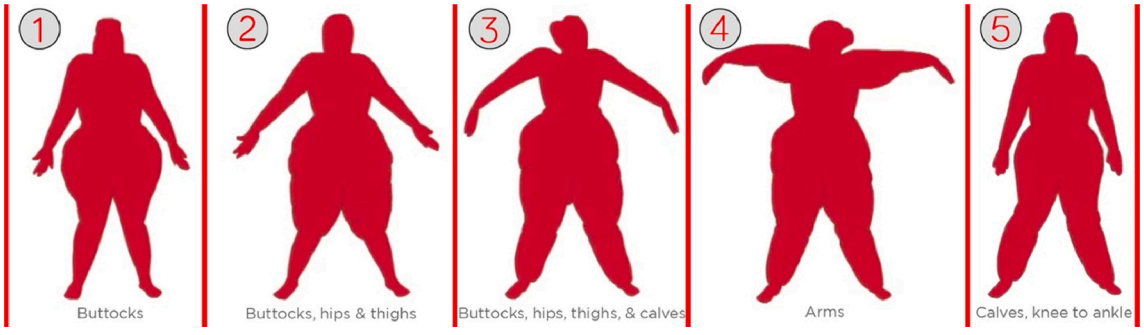

Fig. 1. Types of lipedema (LI). The five types of LI differentiated by distribution of adipose tissue.

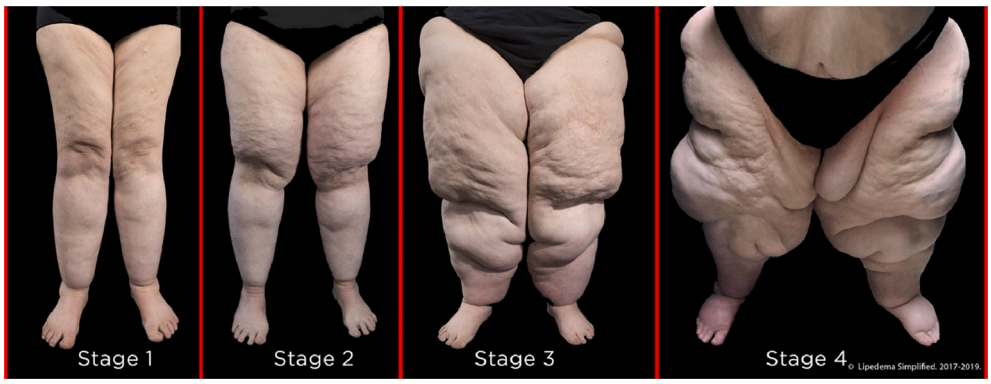

Fig. 2. Stages of lipedema (LI). Examples of the four stages of LI as the disease progresses.

Table 1
Comparison of features important to the diagnosis of lipedema, lymphedema and obesity.

Feature	Lipedema	Lymphedema	Obesity
Gender	Almost exclusively female	Female and male	Female and male
Onset	Menarche, pregnancy, menopause	Primary: Birth, puberty, pregnancy, menopause Secondary: Immediately or delayed after inciting event	Genetic factors or acquired No age of onset, can occur at any time over life span
Development	Affects lower body from waist down bilaterally, involvement is gradual without foot involvement	Usually starts distal and progresses toward proximal	Gradually affects entire body, but may be limited to trunk in some cases
Extent	From the iliac crest to the ankle; no involvement of the dorsum of the feet	Can affect only a portion of the extremity and does not need to be most dependent area	Whole body
Stemmer's Sign	Negative	May be positive	Negative
Distribution	Symmetric distribution of adipose tissue from the hips and ankles; disproportionate distribution between upper and lower body	Unilateral or bilateral distribution; if bilateral, usually asymmetric	Usually symmetric
Pain/ Hypersensitivity	Yes	No	No
Bruising	Yes, commonly	No	No
Edema	Minimal or no pitting edema of the lower legs; pitting only seen after prolonged orthostasis	Pitting in earlier stages; later, fibrosclerosis	No pitting
Hyperkeratosis	No	Yes, in severe cases	No
Cellulitis	No	Yes, commonly	No

Note: adapted with permission from Dayan et al, 2017.

Quality of life and psychological functioning

Survey results and clinical experience show that LI is often associated with lower QoL and impaired psychological functioning [8,30,31]. This may take the form of low self-esteem, feelings of hopelessness and self-blame, depression, anxiety, eating disorders, social isolation, poor body image, and appearance-related distress. In an online survey of 411 women with LI, less than 10% had difficulty with washing or dressing, while 42% reported they suffered from anxiety or depression [32]. The stress of repeated attempts to lose weight, particularly with very low calorie diets, may also result in "diet depression," a cluster of symptoms including anxiety, restlessness, irritability, and nervousness [33]. Many women with LI may also have lowered QoL due to the cultural stigma attached to obesity and suffer from ridicule, bias, and discrimination [34].

Metabolic and hormonal dysfunction

As reviewed by Szèl et al. [13], the onset of LI is associated with changes in reproductive hormonal milieu: puberty, pregnancy, and perimenopause. Even as estrogen has been implicated in the etiology of LI [11], one aspect of the onset of LI remains perplexing: it may occur as estrogen rises during puberty as well as when estrogen declines in menopause. Still, LI is thought to be associated with reproductive hormones, especially estrogen. Although a hormonal etiology of LI has not been firmly established, it remains a promising avenue for intervention, and possibly prevention, of LI [13].

Estrogens promote fuel storage in part by increasing insulin secretion and sensitivity of target tissues and perhaps in part by impeding fatty acid oxidation [35,36]. Insulin, in addition to its other complex effects in the body, promotes storage of metabolic fuels and inhibits breakdown of stored triglyceride. The perception of energy deficit may lead to increased hunger and food intake. In this way, elevated insulin action can ultimately lead to weight gain [37].

Estradiol treatment of rats increases circulating insulin relative to glucagon and reduces the circulating fuels of glucose and free fatty acid [38]. In humans, estradiol increases sensitivity of AT to insulin, so less insulin is required to suppress release of free fatty acids [39]. AT from the hip and thigh region, sites of excessive AT deposition in LI, is particularly sensitive to estrogen action [40]. The high sensitivity of hip and thigh AT to estrogen suggests that variations in these pathways may prove important in LI.

An examination of thyroid hormones in women with LI may prove illuminating with respect to metabolism as well as the AT resistance to diet and exercise heretofore so universally observed. Very little data exist regarding thyroid functioning and LI. In Wold and colleagues' classic paper [2] based on a case series of patients who were the cohort used to essentially identify LI, metabolism was decreased in patients compared to normal subjects. As was typical of the era, the sample size in the study was small, and the methods were not presented, so it is difficult to evaluate the results. In a study of patients with LI conducted in Germany, Foeldi [41] found the prevalence of hypothyroidism in Stage I patients ($n = 65$) to be 38% and in Stage II patients ($n = 96$) to be 43% compared to only 2% in the general German population. In a list of

diagnostic criteria for LI, Buck and Herbst [14] added hypothermia of the skin, which may indicate hypothyroidism.

Patients with LI misdiagnosed with simple obesity typically engage in calorie-restricted diets that may lead to the famine response, further impeding weight loss efforts. The famine response, including decreased metabolism as well as increased hunger and interest in food, occurs in most of the general population during weight loss attempts [42]. Unfortunately, current evaluation of thyroid using thyroid stimulating hormone (TSH) has not detected the decreased thyroid function present in famine response hypothyroidism in subjects with LI, so this is likely not an avenue for intervention [43].

Edema

Edema is defined as an excess of water that has accumulated in body cavities or tissues. The clinical presentation of LI included edema when first described by Wold and Hines [2]. This was most recently emphasized by Ma and colleagues [44] identifying a biomarker (Platelet Factor 4) for lymphatic vasculature dysfunction that is elevated in women with LI. Although the notion of any type of edema associated with LI has lately been disputed [10], the literature generally characterizes edema associated with LI to be non-pitting and orthostatic in earlier stages of the disease and progressing to LE in later stages [45]. Imaging studies demonstrating abnormal lymphatic function in women with LI may indicate a failure point of the lymphatics in LI preventing the evacuation of excess interstitial fluid in LAT [46–48].

However, there is emerging evidence of the existence of increased water content in skin, muscle and AT of women with LI [49]. This increased fluid flux is influenced by increased blood capillary permeability and loose connective tissue [50] as well as elevated sodium content in LAT (see Fig. 3) [49]. AT compliance allows an increase of fluid volume without an increase in interstitial fluid pressure, which may be protective by preventing an increase in blood volume and resultant hypertension [51]. The increased tissue water content may account for the commonly described “boggy” feel to LAT. The accumulation of fluid in LAT is depicted in Fig. 3.

Inflammation

LI, and its common comorbidity obesity, are considered by some researchers to be inflammatory diseases because both cause an ongoing unresolved immune response to dysfunctional adipocytes and AT [28]. LI and obesity exhibit numerous similarities, but significant differences exist between LI and obesity in the pathological decline of adipocytes and tissue [17,28]. Al-Ghadban et al. [28] state inflammation in LI occurs independently from the inflammation caused by obesity.

Repetitious exposure to endogenous sterile stressors causes an excessive immune response in AT, resulting in ongoing low-grade, chronic inflammation and AT remodeling as shown in Fig. 4 [17,52]. The nucleotide-binding domain-like receptor protein 3 (NLRP3) inflammasome is an innate sensor involved in initiating inflammation in dysfunctional adipocytes and AT [53]. Several studies demonstrate the mechanism for NLRP3 activation to be from numerous stimuli (see Fig. 3) [53-57]. However, Muñoz-Planillo and colleagues [58] state that cell potassium (K+) efflux is the only independent agonist in NLRP3 activation. Additionally, pyroptosis, an inflammatory form of cell death that results in the dispersal of highly inflammatory intracellular contents, is regulated by the NLRP3 inflammasome and may serve a key role in chronic inflammation and AT remodeling exhibited in LI [55,59–61].

In LI, neutrophils become prolific in their attempt to remove the inflammatory instigator [62]. This causes tissue damage and macrophages to infiltrate in unusually high numbers and surround the necrotizing adipocytes, forming crown-like structures and giant multinucleated cells (see Fig. 4). This inflammatory process is also seen in obesity; however, in LI, the cell sizes become significantly irregular [17].

Fibrosis

Although not universally accepted, we suggest that chronic inflammation of LAT may progress to fibrosis when left untreated as described in a review by Wynn [63]. Fibrosis is the pathological consequence of AT hypertrophy-induced hypoxia [64] and subsequent chronic inflammation, whereby cells and tissue damaged by an unresolved inflammatory response undergo ongoing, excessive repair mechanisms [63]. An example of known profibrogenic contributors relevant to LI are excessive production of reactive oxygen species (ROS) and disrupted hormones such as low levels of adiponectin and high levels of leptin [65].

The full extent of unresolved fibrosis in LI is unknown and warrants further study. LI fibrosis may even be a factor in lymphatic drainage impairment when adiposopathy is present [66]. Fibrosis can also inhibit adipocyte expansion [64]. Fibrosis in LI is thought to be a significant

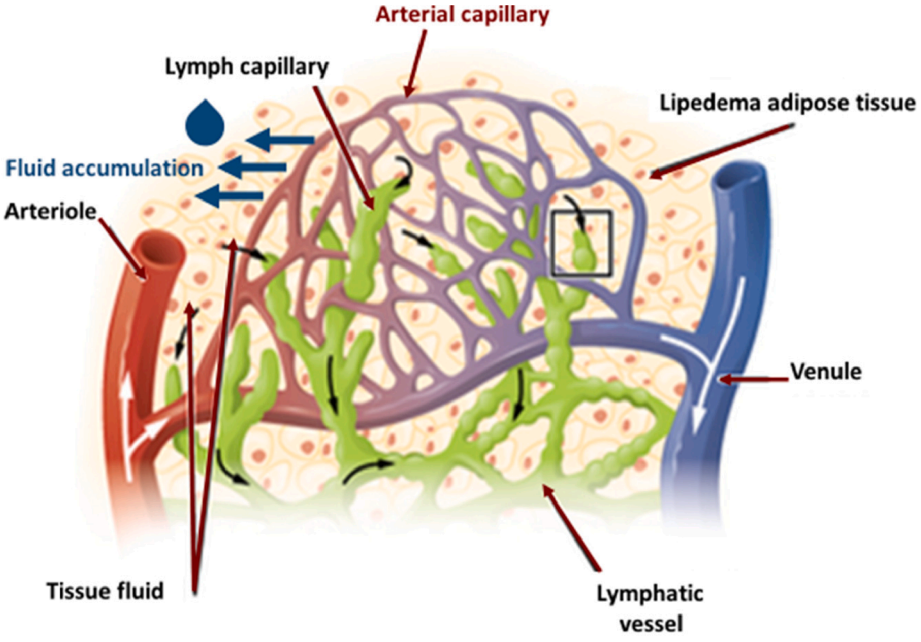

Fig. 3. Edema in lipedema adipose tissue (LAT). Elevated sodium and water content in LAT, increased blood capillary permeability, reduced lymph transport capacity contribute to edema in LAT.

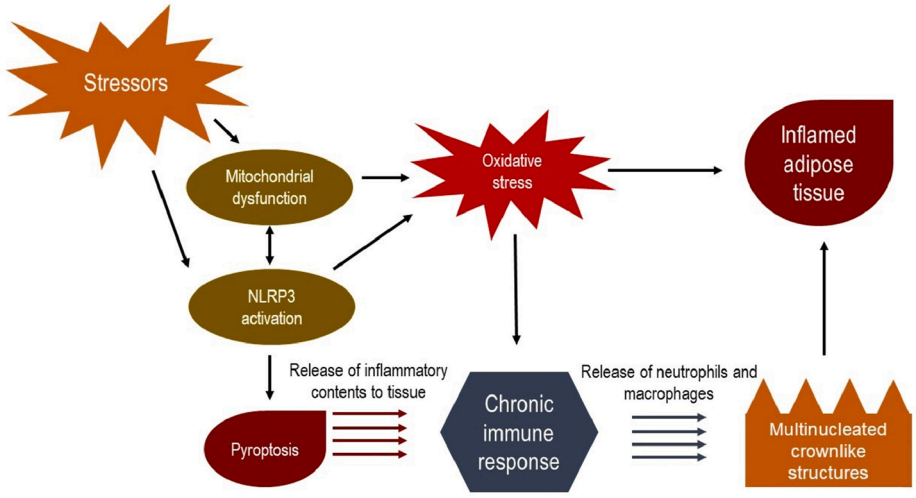

Fig. 4. Lipedema adipose tissue (LAT) remodeling, inflammation and fibrosis. Endogenous stressors include excess glucose intake, ion flux (potassium [K+] and chlorine [Cl-] efflux, calcium [Ca+] and sodium [Na+]), mitochondrial release of reactive oxygen species (ROS) and oxidized mitochondrial deoxyribonucleic acid (DNA), excess extracellular adenosine triphosphate (ATP), oxidized low density lipoprotein (LDL), cholesterol and monosodium urate crystals, hyaluronic acid, adipose hypertrophy, hypoxia, necrosis, estrogen dysregulation. Multifactorial endogenous stressors trigger NLRP3 inflammasome activation that leads to pyroptosis in LAT. The release of inflammatory contents into LAT produces a chronic immune response that remains unresolved. The excessive release of neutrophils and macrophages produces irregularly sized multinucleated crown-like structures that contribute to chronic LAT remodeling, inflammation, and fibrosis.

factor in the progression to lipolymphedema [67].

Conventional treatment for lipedema

The most common conventional treatments for LI may be classified as a set of non-invasive and invasive approaches which can be combined. Non-invasive approaches include complete decongestive therapy (CDT) and lifestyle changes to diet and exercise, while an invasive approach involves surgery [68]. CDT consists of manual lymph drainage, compression therapy, skin care and exercise, and represents the most widely used conservative treatment for LI [69]. Because there is no cure for LI, conservative treatment must focus on symptom relief, complication prevention, and slowing disease progression [46]. Surgical intervention for LI has some power in decreasing pain [70], but it is not a cure for LI, nor is it without risks of complications. As surgical options for LI are starting to be used more frequently, conservative treatment is used as an adjunct in both pre- and post-operative care [3].

Diet and exercise changes are used to address LI symptoms. Dietary treatment approaches may focus on reducing inflammatory foods and/or on herbal supplementation [71]; however, LI has been shown to be highly resistant to conventional diet and exercise interventions. Low calorie diets and intense physical exercise designed to change energy balance and induce weight loss have been frustratingly ineffective in patients with LI [3]. Any weight loss in patients with LI resulting from conventional diet and exercise approaches will inevitably occur only on the upper body, resulting in increased asymmetry, and further body dysmorphia [66].

Adopting a ketogenic diet as therapy for LI

Ketogenic diets (KDs) have been used since the 1920s as an effective therapy for managing intractable epilepsy [72]. KDs restrict carbohydrate (CHO) intake to less than 20 g/day [73,74]. CHO restriction results in an absence of glucose for fuel, inducing fat-burning to produce ketosis [73,74]. This state is generally considered to occur when blood beta-hydroxybutyrate (BHB) is above 0.5 mmol/L [73].

The last ten years have seen an increase in studies on a potential therapeutic role for KDs in a host of metabolic issues including obesity, type 2 diabetes, Alzheimer's disease, multiple sclerosis and cancer [75,76]. KDs were shown to be safe and sustainable long-term in a recent two-year study [77]. Many of the studies found KDs effective. Diet protocols and reasons for efficacy tended to be disease-specific, but most proponents credit the metabolic processes of gluconeogenesis and ketogenesis for positive therapeutic effect [78]. For a more general effect, it is observed that the AT hormone leptin signals satiety, but in obesity, the brain becomes insensitive to leptin [79]. As KDs improve the brain's sensitivity to leptin, satiety increases which could be helpful for patients with both obesity and LI [80].

Considering the evidence that adopting a KD is likely to improve symptoms in patients with LI, in 2016, we (all authors exclusive of Wahi and Gower) began working with individuals with LI willing to adopt a KD to see if their symptoms improved. We modified a ketogenic diet to be more suited for LI including but not limited to elimination of artificial sweeteners, partially hydrogenated seed oils, and nut flours as well as accommodations for individual preferences and food intolerances. From anecdotal experiences with these patients with LI, as well as reports from hundreds of others who participate in our online meetings and support groups, we came to believe that adopting a KD reduces LI symptoms for most patients. This paper presents our hypothesized mechanisms behind these observed effects.

Hypothesis

We hypothesize that a KD modified specifically to treat LI can reduce symptoms, providing both symptom relief as well as a substantial reduction in AT. There is strong evidence that a KD will impact three generally recognized symptoms of LI: (1) reduction of weight and excessive AT deposition, (2) pain reduction, and (3) QoL improvement. We also present the evidence for the effectiveness of a KD in four additional less acknowledged symptoms of LI as promising and worth investigating further: (1) alterations in metabolism and hormonal function, (2) edema or tissue water content reduction, (3) inflammation reduction, and (4) fibrosis prevention and reduction. Anecdotally, we have observed all these effects in patients adopting a KD adapted for LI. In this paper, we present our proposed mechanisms behind these seven observed effects.

Reduction of weight and excessive AT deposition

As noted above, KDs have long been effective at producing rapid adipose loss. From the first known book on diet published in 1869, *Letter on Corpulence* [81], to modern iterations of the Atkins diet [82], CHO restriction has been shown to be a potent tool for weight loss. KDs are effective for weight loss primarily due to its ability to decrease insulin and the increased satiety experienced with a high fat intake [83]. This shift in cellular energy metabolism from 'glucocentric' to 'adipocentric' (deriving most energy from fatty acids and ketones) sets up the perfect sustainable lipolytic environment without the risk of sarcopenia that occurs with calorie restricted diets [84].

Several possible explanations exist for why KDs appear to permit AT

loss in LI while conventional diets do not. LI adipocytes may require much lower levels of insulin than other adipose cells for lipolysis to occur, have impaired glucagon sensitivity, and/or be insulin resistant despite the presence of systemic insulin sensitivity. This third possibility is perhaps the most promising, since the onset of LI occurs during times of systemic insulin resistance [85], and hypertrophied adipocytes are linked to insulin resistance [86].

Adipocyte size, plasma insulin levels, and leptin levels decrease with KDs [87]. As higher insulin levels promote lipogenesis and adipocyte hypertrophy, a diet low in CHO results in lower and more stable blood glucose and insulin [88]. These effects are important considerations for treating LI. We suggest the metabolic changes induced by nutritional ketosis may have far-reaching implications for managing the dramatic proliferation of adipocytes and the hyper-inflammatory response found in LI in three distinct ways: (1) by reducing overall adiposity through energy demand driven lipolysis, (2) by driving insulin low enough to allow lipolysis of LI adipocytes while simultaneously suppressing appetite through an influx in glucagon, and (3) by preventing any further progression of the disease, previously considered to be impossible.

Glucagon, as the primary catabolic hormone, works in opposition to insulin, which functions as an anabolic, or storage, hormone. Previously thought to only be involved in prevention of hypoglycemia by increasing the glucose output from the liver, glucagon is now known to also be involved in energy homeostasis and lipid and amino acid metabolism, and also serves as a key stress hormone [89,90]. Energy regulation is sustained by glucagon through an increase in satiety which in turn reduces food intake while simultaneously increasing energy expenditure and creating heat [90].

Glucagon resistance may result in hypoglycemia and/or hypertriglyceridemia [91]. At least one study found that women with LI tended to have higher serum cholesterol and triglycerides compared to controls [5], although this is contradicted in more recent research [4]. Impaired glucagon sensitivity may contribute to excessive AT deposition, reduced tissue temperature, and poor satiety found in patients with LI, despite there being a low prevalence of insulin resistance and type 2 diabetes among patients with LI. If glucagon resistance is found to be associated with LI, this may contribute to excess adiposity and difficulty losing weight. Because ketosis has been found to normalize insulin and glucose secretions, a KD may be beneficial in reversing glucagon resistance [92].

Reducing pain

Researchers have suggested that due to shared mechanisms of seizures, neuropathic pain, and inflammation, the effects of therapeutic ketosis induced by a KD may also reduce pain and support the management of chronic pain [75]. Several animal studies have shown a reduction in sensitivity to thermal pain, mechanical pain, and/or neuropathy after several weeks of a KD [93–95]. Masino and Ruskin [75] hypothesize that CHO restriction decreases the excitability of neurons, which can suppress the perception of pain, block glycolysis, reduce inflammation, and boost levels of adenosine, a natural analgesic.

In a randomized controlled trial of older adults with osteoarthritic knee pain comparing a low fat diet (LF) with a low CHO diet (LC), the LC group had significantly greater reductions in pain with a similar amount of weight loss [96]. The authors postulate that oxidative stress from CHO consumption in the LF group resulted in higher pain and inflammation from elevated levels of ROS, while the LC group enjoyed decreases in all these measures [96]. The finding was similar in a previous study of overweight adults by Yancy et al. [97] in which the LC KD group had superior results in all health related QoL measures, including pain, compared to a LF group.

The effect of CHO restriction on pain was also observed in a clinical trial of women with LI after seven weeks of a KD [98]. Pain was significantly reduced at week seven but returned to previous levels after six weeks of a diet of standard Norwegian fare, despite maintenance of weight loss. We have found the same profound reduction of LI pain with as little as two weeks of CHO restriction within various online support groups and through clinical treatment. Consistent with Shin and colleagues [29], we hypothesize that pain in LI is largely due to inflammation, which is curtailed under a KD and may be completely independent of any weight lost.

Improving quality of life and psychological functioning

Recent research demonstrates that symptom severity may be an important predictor of QoL in LI [8,30]. Since a well-formulated KD has been shown to be effective in reducing weight and pain, the severity of other symptoms associated with LI may also be affected. As has been shown in weight reduction in individuals with obesity, losing weight will likely lead indirectly to improvement in QoL for those with LI [99]. Additionally, reduction in weight and size, particularly in body areas most affected, decreases appearance-related distress and depression, which are important aspects of psychological functioning [30].

Conversely, diets high in CHO (defined as greater than 45% of calories) [18] have been shown to be associated with a higher incidence of depressive, anxiety, and somatoform disorders in several large epidemiologic cohort studies [100–103]. Although these findings are not specific to patients with LI, the unhealthy interaction between eating disorders, CHO cravings, and mood dysregulation seen in the general population as well as in patients with LI [104] may be successfully disrupted by the CHO restriction found in KDs.

Also outside of patients with LI, research in both animals and humans has shown that adopting a KD improves mood, attention, and social interactions, and also reduces depression through possible underlying mechanisms affecting brain function [105,106]. These mechanisms may include diet-induced changes in energy consumption or neurotransmitter usage (GABAergic/glutamatergic transmission and monoamine modulation) and by altering biological mediators present in mood disorders that can then reduce depression [107]. KDs increase neurotrophin BDNF [108], improve oxidative imbalances [109,110] and reduce systemic inflammation common in people with mood disorders [111,112]. However, due to limited generalizability of animal models to analogous conditions in humans, and due to the lack of research specifically directed at patients with LI, further research is needed into how adopting a KD may improve QoL in LI [113].

Thyroid function

Thyroid function decreases in hypocaloric conditions to defend against weight loss during famine. We call this condition “famine response hypothyroidism.” This phenomenon involves a resetting of the hypothalamic thermostat downward to maintain a decreased metabolism by defending the active thyroid hormone liothyronine (T3) at the low end of normal [114]. Levothyroxine (T4), the main circulating thyroid hormone, is inactive and is converted to both T3 and reverse T3 (rT3), a form of the hormone which may inhibit metabolism (see Fig. 5). Famine response hypothyroidism may occur with either low levels of T3 or somewhat low levels of T3 coupled with high levels of rT3. The effect of KDs on thyroid function is less clear than that of hypocaloric diets.

Thyroid function in KDs has been studied in adults with obesity and children with epilepsy. In weight loss attempts with human subjects using KDs, aspects of famine response hypothyroidism occur [115–117]: KDs decrease the active hormone free T_3 [115] and total T_3 (TT_3) [116], and increase rT_3 [117]. As is typical in famine response, FT_4 and total T_4 (TT_4) remain stable with similar dietary interventions in humans [115]. In famine response in humans, these changes in thyroid are regulated by leptin [118]. In weight-stable patients, Volek et al. [119] found an increase in TT_4 and no change in T_3 uptake (measure of degree of saturation of the thyroid binding globulin with thyroxine in the blood rather than an assessment of T_3). In a study of a diet designed for weight

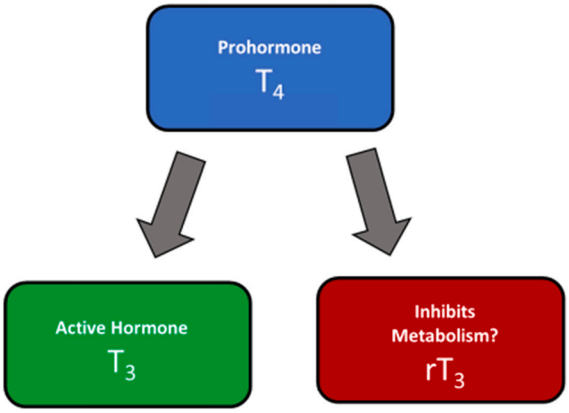

Fig. 5. Main thyroid hormone pathways. The prohormone levothyroxine (T_4), the main circulating form, is inactive and is converted to both liothyronine (T_3) and reverse T_3 (rT_3). rT_3 is a form of the hormone which may inhibit metabolism. The amounts and ratio of conversions to T_3 and rT_3 are important in famine response hypothyroidism.

maintenance, average T_3 levels were in the lowest quartile of the reference range both before and after treatment [120]. A decrease during treatment was not significant, but the small sample size ($n = 4$ each group) precludes ruling out an effect. None of these studies examined thyroid symptoms. Without information on symptoms, we cannot determine whether famine response hypothyroidism is occurring in KD, but the results are suggestive.

These hormonal results lead us to hypothesize that part of the extreme resistance to weight loss in patients with LI may be related to famine response hypothyroidism, undetected by standard measurement of TSH. Despite the fact that low metabolism was identified as one of the characteristics of LI in the original work [2], evaluation and treatment strategies have not been pursued for this population. As described by Rowsemitt and Najarian [43], we believe that by assessing hypothyroid symptoms, FT_3, rT_3, and FT_3/rT_3 ratio, famine response hypothyroidism will be revealed in many individuals with LI.

Although there are no studies of thyroid function on KDs in LI, we have seen numerous patients with LI who are symptomatic of low thyroid on KD. To date, we have measured ratios of FT_3/rT_3 in nine such patients. Low ratios (<0.20) were found in 8/9 patients with the remaining patient having FT3 < mid-range. Thus, all of them qualified as famine response hypothyroidism. Three had uncommonly low ratios (0.06–0.08). The two with the highest ratios (0.41 and 0.17) were on some thyroid treatment including both T3 and T4. The only other treated patient was on T4 only and had a ratio of 0.13. Median ratio was 0.13. (Rowsemitt, clinical observation). Treating this condition with straight T_3 for those with a low ratio may prove to be an important factor in helping many people with LI lose weight as well as improve other symptoms of hypothyroidism, such as fatigue, depression and hair loss. We believe that medical management of famine response hypothyroidism will enhance the response to a ketogenic diet modified for LI and potentially strengthen positive outcomes.

Estrogen/insulin connection and weight loss

Substantial differences occur regarding the estrogen-insulin connection between populations. Compared to Caucasian women, African-American (AA) women have greater obesity prevalence [121], higher circulating estradiol [122,123], and dramatically higher circulating insulin when given a glucose challenge [124]. Thus, AA women's endocrinology is optimized for fuel storage, as appears to be also true in LI. In AA adult women, greater insulin sensitivity at baseline was associated with greater weight (adipose) gain over a year but not in Caucasian women [125]. The effect of insulin sensitivity was exaggerated in women who consumed a high glycemic diet, which promotes insulin secretion. In prospective interventional research, a low glycemic diet, in contrast to a low fat diet, was more effective at promoting adipose loss in AA vs Caucasian participants [126]. These studies suggest that naturally occurring variation in concentrations and/or actions of estrogen and insulin can facilitate the accumulation of AT. However, a low CHO diet is a possible solution to estrogen/insulin-driven obesity. Studies of the estrogen-insulin relationship should be explored in LI, particularly regarding the questions of onset at both puberty and menopause.

Reducing edema

Edema results from a fluid imbalance due to lymphatic system dysfunction, either through fluid overload or impaired fluid transport. Assuming edema co-occurs with LI, both causes may be present, but with respect to KDs, we would like to focus on the potential cause of fluid overload in body regions affected by LI possibly influenced by capillary permeability and elevated sodium content (as shown in Fig. 3). We postulate that the CHO restriction paired with fat consumption promoted as part of a well-formulated KD can reduce the excess tissue water content found in LI. In fact, this dietary intervention was found to be successful in a pilot study of 12 adults with obesity and LE [127]. Participants who adopted a KD were able to achieve greater reduction in lymphedematous limb volume. However, no studies have been performed to assess the effect of a KD on edema or tissue water content in LI.

A high CHO diet composed of >45% of total daily calories [18] has been found to cause water retention that ultimately contributes to overwhelming lymphatic load. Additionally, glycogen storage requires a minimum 1:3–4 ratio with water, and can be as high as 1:17 in certain conditions, leading to fluid retention to accommodate glycogen storage [128]. This excess fluid needed for glycogen storage accounts for the large immediate weight loss that frequently occurs with the onset of either caloric or CHO restriction in the general population [129]. For this reason, we hypothesize the CHO restriction in KD may reduce the fluid burden on the lymphatic system, thus reducing tissue water content in women with LI.

Further, in LI a KD may increase lymphatic transport due to decreased lymphatic endothelial cell permeability. Lymph capillary endothelial integrity is impaired with insulin resistance, type 2 diabetes [130,131] and metabolic syndrome [132], all conditions that are associated with high CHO intake. Therefore, a KD may lessen fluid load due to a reduced assault on lymph capillary endothelium. Scallan et al. [131] found reduced lymph vessel permeability in the presence of increased nitric oxide (NO) action in transgenic mice. NO bioavailability is enhanced by L-arginine, an essential amino acid amply provided by KDs. Additionally, higher levels of the AT-derived hormone adiponectin, are associated with lymph vessel formation and improved vessel integrity [133]. Increased levels of adiponectin occur with high fat consumption, ketosis, and KDs [134,135].

Decreasing inflammation

Although historically non-pharmacologic interventions were thought to be ineffective against inflammation, several studies utilizing a form of KD consistently show reduced inflammatory markers [77,135,136]. However, studies have not been done to assess inflammatory biomarkers for LI, so here we look to the effect of KDs on inflammation in other conditions. Observations of the anti-inflammatory effect of KDs in other patient groups can suggest possible mechanisms for this effect in LI.

High-sensitivity C-reactive protein (hsCRP) is a common measure of generalized inflammation and cardiovascular risk. In studies examining cardiovascular disease, a KD was associated with statistically significant hsCRP reduction [77,136]. Santos et al. [137] had a similar finding in a meta-analysis of 23 controlled clinical trials of low CHO diets. In a pre-

bariatric surgery study of 22 patients with obesity, those on a KD had a statistically significant 46% increase in adiponectin, an anti-inflammatory adipokine, compared to those not on a KD [138].

Ketone bodies play a key role in modulating inflammation and reducing oxidative stress [139]. The ketone BHB has been proposed as a potential clinical therapeutic intervention for suppressing NLRP3-mediated pro-inflammatory diseases in animal studies [57] (see Fig. 6). KDs are associated with improved mitochondrial respiration and inhibition of NLRP3 activation. This is accomplished by halting K+ efflux from the cell [57] and decreasing both oxidative stress [110] and extracellular adenosine 5′-triphosphate (eATP) [57,140] as depicted in Fig. 6.

Results from a randomized controlled trial of overweight men and women with dyslipidemia [141] comparing a KD to a low-fat diet suggest that it is the macronutrient composition, and not caloric restriction or weight loss alone, that produces greater anti-inflammatory effects. With respect to patients with LI, it is also important to note that diets targeting reduction of inflammation have been highly recommended by leading LI clinicians and researchers, albeit based on their own expert opinion, anecdotal evidence, and experience [28,142].

Preventing and decreasing fibrosis

While little is known about the natural history of fibrosis in LI, it has been shown that anti-inflammatory KDs are associated with decreased fibrosis in non-alcoholic fatty liver disease (NAFLD). A small pilot study ($n = 5$) in 2007 demonstrated a reduction in inflammation and fibrosis in NAFLD patients who undertook a 6-month KD [143]. Peng et al. [144] and Glass et al. [145] also observed reductions in hepatic fibrosis using a KD to treat NAFLD.

KDs increase adiponectin levels, which may contribute to inhibiting fibrogenesis. Profibrogenic factors such as ROS and leptin are decreased with KDs [110,138,146]. We speculate that a KD may prevent and/or reverse fibrosis in LI, but formal studies are needed to evaluate this prospect.

Conclusion

In conclusion, we present our hypothesis, which is that adopting a KD in patients with LI could directly positively impact the clinical course of their disease, and we describe the proposed mechanisms behind these effects. Studies of these mechanisms need to be done directly on patients with LI (both with and without obesity) who agree to undergo a therapeutic KD. Research should focus on the seven LI impacts described in this paper, and how these are influenced by applying a KD in patients with LI.

In actuality, cross-sectional and observational longitudinal studies of patients with LI, regardless of the type of interventions participants may be using, should seek to gather measurements of all of these seven topics in as optimal a way as possible, and if the research is longitudinal, these measurements should be tracked over time. That way, researchers will have a better understanding of these features of patients with LI in many different life circumstances and undergoing different therapeutic plans, in order to reasonably estimate the actual impact on these factors when applying a KD to this patient population.

Applying KDs in patients with LI can be done in the context of research, but studies must be designed carefully. Clinical trials of diets cannot be blinded, and many patients with obesity and LI have a history of serial dieting. Although diet studies have generally seen low adherence, our experience with our cohort of patients with LI has been the diametric opposite, in that they have been very engaged and adherent. Nevertheless, the research context portends challenges in defining the sample homogenously through inclusion and exclusion criteria (and still recruiting a large enough sample), having accurate and appropriate measurements for all the factors, and, if conducting a clinical trial, having an effective randomization scheme that creates an adequate comparison group representing the counterfactual. One solution to this could be a cross-over design, where diets A and B are studied, and each patient with LI is randomized to either participate in A for a period of time then cross over to B, or vice versa. In a cross-over design, each patient serves as their own control, but time trends can complicate establishing a true counterfactual. What the true counterfactual should be can be debated: is it traditional dieting, since there is no “usual care” for patients with LI?

The purpose of this paper is to encourage research into patients with LI in these seven areas, and to specifically encourage research that examines the potential therapeutic impacts of adopting a KD in this patient population. Although a vast amount of research is needed, not all studies need to be extensive. Small scale researchers with access to patients with LI could lead laboratory studies so that biomarker levels of these patients are better known (especially with respect to thyroid biomarkers). Clinical researchers treating patients with LI could work to design validated instruments to measure LI-related pain or QoL. Due to the large gap in the scientific literature about patients with LI, high quality studies are welcome that help elucidate the topics and mechanisms discussed in this paper to contribute to knowledge about LI in general. Because we feel

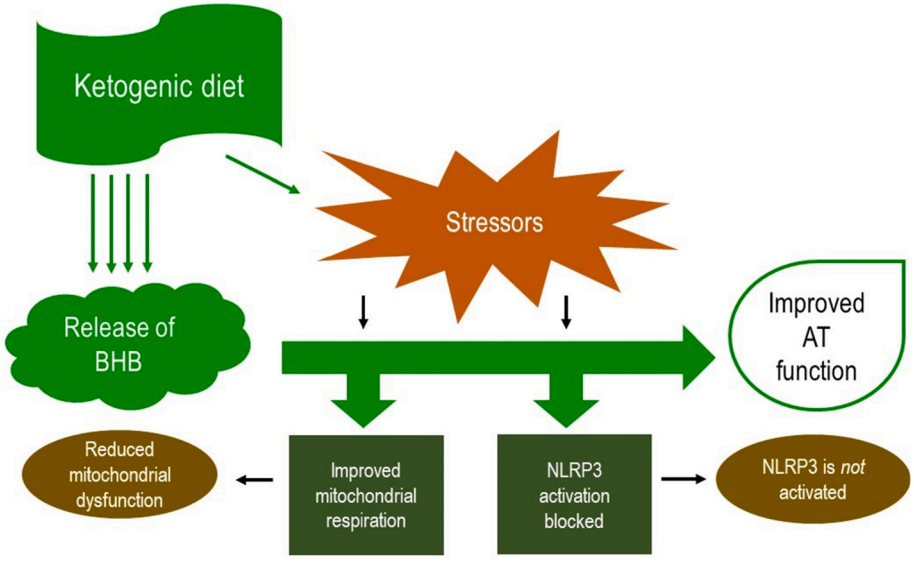

Fig. 6. How a ketogenic diet improves adipose tissue (AT) function. BHB = beta hydroxybutyrate. Stressors reduced include low or zero glucose intake, decreased adipocyte hypertrophy/hyperplasia/hypoxia/necrosis, inhibition of potassium (K+) efflux and reduced ion flux, reduced reactive oxygen species (ROS) and oxidized low density lipoprotein (LDL) improved resistance to oxidative stress and mitochondrial deoxyribonucleic acid (DNA) damage, and improved hormonal regulation. Ketones, such as BHB, are produced, and endogenous stressors are reduced with a ketogenic diet. BHB interrupts NLRP3 inflammasome activation and improves mitochondrial respiration leading to improved AT function.

that currently the most promising treatment for LI appears to be application of a KD, we would specifically recommend that this research includes testing the efficacy of applying a KD. Gathering evidence around the use of KDs in patients with LI can generate further elucidation so that the impacts of this diet are better understood.

Acknowledgements

We thank and acknowledge a worldwide community of lipedema ladies who are brave and stalwart in their efforts to make a difference in their own lives. We also thank those doctors, researchers, surgeons, therapists, advocates, scientists, and other healthcare providers who have stepped forward in support and care for patients with lipedema despite obstacles within the healthcare system.

Conflict of Interest Statement

The authors declare that there is no conflict of interest.

References

[1] Allen EV, Hines EA. Lipedema of the legs: a syndrome characterized by fat legs and orthostatic edema. Proc Staff Meet Mayo Clin 1940;15:184–7.
[2] Wold LE, Hines EA, Allen EV. Lipedema of the legs; a syndrome characterized by fat legs and edema. Ann Intern Med 1951;34:1243–50.
[3] Dayan E, Kim JN, Smith ML, Seo CA, Damstra RJ, Schmeller W, et al. Lipedema - The Disease They Call FAT: An Overview for Clinicians. Boston, MA: Lipedema Simplified Publications; 2017.
[4] Sanchez-De la Torre Y, Wadeea R, Rosas V, Herbst KL. Lipedema: friend and foe. Horm Mol Biol Clin Investig 2018;33. DOI:10.1515/hmbci-2017-0076.
[5] Beninson J, Edelglass JW. Lipedema — the non-lymphatic masquerader. Angiology 1984;35:506–10. https://doi.org/10.1177/000331978403500806.
[6] Herbst KL. Rare adipose disorders (RADs) masquerading as obesity. Acta Pharmacol Sin 2012;33:155–72. https://doi.org/10.1038/aps.2011.153.
[7] Foeldi M, Foeldi E. Földi's Textbook of Lymphology: for Pysicians and Lymphedema Therapists. München: Elsevier Urban & Fischer; 2012.
[8] Dudek JE, Białaszek W, Ostaszewski P. Quality of life in women with lipoedema: a contextual behavioral approach. Qual Life Res 2016;25:401–8. https://doi.org/10.1007/s11136-015-1080-x.
[9] Keast DH, Moffatt C, Janmohammad A. Lymphedema impact and prevalence international study: the Canadian Data. Lymphatic Res Biol 2019;17:178–86. https://doi.org/10.1089/lrb.2019.0014.
[10] Bertsch T, Erbacher G. Lipödem – mythen und fakten teil 1. Phlebologie 2018;47:84–92. https://doi.org/10.12687/phleb2411-2-2018.
[11] Child AH, Gordon KD, Sharpe P, Brice G, Ostergaard P, Jeffery S, Mortimer PS. Lipedema: an inherited condition. Am J Med Genet 2010;152A:970–6. https://doi.org/10.1002/ajmg.a.33313.
[12] Paolacci S, Precone V, Acquaviva F, Chiurazzi P, Fulcheri E, Pinelli M, et al. Genetics of lipedema: new perspectives on genetic research and molecular diagnoses. Eur Rev Med Pharmacol Sci 2019;23:5581–94. https://doi.org/10.26355/eurrev_201907_18292.
[13] Szél E, Kemény L, Groma G, Szolnoky G. Pathophysiological dilemmas of lipedema. Med Hypotheses 2014;83:599–606. https://doi.org/10.1016/j.mehy.2014.08.011.
[14] Buck II DW, Herbst KL. Lipedema: a relatively common disease with extremely common misconceptions. Plastic Reconstr Surg - Global Open 2016;4:e1043. https://doi.org/10.1097/GOX.0000000000001043.
[15] Brown PJ, Konner M. An Anthropological Perspective on Obesity - BROWN - 1987 - Annals of the New York Academy of Sciences - Wiley Online Library 1987. DOI:10.1111/j.1749-6632.1987.tb36195.x (accessed February 3, 2020).
[16] Puhl R, Brownell KD. Bias, discrimination, and obesity. Obes Res 2001;9:788–805. DOI:10.1038/oby.2001.108.
[17] Suga H, Araki J, Aoi N, Kato H, Higashino T, Yoshimura K. Adipose tissue remodeling in lipedema: adipocyte death and concurrent regeneration. J Cutan Pathol 2009;36:1293–8. https://doi.org/10.1111/j.1600-0560.2009.01256.x.
[18] Feinman RD, Pogozelski WK, Astrup A, Bernstein RK, Fine EJ, Westman EC, et al. Dietary carbohydrate restriction as the first approach in diabetes management: critical review and evidence base. Nutrition 2015;31:1–13. https://doi.org/10.1016/j.nut.2014.06.011.
[19] Priglinger E, Wurzer C, Steffenhagen C, Maier J, Hofer V, Peterbauer A, et al. The adipose tissue–derived stromal vascular fraction cells from lipedema patients: are they different? Cytotherapy 2017;19:849–60. https://doi.org/10.1016/j.jcyt.2017.03.073.
[20] Manolopoulos KN, Karpe F, Frayn KN. Gluteofemoral body fat as a determinant of metabolic health. Int J Obes 2010;34:949–59. https://doi.org/10.1038/ijo.2009.286.
[21] Eaton SA, Sethi JK. Immunometabolic links between estrogen, adipose tissue and female reproductive metabolism. Biology 2019;8:8. DOI:10.3390/biology8010008.
[22] Fife CE, Maus EA, Carter MJ. Lipedema: a frequently misdiagnosed and misunderstood fatty deposition syndrome. Adv Skin Wound Care 2010;23:81–92. https://doi.org/10.1097/01.ASW.0000363503.92360.91.
[23] Herbst KL, Mirkovskaya L, Bharhagava A, Chava Y, Te CHT. Lipedema Fat and Signs and Symptoms of Illness, Increase with Advancing Stage. Arch Med 2015;7.
[24] Langendoen SI, Habbema L, Nijsten TEC, Neumann HAM. Lipoedema: From clinical presentation to therapy. A review of the literature. Br J Dermatol 2009;161:980–6. DOI:10.1111/j.1365-2133.2009.09413.x.
[25] Shavit E, Wollina U, Alavi A. Lipoedema is not lymphoedema: a review of current literature. Int Wound J 2018;15:921–8. https://doi.org/10.1111/iwj.12949.
[26] Stutz J. Liposuction in lipedema to prevent later joint complications. Vasomed 2011;23.
[27] Warren-Peled A, Kappos EA. Lipedema: diagnostic and management challenges. Int J Womens Health 2016;8:389–95. https://doi.org/10.2147/IJWH.S106227.
[28] AL-Ghadban S, Cromer W, Allen M, Ussery C, Badowski M, Harris D, et al. Dilated blood and lymphatic microvessels, angiogenesis, increased macrophages, and adipocyte hypertrophy in lipedema thigh skin and fat tissue. J Obesity 2019;2019:1–10. https://doi.org/10.1155/2019/8747461.
[29] Shin BW, Sim Y-J, Jeong HJ, Kim GC. Lipedema, a rare disease. Ann Rehabil Med 2011;35:922. https://doi.org/10.5535/arm.2011.35.6.922.
[30] Dudek JE, Białaszek W, Ostaszewski P, Smidt T. Depression and appearance-related distress in functioning with lipedema. Psychol, Health Med 2018;23:846–53. https://doi.org/10.1080/13548506.2018.1459750.
[31] Fetzer A, Wise C. Living with lipoedema: reviewing different self-management techniques. Br J Commun Nursing 2015;20:S14–9. https://doi.org/10.12968/bjcn.2015.20.Sup10.S14.
[32] Romeijn JRM, de Rooij MJM, Janssen L, Martens H. Exploration of patient characteristics and quality of life in patients with lipoedema using a survey. Dermatol Ther (Heidelb) 2018;8:303–11. https://doi.org/10.1007/s13555-018-0241-6.
[33] Karasu SR. Of mind and matter: psychological dimensions in obesity. APT 2012;66:111–28. https://doi.org/10.1176/appi.psychotherapy.2012.66.2.111.
[34] Fetzer A, Fetzer S. Early lipoedema diagnosis and the RCGP e-learning course. Br J Commun Nursing 2015;20:S22–8. https://doi.org/10.12968/bjcn.2015.20.Sup4.S22.
[35] Kalkhoff RK. Metabolic effects of progesterone. Am J Obstet Gynecol 1982;142:735–8. https://doi.org/10.1016/S0002-9378(16)32480-2.
[36] Mauvais-Jarvis F, Clegg DJ, Hevener AL. The role of estrogens in control of energy balance and glucose. Homeostasis 2013;34:309–38. https://doi.org/10.1210/er.2012-1055.
[37] Ludwig DS, Friedman MI. Increasing adiposity: consequence or cause of overeating? JAMA 2014;311:2167. https://doi.org/10.1001/jama.2014.4133.
[38] Gower BA, Nagy TR, Blaylock ML, Wang C, Nyman L. Estradiol may limit lipid oxidation via Cpt 1 expression and hormonal mechanisms. Obes Res 2002;10:167–72. DOI:10.1038/oby.2002.26.
[39] Pereira RI, Casey BA, Swibas TA, Erickson CB, Wolfe P, Van Pelt RE. Timing of estradiol treatment after menopause may determine benefit or harm to insulin action. J Clin Endocrinol Metab 2015;100:4456–62. https://doi.org/10.1210/jc.2015-3084.
[40] Lindberg U-B, Crona N, Silfverstolpe G, Björntorp P, Rebuffé-Scrive M. Regional adipose tissue metabolism in postmenopausal women after treatment with exogenous sex steroids. Horm Metab Res 1990;22:345–51. https://doi.org/10.1055/s-2007-1004917.
[41] Foeldi E. Lymph/lipoedema treatment in its different approaches. Facts Lipoedema Lymphlipoedema, Emmerich Am Rhein, Germany: BSN-Jobst GmbH & HealthComm UK Ltd; 2009, p. 36–40.
[42] Ochner CN, Barrios DM, Lee CD, Pi-Sunyer FX. Biological mechanisms that promote weight regain following weight loss in obese humans. Physiol Behav 2013;120:106–13. https://doi.org/10.1016/j.physbeh.2013.07.009.
[43] Rowsemitt C, Najarian T. TSH is not the answer: Rationale for a new paradigm to evaluate and treat hypothyroidism, particularly associated with weight loss. Thyroid Sci 2011;6:H1–16.
[44] Ma W, Gil HJ, Escobedo N, Benito-Martín A, Ximénez-Embún P, Muñoz J, et al. Platelet factor 4 is a biomarker for lymphatic-promoted disorders 2020. DOI:10.1172/jci.insight.135109.
[45] Forner-Cordero I, Szolnoky G, Forner-Cordero A, Kemény L. Lipedema: an overview of its clinical manifestations, diagnosis and treatment of the disproportional fatty deposition syndrome - systematic review: lipedema: systematic review. Clin Obesity 2012;2:86–95. https://doi.org/10.1111/j.1758-8111.2012.00045.x.
[46] Forner-Cordero I, Oliván-Sasot P, Ruiz-Llorca C, Muñoz-Langa J. Hallazgos linfogammagráficos en pacientes con lipedema. Rev Esp Med Nucl E Imagen Mol 2018;37:341–8. https://doi.org/10.1016/j.remn.2018.06.008.
[47] Gould DJ, El-Sabawi B, Goel P, Badash I, Colletti P, Patel KM. Uncovering lymphatic transport abnormalities in patients with primary lipedema. J reconstr Microsurg 2020;36:136–41. https://doi.org/10.1055/s-0039-1697904.
[48] Lohrmann C, Foeldi E, Langer M. MR imaging of the lymphatic system in patients with lipedema and lipo-lymphedema. Microvasc Res 2009;77:335–9. https://doi.org/10.1016/j.mvr.2009.01.005.
[49] Crescenzi R, Marton A, Donahue PMC, Mahany HB, Lants SK, Wang P, et al. Tissue sodium content is elevated in the skin and subcutaneous adipose tissue in women with lipedema: tissue sodium is elevated in women with lipedema. Obesity 2018;26:310–7. https://doi.org/10.1002/oby.22090.
[50] Reed RK, Lidén Å, Rubin K. Edema and fluid dynamics in connective tissue remodelling. J Mol Cell Cardiol 2010;48:518–23. https://doi.org/10.1016/j.yjmcc.2009.06.023.

[51] Bhave G, Neilson EG. Body fluid dynamics: back to the future. JASN 2011;22:2166–81. https://doi.org/10.1681/ASN.2011080865.
[52] Monteiro R, Azevedo I. Chronic inflammation in obesity and the metabolic syndrome. Mediators Inflamm 2010;2010:1–10. https://doi.org/10.1155/2010/289645.
[53] Barra NG, Henriksbo BD, Anhê FF, Schertzer JD. The NLRP3 inflammasome regulates adipose tissue metabolism. Biochem J 2020;477:1089–107. https://doi.org/10.1042/BCJ20190472.
[54] Giordano A, Murano I, Mondini E, Perugini J, Smorlesi A, Severi I, et al. Obese adipocytes show ultrastructural features of stressed cells and die of pyroptosis. J. Lipid Res 2013;54:2423–36. https://doi.org/10.1194/jlr.M038638.
[55] Guo H, Callaway JB, Ting J-Y. Inflammasomes: mechanism of action, role in disease, and therapeutics. Nat Med 2015;21:677–87. https://doi.org/10.1038/nm.3893.
[56] Xu Y, Sheng H, Bao Q, Wang Y, Lu J, Ni X. NLRP3 inflammasome activation mediates estrogen deficiency-induced depression- and anxiety-like behavior and hippocampal inflammation in mice. Brain Behav Immun 2016;56:175–86. https://doi.org/10.1016/j.bbi.2016.02.022.
[57] Youm Y-H. The ketone metabolite β-hydroxybutyrate blocks NLRP3 inflammasome–mediated inflammatory disease. Nat Med 2015;21:263–9. https://doi.org/10.1038/nm.3804.
[58] Muñoz-Planillo R, Kuffa P, Martínez-Colón G, Smith B, Rajendiran T, Núñez G. K + efflux is the common trigger of NLRP3 inflammasome activation by bacterial toxins and particulate matter. Immunity 2013;38:1142–53. https://doi.org/10.1016/j.immuni.2013.05.016.
[59] Bergsbaken T, Fink SL, Cookson BT. Pyroptosis: host cell death and inflammation. Nat Rev Microbiol 2009;7:99–109. https://doi.org/10.1038/nrmicro2070.
[60] Itoh M, Suganami T, Hachiya R, Ogawa Y. Adipose tissue remodeling as homeostatic inflammation. Int J Inflamm 2011;2011:1–8. https://doi.org/10.4061/2011/720926.
[61] Latz E, et al. Activation and regulation of the inflammasomes. Nat Rev Immunol 2013;13:397–411. https://doi.org/10.1038/nri3452.
[62] Selders GS, Fetz AE, Radic MZ, Bowlin GL. An overview of the role of neutrophils in innate immunity, inflammation and host-biomaterial integration. Regen Biomater 2017;4:55–68. https://doi.org/10.1093/rb/rbw041.
[63] Wynn T. Cellular and molecular mechanisms of fibrosis. J Pathol 2008;214:199–210. https://doi.org/10.1002/path.2277.
[64] Buechler C, Krautbauer S, Eisinger K. Adipose tissue fibrosis. WJD 2015;6:548. https://doi.org/10.4239/wjd.v6.i4.548.
[65] Marra F. Leptin and liver fibrosis: a matter of fat. Gastroenterology 2002;122:1529–32. https://doi.org/10.1053/gast.2002.33369.
[66] Buso G, Depairon M, Tomson D, Raffoul W, Vettor R, Mazzolai L. Lipedema: a call to action! Obesity 2019;27:1567–76. https://doi.org/10.1002/oby.22597.
[67] Thielitz A, Bellutti M, Bonnekoh B, Franke I, Wiede A, Lotzing M, et al. Progressive lipo-lymphedema associated with increased activity of dermal fibroblasts in monoclonal gammopathy of undetermined significance: Is there a causal relationship? Lymphology 2012;45:124–9.
[68] Wagner. Lymphedema and lipedema - an overview of conservative treatment. Vasa 2011;40:271–9. https://doi.org/10.1024/0301-1526/a000115.
[69] Szolnoky G, Varga E, Varga M, Tuczai M, Dosa-Racz E, Kemeny L. Lymphedema treatment decreases pain intensity in lipedema. Lymphology 2011;44:178–82.
[70] Schmeller W, Meier-Vollrath I. Tumescent liposuction: a new and successful therapy for lipedema. J Cutan Med Surg 2006;10:7–10. https://doi.org/10.1007/7140.2006.00006.
[71] Nourollahi S, Mondry T, Herbst K. Bucher's Broom and selenium improve lipedema: A retrospective case study. Altern Integr Med 2013;02. DOI:10.4172/2327-5162.1000119.
[72] Helmholz HF. The treatment of epilepsy in childhood: five years' experience with the ketogenic diet. JAMA 1927;88:2028–32. https://doi.org/10.1001/jama.1927.02680520018008.
[73] McKenzie AL, Hallberg SJ, Creighton BC, Volk BM, Link TM, Abner MK, et al. A Novel intervention including individualized nutritional recommendations reduces hemoglobin A1c level, medication use, and weight in type 2 diabetes. JMIR Diabetes 2017;2:e5. DOI:10.2196/diabetes.6981.
[74] Volek JS, Fernandez ML, Feinman RD, Phinney SD. Dietary carbohydrate restriction induces a unique metabolic state positively affecting atherogenic dyslipidemia, fatty acid partitioning, and metabolic syndrome. Prog Lipid Res 2008;47:307–18. https://doi.org/10.1016/j.plipres.2008.02.003.
[75] Masino SA, Ruskin DN. Ketogenic diets and pain. J Child Neurol 2013;28:993–1001. https://doi.org/10.1177/0883073813487595.
[76] Seyfried TN. Cancer as a Metabolic Disease: On the Origin, Management, and Prevention of Cancer. Hoboken, N.J: Wiley; 2012.
[77] Athinarayanan SJ, Adams RN, Hallberg SJ, McKenzie AL, Bhanpuri NH, Campbell WW, et al. Long-term effects of a novel continuous remote care intervention including nutritional ketosis for the management of type 2 diabetes: A 2-year non-randomized clinical trial. Front Endocrinol 2019;10. DOI:10.3389/fendo.2019.00348.
[78] Masood W, Uppaluri KR. Ketogenic Diet. StatPearls, Treasure Island (FL): StatPearls Publishing; 2020.
[79] de Git KCG, Adan RAH. Leptin resistance in diet-induced obesity: the role of hypothalamic inflammation: Leptin resistance and inflammation. Obes Rev 2015;16:207–24. https://doi.org/10.1111/obr.12243.
[80] Kinzig KP, Honors MA, Hargrave SL, Davenport BM, Strader AD, Wendt D. Sensitivity to the anorectic effects of leptin is retained in rats maintained on a ketogenic diet despite increased adiposity. Neuroendocrinology 2010;92:100–11. https://doi.org/10.1159/000314180.
[81] Banting W. Letter on Corpulence, addressed to the public ... Second edition, with addenda. Harrison; 1869.
[82] Westman EC, Phinney SD, Volek J. The New Atkins for a New You: The Ultimate Diet for Shedding Weight and Feeling Great Forever. New York: Simon & Schuster; 2010.
[83] Gershuni VM, Yan SL, Medici V. Nutritional ketosis for weight management and reversal of metabolic syndrome. Curr Nutr Rep 2018;7:97–106. https://doi.org/10.1007/s13668-018-0235-0.
[84] Westman EC, Mavropoulos J, Yancy Jr WS, Volek JS. A review of low-carbohydrate ketogenic diets. Curr Atheroscler Rep 2003;5:476–83. https://doi.org/10.1007/s11883-003-0038-6.
[85] Hoyt LT, Falconi AM. Puberty and perimenopause: reproductive transitions and their implications for women's health. Soc Sci Med 2015;132:103–12. https://doi.org/10.1016/j.socscimed.2015.03.031.
[86] Gustafson B, Hedjazifar S, Gogg S, Hammarstedt A, Smith U. Insulin resistance and impaired adipogenesis. Trends Endocrinol Metab 2015;26:193–200. https://doi.org/10.1016/j.tem.2015.01.006.
[87] Holland AM, Kephart WC, Mumford PW, Lowery RP, Mobley CB, Healy J, et al. The effects of a ketogenic diet and physical activity on adipose tissue characteristics. FASEB J 2016;30. https://doi.org/10.1096/fasebj.30.1_supplement.lb223. lb223–lb223.
[88] Rasmussen L, Christensen ML, Poulsen CW, Rud C, Christensen AS, Andersen JR, et al. Effect of high versus low carbohydrate intake in the morning on glycemic variability and glycemic control measured by continuous blood glucose monitoring in women with gestational diabetes mellitus—A randomized crossover study. Nutrients 2020;12:475. DOI:10.3390/nu12020475.
[89] Habegger KM, Heppner KM, Geary N, Bartness TJ, DiMarchi R, Tschöp MH. The metabolic actions of glucagon revisited. Nat Rev Endocrinol 2010;6:689–97. https://doi.org/10.1038/nrendo.2010.187.
[90] Jones BJ, Tan T, Bloom SR. Minireview: Glucagon in stress and energy homeostasis. Endocrinology 2012;153:1049–54. DOI:10.1210/en.2011-1979.
[91] Eaton RP, Schade DS. Glucagon resistance as a hormonal basis for endogenous hyperlipaemia. Lancet 1973;301:973–4. https://doi.org/10.1016/S0140-6736(73)91605-X.
[92] Savage PJ, Bennion LJ, Bennett PH. Normalization of insulin and glucagon secretion in ketosis-resistant diabetes mellitus with prolonged diet therapy*. J Clin Endocrinol Metab 1979;49:830–3. https://doi.org/10.1210/jcem-49-6-830.
[93] Cooper MA, Menta BW, Perez-Sanchez C, Jack MM, Khan ZW, Ryals JM, Winter M, Wright DE. A ketogenic diet reduces metabolic syndrome-induced allodynia and promotes peripheral nerve growth in mice. Exp Neurol 2018;306:149–57. https://doi.org/10.1016/j.expneurol.2018.05.011.
[94] Ruskin DN, Kawamura M, Masino SA. Reduced pain and inflammation in juvenile and adult rats fed a ketogenic diet. PLoS ONE 2009;4. DOI:10.1371/journal.pone.0008349.
[95] Totsch SK, Waite ME, Tomkovich A, Quinn TL, Gower BA, Sorge RE. Total Western Diet (TWD) alters mechanical and thermal sensitivity and prolongs hypersensitivity following Complete Freund's Adjuvant in mice. J Pain Off J Am Pain Soc 2016;17:119–25. https://doi.org/10.1016/j.jpain.2015.10.006.
[96] Strath LJ, Jones CD, Philip George A, Lukens SL, Morrison SA, Soleymani T, et al. The Effect of Low-Carbohydrate and Low-Fat Diets on Pain in Individuals with Knee Osteoarthritis. Pain Med 2019. DOI:10.1093/pm/pnz022.
[97] Yancy Jr WS, Almirall D, Maciejewski ML, Kolotkin RL, McDuffie JR, Westman EC. Effects of two weight-loss diets on health-related quality of life. Qual Life Res 2009;18. https://doi.org/10.1007/s11136-009-9444-8.
[98] Lipodiet SV. Effect of a low-carbohydrate high fat-diet on pain and quality of life in patients with lipedema. Masters Thesis. University of Oslo; 2019.
[99] Petroni ML, Villanova N, Avagnina S, Fusco MA, Fatati G, Compare A, Marchesini G. Psychological distress in morbid obesity in relation to weight history. Obes Surg 2007;17:391–9. https://doi.org/10.1007/s11695-007-9069-3.
[100] Gangwisch JE, Hale L, Garcia L, Malaspina D, Opler MG, Payne ME, et al. High glycemic index diet as a risk factor for depression: Analyses from the Women's Health Initiative. Am J Clin Nutr 2015;102:454–63. DOI:10.3945/ajcn.114.103846.
[101] Matta J, Czernichow S, Kesse-Guyot E, Hoertel N, Limosin F, Goldberg M, et al. Depressive symptoms and vegetarian diets: Results from the Constances Cohort. Nutrients 2018;10. DOI:10.3390/nu10111695.
[102] Meesters ANR, Maukonen M, Partonen T, Männistö S, Gordijn MCM, Meesters Y. Is there a relationship between vegetarianism and seasonal affective disorder? A pilot study. Neuropsychobiology 2016;74:202–6. DOI:10.1159/000477247.
[103] Michalak J, Zhang X, Jacobi F. Vegetarian diet and mental disorders: results from a representative community survey. Int J Behav Nutr Phys Act 2012;9(1):67. https://doi.org/10.1186/1479-5868-9-67.
[104] Spring B, Schneider K, Smith M, Kendzor D, Appelhans B, Hedeker D, Pagoto S. Abuse potential of carbohydrates for overweight carbohydrate cravers. Psychopharmacology 2008;197:637–47. https://doi.org/10.1007/s00213-008-1085-z.
[105] Garcia-Penas JJ. Epilepsy, cognition and ketogenic diet. Rev Neurol 2018;66:S71–5.
[106] Murphy P, Likhodii S, Nylen K, Burnham WM. The antidepressant properties of the ketogenic diet. Biol Psychiatry 2004;56:981–3. https://doi.org/10.1016/j.biopsych.2004.09.019.
[107] Brietzke E, Mansur RB, Subramaniapillai M, Balanzá-Martínez V, Vinberg M, González-Pinto A, Rosenblat JD, Ho R, McIntyre RS. Ketogenic diet as a metabolic therapy for mood disorders: evidence and developments. Neurosci Biobehav Rev 2018;94:11–6. https://doi.org/10.1016/j.neubiorev.2018.07.020.

[108] Koppel SJ, Swerdlow RH. Neuroketotherapeutics: a modern review of a century-old therapy. Neurochem Int 2018;117:114–25. https://doi.org/10.1016/j.neuint.2017.05.019.
[109] Achanta LB, Rae CD. β-Hydroxybutyrate in the brain: one molecule, multiple mechanisms. Neurochem Res 2017;42:35–49. https://doi.org/10.1007/s11064-016-2099-2.
[110] Pinto A, Bonucci A, Maggi E, Corsi M, Businaro R. Anti-Oxidant and Anti-Inflammatory Activity of Ketogenic Diet: New Perspectives for Neuroprotection in Alzheimer's Disease. Antioxidants 2018;7:63. DOI:10.3390/antiox7050063.
[111] Raison CL. The Promise and Limitations of Anti-inflammatory Agents for the Treatment of Major Depressive Disorder. In: Dantzer R, Capuron L, editors. Inflamm.-Assoc. Depress. Evid. Mech. Implic., Cham: Springer International Publishing; 2017, p. 287–302. DOI:10.1007/7854_2016_26.
[112] Shariq AS, Brietzke E, Rosenblat JD, Barendra V, Pan Z, McIntyre RS. Targeting cytokines in reduction of depressive symptoms: a comprehensive review. Prog Neuro-Psychopharmacol Biol Psychiatry 2018;83:86–91. https://doi.org/10.1016/j.pnpbp.2018.01.003.
[113] Bostock ECS, Kirkby KC, Taylor BVM. The current status of the ketogenic diet in psychiatry. Front Psychiatry 2017;8. DOI:10.3389/fpsyt.2017.00043.
[114] Gardner DF, Kaplan MM, Stanley CA, Utiger RD. Effect of tri-iodothyronine replacement on the metabolic and pituitary responses to starvation. N Engl J Med 1979;300:579–84. https://doi.org/10.1056/NEJM197903153001102.
[115] Gomez-Arbelaez D, Crujeiras AB, Castro AI, Martinez-Olmos MA, Canton A, Ordoñez-Mayan L, Sajoux I, Galban C, Bellido D, Casanueva FF. Resting metabolic rate of obese patients under very low calorie ketogenic diet. Nutr Metab (Lond) 2018;15. https://doi.org/10.1186/s12986-018-0249-z.
[116] Mathieson RA, Walberg JL, Gwazdauskas FC, Hinkle DE, Gregg JM. The effect of varying carbohydrate content of a very-low-caloric diet on resting metabolic rate and thyroid hormones. Metabolism 1986;35:394–8. https://doi.org/10.1016/0026-0495(86)90126-5.
[117] Pasquali R, Parenti M, Mattioli L, Capelli M, Cavazzini G, Baraldi G, Sorrenti G, De Benedettis G, Biso P, Melchionda N. Effect of dietary carbohydrates during hypocaloric treatment of obesity on peripheral thyroid hormone metabolism. J Endocrinol Invest 1982;5:47–52. https://doi.org/10.1007/BF03350482.
[118] Douyon L, Schteingart DE. Effect of obesity and starvation on thyroid hormone, growth hormone, and cortisol secretion. Endocrinol Metab Clin North Am 2002;31:173–89. https://doi.org/10.1016/S0889-8529(01)00023-8.
[119] Volek JS, Sharman MJ, Love DM, Avery NG, G[oacute]mez AL, Scheett TP, Kraemer WJ. Body composition and hormonal responses to a carbohydrate-restricted diet. Metabolism 2002;51:864–70. https://doi.org/10.1053/meta.2002.32037.
[120] Nuttall FQ, Gannon MC. The metabolic response to a high-protein, low-carbohydrate diet in men with type 2 diabetes mellitus. Metabolism 2006;55:243–51. https://doi.org/10.1016/j.metabol.2005.08.027.
[121] Hales CM, Carroll MD, Fryar CD, Ogden CL. Prevalence of obesity among adults and youth: United States, 2015–2016. NCHS Data Brief 2017:1–8.
[122] Casazza K, Goran MI, Gower BA. Associations among insulin, estrogen, and fat mass gain over the pubertal transition in African-American and European-American girls. J Clin Endocrinol Metab 2008;93:2610–5. DOI:10.1210/jc.2007-2776.
[123] Marsh EE, Shaw ND, Klingman KM, Tiamfook-Morgan TO, Yialamas MA, Sluss PM, et al. Estrogen levels are higher across the menstrual cycle in African-American women compared with Caucasian women. J Clin Endocrinol Metab 2011;96:3199–206. DOI:10.1210/jc.2011-1314.
[124] Chandler-Laney PC, Phadke RP, Granger WM, Fernández JR, Muñoz JA, Man CD, et al. Age-related changes in insulin sensitivity and β-cell function among European-American and African-American women. Obesity 2011;19:528–35. DOI:10.1038/oby.2010.212.
[125] Gower BA, Alvarez JA, Bush NC, Hunter GR. Insulin sensitivity affects propensity to obesity in an ethnic-specific manner: results from two controlled weight loss intervention studies. Nutr Metab (Lond) 2013;10:3. https://doi.org/10.1186/1743-7075-10-3.
[126] Gower BA, Goss AM. A lower-carbohydrate, higher-fat diet reduces abdominal and intermuscular fat and increases insulin sensitivity in adults at risk of type 2 diabetes. J Nutr 2015;145:177S-183S. DOI:10.3945/jn.114.195065.
[127] Keith L, Rowsemitt C, Richards LG. Lifestyle modification group for lymphedema and obesity results in significant health outcomes. Am J Lifestyle Med 2020;14:420–8. https://doi.org/10.1177/1559827617742108.
[128] Fernández-Elías VE, Ortega JF, Nelson RK, Mora-Rodriguez R. Relationship between muscle water and glycogen recovery after prolonged exercise in the heat in humans. Eur J Appl Physiol 2015;115:1919–26. https://doi.org/10.1007/s00421-015-3175-z.
[129] Kreitzman SN, Coxon AY, Szaz KF. Glycogen storage: Illusions of easy weight loss, excessive weight regain, and distortions in estimates of body composition. Am J Clin Nutr 1992;56:292S-293S. DOI:10.1093/ajcn/56.1.292S.
[130] Lee Y, Chakraborty S, Meininger CJ, Muthuchamy M. Insulin resistance disrupts cell integrity, mitochondrial function, and inflammatory signaling in lymphatic endothelium. Microcirculation 2018;25:e12492. https://doi.org/10.1111/micc.12492.
[131] Scallan JP, Hill MA, Davis MJ. Lymphatic vascular integrity is disrupted in type 2 diabetes due to impaired nitric oxide signalling. Cardiovasc Res 2015;107:89–97. DOI:10.1093/cvr/cvv117.
[132] Zawieja SD, Wang W, Wu X, Nepiyushchikh ZV, Zawieja DC, Muthuchamy M. Impairments in the intrinsic contractility of mesenteric collecting lymphatics in a rat model of metabolic syndrome. Am J Physiol-Heart Circ Physiol 2012;302:H643–53. https://doi.org/10.1152/ajpheart.00606.2011.
[133] Shimizu Y, Shibata R, Ishii M, Ohashi K, Kambara T, Uemura Y, Yuasa D, Kataoka Y, Kihara S, Murohara T, Ouchi N. Adiponectin-mediated modulation of lymphatic vessel formation and lymphedema. JAHA 2013;2. https://doi.org/10.1161/JAHA.113.000438.
[134] Bertoli S, Neri IG, Trentani C, Ferraris C, De Amicis R, Battezzati A, Veggiotti P, De Giorgis V, Tagliabue A. Short-term effects of ketogenic diet on anthropometric parameters, body fat distribution, and inflammatory cytokine production in GLUT1 deficiency syndrome. Nutrition 2015;31:981–7. https://doi.org/10.1016/j.nut.2015.02.017.
[135] Partsalaki I, Karvela A, Spiliotis BE. Metabolic impact of a ketogenic diet compared to a hypocaloric diet in obese children and adolescents. J Pediatr Endocrinol Metab JPEM 2012;25:697–704. https://doi.org/10.1515/jpem-2012-0131.
[136] Bhanpuri et al. Cardiovascular disease risk factor responses to a type 2 diabetes care model including nutritional ketosis induced by sustained carbohydrate restriction at 1 year: an open label, non-randomized, controlled study 2018. https://doi.org/10.1186/s12933-018-0698-8.
[137] Santos. Systematic review and meta-analysis of clinical trials of the effects of low carbohydrate diets on cardiovascular risk factor 2012. DOI:10.1111/j.1467-789X.2012.01021.x.
[138] Yang W-S, Lee W-J, Funahashi T, Tanaka S, Matsuzawa Y, Chao C-L, Chen C-L, Tai T-Y, Chuang L-M. Weight reduction increases plasma levels of an adipose-derived anti-inflammatory. Protein Adiponectin 2001;86:3815–9. https://doi.org/10.1210/jcem.86.8.7741.
[139] Puchalska P, Crawford PA. Multi-dimensional roles of ketone bodies in fuel metabolism, signaling, and therapeutics. Cell Metab 2017;25:262–84. https://doi.org/10.1016/j.cmet.2016.12.022.
[140] Dela Cruz CS, Kang M-J. Mitochondrial dysfunction and damage associated molecular patterns (DAMPs) in chronic inflammatory diseases. Mitochondrion 2018;41:37–44. https://doi.org/10.1016/j.mito.2017.12.001.
[141] Forsythe CE, Phinney SD, Fernandez ML, Quann EE, Wood RJ, Bibus DM, Kraemer WJ, Feinman RD, Volek JS. Comparison of low fat and low carbohydrate diets on circulating fatty acid composition and markers of inflammation. Lipids 2008;43:65–77. https://doi.org/10.1007/s11745-007-3132-7.
[142] Faerber G. Adipositas und chronische Inflammation bei phlebologischen und lymphologischen Erkrankungen. Phlebologie 2018;47:55–65. https://doi.org/10.12687/phleb2413-2-2018.
[143] Tendler D, Lin S, Yancy Jr WS, Mavropoulos J, Sylvestre P, Rockey DC, Westman EC. The effect of a low-carbohydrate, ketogenic diet on nonalcoholic fatty liver disease: a pilot study. Dig Dis Sci 2007;52:589–93. https://doi.org/10.1007/s10620-006-9433-5.
[144] Peng Y, Rideout DA, Rakita SS, Gower Jr WR, You M, Murr MM. Does LKB1 Mediate Activation of Hepatic AMP-Protein Kinase (AMPK) and Sirtuin1 (SIRT1) After Roux-en-Y Gastric Bypass in Obese Rats? J Gastrointest Surg 2010;14:221–8. https://doi.org/10.1007/s11605-009-1102-5.
[145] Glass LM, Dickson RC, Anderson JC, Suriawinata AA, Putra J, Berk BS, Toor A. Total Body Weight Loss of ≥10 % is associated with improved hepatic fibrosis in patients with nonalcoholic steatohepatitis. Dig Dis Sci 2015;60:1024–30. https://doi.org/10.1007/s10620-014-3380-3.
[146] Fragala MS, Kraemer WJ, Volek JS, Maresh CM, Puglisi MJ, Vingren JL, Ho J-Y, Hatfield DL, Spiering BA, Forsythe CE, Thomas GA, Quann EE, Anderson JM, Hesslink Jr RL. Influences of a dietary supplement in combination with an exercise and diet regimen on adipocytokines and adiposity in women who are overweight. Eur J Appl Physiol 2009;105(5). https://doi.org/10.1007/s00421-008-0944-y.