

Review

Ketogenic Diet and Weight Loss: Is There an Effect on Energy Expenditure?

Alessio Basolo , Silvia Magno , Ferruccio Santini  and Giovanni Ceccarini * 

Obesity and Lipodystrophy Center, Endocrinology Unit, University Hospital of Pisa, 56124 Pisa, Italy; alessio.basolo@med.unipi.it (A.B.); silviagemagno9@gmail.com (S.M.); ferruccio.santini@unipi.it (F.S.)

* Correspondence: giovanni.ceccarini@unipi.it; Tel.: +39-050-997380; Fax: +39-050-578772

Abstract: A dysregulation between energy intake (EI) and energy expenditure (EE), the two components of the energy balance equation, is one of the mechanisms responsible for the development of obesity. Conservation of energy equilibrium is deemed a dynamic process and alterations of one component (energy intake or energy expenditure) lead to biological and/or behavioral compensatory changes in the counterpart. The interplay between energy demand and caloric intake appears designed to guarantee an adequate fuel supply in variable life contexts. In the past decades, researchers focused their attention on finding efficient strategies to fight the obesity pandemic. The ketogenic or “keto” diet (KD) gained substantial consideration as a potential weight-loss strategy, whereby the concentration of blood ketones (acetoacetate, 3- β -hydroxybutyrate, and acetone) increases as a result of increased fatty acid breakdown and the activity of ketogenic enzymes. It has been hypothesized that during the first phase of KDs when glucose utilization is still prevalent, an increase in EE may occur, due to increased hepatic oxygen consumption for gluconeogenesis and for triglyceride-fatty acid recycling. Later, a decrease in 24-h EE may ensue due to the slowing of gluconeogenesis and increase in fatty acid oxidation, with a reduction of the respiratory quotient and possibly the direct action of additional hormonal signals.

Keywords: ketogenic diet; energy expenditure; food intake; thermic effect of food



Citation: Basolo, A.; Magno, S.; Santini, F.; Ceccarini, G. Ketogenic Diet and Weight Loss: Is There an Effect on Energy Expenditure? *Nutrients* **2022**, *14*, 1814. <https://doi.org/10.3390/nu14091814>

Academic Editors: Carla Lubrano, Giovanni Spera, Mikiko Watanabe and Silvia Savastano

Received: 22 March 2022

Accepted: 24 April 2022

Published: 26 April 2022

Publisher's Note: MDPI stays neutral with regard to jurisdictional claims in published maps and institutional affiliations.



Copyright: © 2022 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<https://creativecommons.org/licenses/by/4.0/>).

1. Introduction

Obesity is a relevant public health issue, and its prevalence has increased dramatically in the past decades. It is estimated that 39% of the globe population is overweight and 13% suffer from obesity [1]. The chronic uncoupling of the two components of the energy balance equation, energy intake (EI) and energy expenditure (EE), is classically thought to be responsible for the progressive increase in body weight [2–4]. Daily caloric intake oscillates due to various individual and environmental factors. On the other hand, energy expenditure is influenced by body composition, physical activity, and food utilization [5]. Although a “lifestyle change approach”, aimed at reducing caloric intake and increasing physical activity, is crucial to promote weight loss, there is no strong evidence to recommend one dietary regimen as more effective over another. For the theory based on the “carbohydrate–insulin model”, a relative increase in carbohydrate intake leads to an increase in insulin secretion that facilitates the accumulation of body fat [6,7]. This model has been disputed [8] since it claims the exclusivity of the insulin and carbohydrate role in the development of obesity. Indeed, adipose fat storage might also occur during low-carbohydrate dietary regimens whenever energy consumption exceeds expenditure. Variations of leptin and incretin levels, amino acid intake, and the autonomic neural system activity all converge on the central mechanisms of control of energy balance and may favor an increased body adiposity, independently of carbohydrate intake or insulin levels [9–12]. In any case, the physiological premise of ketogenic diets (KDs) is that by reducing carbohydrate intake, without altering the protein load, a decrease in insulin secretion will

follow, promoting fatty acid oxidation. Fat mobilization will occur in case a caloric deficit is established, which is facilitated by the anorectic effect of ketone bodies, with minor effects on lean body mass. Whether KDs affect energy expenditure is poorly understood and, to date, very few studies have evaluated the impact of KDs on energy consumption. The aim of the current review was to describe the current evidence on the potential effect of KDs on energy expenditure in subjects with obesity.

2. The Ketogenic Diet

KDs are characterized by a markedly reduced carbohydrate intake (<30 g/day) and a normal protein contribution (1.2–1.5 g/kg of ideal body weight or 1.0–1.2 g/kg of fat free mass). They are frequently used as therapeutic strategies in the treatment of obesity, type 2 diabetes mellitus, and other medical conditions, such as migraine [13–15], polycystic ovary syndrome [16], cancer [17], neurodegenerative diseases [18–20], and epilepsy [21]. Furthermore, it has been proposed that ketone bodies might play a role in the regulation of biological processes (meal timing, appetite, and sleep cycle) involved in the maintenance of circadian rhythms (elegantly reviewed in [22]), the desynchronization of which might lead to development of obesity [4]. A reduction of mitochondrial function leading to the excessive production of reactive oxygen species appears to be involved in the etiology of several chronic diseases, including obesity and diabetes [23]. It has been hypothesized that KDs may stimulate the mitochondrial function and the endogenous antioxidant defense, by increasing hormones (i.e., adiponectin) that activate key enzymes involved in the induction of signal transduction, including AMP-activated protein kinase (AMPK) [24]. KDs gained substantial consideration in 1970s when they were advertised and commercialized by Dr. Atkins as an efficacious weight-loss strategy [25]. The most used variants of KDs in obesity management can be distinguished in two types, based on calories introduced: (1) LCKD: low calorie ketogenic diet, providing a total daily energy intake of 800–1200 [26,27]; (2) VLCKD: very low calorie ketogenic diet, with an energy intake of <800 kcal/day [28–30].

The reduction of insulin concentration, caused by a low carbohydrate intake, leads to metabolic changes, such as increased glycogenolysis, gluconeogenesis, and lipolysis [31–35]. When the stored glucose is fully depleted, the body starts to use fat as the primary energetic substrate. The latter catabolic pathway is responsible for the production of free fatty acids which, in turn, are broken down to acetyl coenzyme A (CoA) through beta-oxidation in the mitochondria of hepatocytes. Acetyl coenzyme A (CoA) is converted to 3-hydroxy-3-methyl-glutaryl-CoA (HMG CoA) which, in turn, generates the ketone body acetoacetate [36], starting the ketogenic process. Further, acetoacetate can be converted to acetone or 3- β -hydroxybutyrate [36]. Ketone bodies are an alternative energetic substrate generated from stored fat for specific organs, including the heart, brain, and skeletal muscle [31,36–38] (Figure 1). The metabolic state of ketosis observed during fasting or KD is benign and should not be confused with the pathological ketoacidosis occurring in type I diabetes mellitus [32], a harmful condition [39].

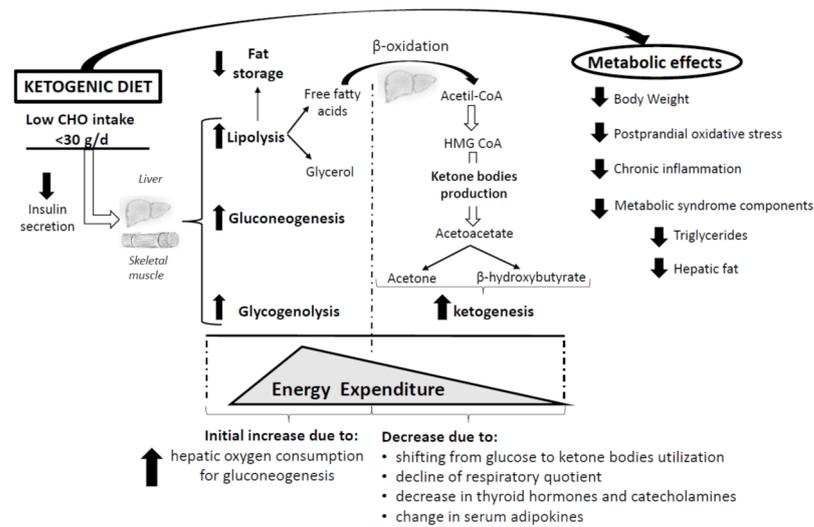


Figure 1. Metabolic effects of ketogenic diets. Carbohydrates are the primary source of energy production in body tissues. When carbohydrate intake is less than 30 g per day, insulin secretion decreases, leading to an increase in glycogenolysis, gluconeogenesis, and lipolysis. When glucose disposal decreases further, gluconeogenesis cannot replace the necessary needs of the body. Thus, the increased lipolysis leads to the enhanced production of free fatty acids which, in turn, are converted to Acetyl-CoA through beta-oxidation. This process leads to the production of ketone bodies (acetoacetate, acetone, and 3- β -hydroxybutyrate) that provide “extra fuel” to various tissues. The beneficial metabolic effects of the KDs are represented on the right side of Table 1. Regarding the effects on energy metabolism, it has been hypothesized that a rapid increase in EE may initially occur due to increased hepatic oxygen consumption for gluconeogenesis. Later, a decrease in 24-h EE occurs due to the slowing of gluconeogenesis, a decrease in the respiratory quotient due to increased utilization of ketone bodies, a reduction of thyroid hormones and catecholamines, and changes in serum adipokines. g/d: grams per day.

3. Hints on Energy Expenditure Components

The rate of whole-body energy expenditure (EE) changes significantly over the 24-h period and can be precisely measured with an open circuit whole room indirect calorimeter, also known as the respiratory chamber [40,41]. This method is considered the gold standard for the measurement of energy expenditure over 24 h because of the ability to differentiate its components, such as resting metabolic rate (RMR), thermogenic effect of food, and the energy cost of physical activity.

Lean body mass is the main determinant of RMR, accounting for ~70% of its variance [5,42,43], while other factors, such as fat mass, sex, age, race, and familial genetic background, explain an extra ~15% [44]. The raise in energy needed to digest and absorb nutrients following food consumption [45] is defined as thermogenic effect of food and it accounts for ~10% of the 24-h EE [46,47], although a large variability among subjects can be observed. The energy consumed for spontaneous and voluntary physical activity has proven the most flexible element of 24-h EE, diverging from ~15% in sedentary individuals to ~50% in active subjects [48].

4. Energy Balance Regulation and Metabolic Adaption

Historically, the mechanisms underlying the pathogenesis of obesity are based on a simplistic model of energy balance, which implies that a chronic positive energy balance (i.e., caloric intake constantly overcoming energy expenditure) causes a storage of energy surplus with a consequent increase in body weight [2]. This static model presumes that oscillations in energy intake and energy expenditure affect the energy balance in an independent manner. Emerging evidence suggests that these components are controlled by a more complex model in which the perturbation of one component (energy intake or energy

expenditure) leads to biological and/or behavioral compensatory changes in the other, with the aim of preserving body weight and body energy stores within a steady range. Specifically, an increase in the energy expenditure would lead to increased food intake (and vice versa), whereas a decrease in the energy demand would lead to reduction of the energy intake (and vice versa) [3,49,50]. Recently, researchers have focused their attention on studying the adaptive response of one component to changes of the other constituent of the energy balance equation. These studies have led to the identification of different metabolic phenotypes (“spendthrift” and “thrifty”) that are classified based on changes in EE during acute (fasting or overfeeding) dietary interventions [51–54]. The “spendthrift” phenotype is characterized by smaller decreases in EE during fasting and larger increases in EE during overfeeding, whereas the “thrifty” one is an energy-efficient phenotype characterized by a larger decrease in EE during fasting and modest increases in EE during over-feeding [3,4]. Although the mechanisms underlying the metabolic EE response to dietary intervention are not fully elucidated, it has been suggested that changes in body composition [47], hormone levels [55–58], core body temperature [53] brown adipose tissue activity [59,60], and sympathetic nervous system tone [61–63] might play a role in the regulation of the “adaptive metabolic mechanism”.

“Metabolic adaption” is defined as a physiological mechanism leading to a reduction in RMR following weight loss, which is greater than that predicted by fat mass and fat free mass reduction [64]. This adaptation is thought to be one of the mechanisms whereby the body resists further weight loss, thus leading subjects to easily regain weight. Milestone studies have demonstrated a marked and persistent metabolic adaption following weight loss both in normal weight and obese subjects [65,66]. The degree of metabolic adaptation is related not only to the extent of weight loss, but also to the velocity of body weight reduction [67]. In subjects with obesity who participated in the televised weight-loss competition “Biggest Loser” and lost nearly 40% of their initial body weight during a 30 week-program thanks to a calorie-restricted diet greater than 70% of their baseline energy requirements and supervised vigorous training, a very remarkable metabolic adaption could be demonstrated, despite a relative preservation of their fat-free mass [67]. Fothergill et al. demonstrated that contestants of “The Biggest Loser” showed a metabolic adaption (of approximately 500 kcal/day) which persisted six years after the end of the TV-show and despite a marked weight regain [68]. In recent perspectives [64,69], it has been highlighted that a major reduction in body weight, such as the one obtained by the participants of the “Biggest Loser”, is almost impossible to be maintained when subjects return to their natural environment unless an extraordinarily high level of physical activity is kept. Major physiological responses to weight loss, which explain the weight regain phenomenon, are the persistence of a lower RMR, limited attitude towards physical activity, reduction in fat oxidation, and persistence of an increased appetite caused by the simultaneous increase of orexigenic and reduction of anorexic signals [70]. In particular, hormones, such as leptin, insulin, peptide YY (PYY), oxyntomodulin, irisin, adiponectin, and ghrelin, control food intake and energy balance by regulating orexigenic and anorexic pathways acting on the hypothalamic nuclei [49,71,72].

5. The Impact of Ketogenic Diet on Energy Expenditure

With this premise in mind, it is intriguing to ask which effects KD, a calorie-restricted dietary intervention for weight loss, may display on energy expenditure. Studies on this topic are unfortunately scant and somehow controversial. Furthermore, no studies have been conducted following patients in the long-term and possibly documenting the effects of KD on metabolic adaption. In the last decade, some clinical trials evaluating the role of KD on body weight and body composition have shown that patients assigned to a VLCKD and compared to individuals fed with a standard LC diet showed a higher reduction in body weight, waist circumference, and body fat mass with no measurable change in the fat free mass [27,73–75], suggesting a role of KD in sparing the lean mass.

In the study of Ebbeling et al. [76], 21 individuals with overweight or obesity, after reaching a 10–15% reduction of body weight with a run-in diet, were randomized by a cross-over trial to an isocaloric low-fat diet (60% of energy from carbohydrate, 20% from fat, 20% from protein; high glycemic load), low-glycemic index diet (40% from carbohydrate, 40% from fat, and 20% from protein; moderate glycemic load), and very low-carbohydrate diet (10% from carbohydrate, 60% from fat, and 30% from protein; low glycemic load) for a four-week-period. During isocaloric feeding following weight loss, TEE was about 300 kcal/day greater with the VLC diet compared to the LF diet. At variance, in the study by Hall et al. in males with overweight or obesity, fed initially with a high-carbohydrate high-sugar diet for four weeks followed by a KD of the same caloric intake with comparable protein amount, only a small increase in TEE (by ~100 kcal/day) in the first week of KD intervention was observed, followed by a linear decrease of TEE over time [77]. In that study, the increase of EE was observed during sleep, whereas no change in PA and TEF were observed. In a study conducted in women with obesity randomly assigned to a VLCKD or LF diet with similar caloric intake, although the reduction in fat mass and fat free mass was twice higher in those fed with VLCKD, no difference in REE measured by indirect calorimeter was observed [78]. In a randomized controlled trial [79], 32 individuals with overweight were divided into two groups. One underwent three dietary intervention steps (20-day period of LCKD with 848 kcal/day; 20-day period of LC non-ketogenic diet with 938 kcal/day; two-month period of Mediterranean diet (MD) with 1400 kcal/day), whereas the other group was assigned to a three-step regimen (20-day period of MD with 1200 kcal/day, 20-day period of MD with 1400 kcal/day, two-month period of MD with 1400 kcal/day). No difference in REE was observed between KD and MD. Similarly, in a recent study conducted in 16 male soccer players randomized to VLCKD or Western diet, despite a reduction in fat free mass, no change in REE measured with indirect calorimetry was observed between the two groups [80]. The most important clinical trials investigating the effect of KD on energy expenditure are reported in Table 1.

Table 1. Clinical trials investigating the effect of KD on energy expenditure.

Study	Study Design	Effect on Energy Expenditure
Ebbeling et al. [76]	21 individuals with overweight or obesity, after reaching a 10 to 15% reduction of body weight with a run-in diet, were randomized by a cross-over trial to an isocaloric low-fat diet (LF: 60% of energy from carbohydrate, 20% from fat, 20% from protein; high glycemic load), low-glycemic index diet (LGI: 40% from carbohydrate, 40% from fat, and 20% from protein; moderate glycemic load), and very low-carbohydrate diet (VLC:10% from carbohydrate, 60% from fat, and 30% from protein; low glycemic load) for a 4 week-period	TEE was about 300 kcal/day greater with the VLC diet compared to the LF diet. REE was 67 kcal/day higher with the VLC diet compared with the LF diet.
Hall et al. [77]	17 subjects with obesity fed with a high-carbohydrate baseline diet (BD) for 4 weeks followed by 4 weeks of an isocaloric KD with clamped protein	Small increase in TEE (by ~100 kcal/day) in the first week of KD intervention was observed, followed by a linear decrease of TEE over time. The increase of EE was observed during sleep whereas no change in PA and TEF were observed
Brehm [78]	50 women with obesity were randomized to 4 months of an ad libitum LC diet or an energy-restricted, low-fat diet	No difference in REE measured by indirect calorimeter was observed
Rubini [79]	32 healthy subjects were divided into 2 groups: one underwent 3 dietary intervention steps (20-day period of LCKD with 848 kcal/day; 20-day period of LC non-ketogenic diet with 938 kcal/day; 2-month period of Mediterranean diet (MD) with 1400 kcal/day) whereas the other group was assigned to a 3 step-regimen (20-day period of MD with 1200 kcal/day, 20-day period of MD with 1400 kcal/day, 2-month period of MD with 1400 kcal/day).	No difference in REE was observed between KD and MD
Paoli [80]	16 male soccer players randomized to VLCKD or Western Diet	No change in REE

TEE: total energy expenditure; REE: resting energy expenditure; TEF; thermogenic effect of food; PA: physical activity.

It has to be acknowledged that some of the studies reported in the literature may have significant limitations, which include different study design, lack of measurements of body composition, and imperfect measurements of energy expenditure and its components

over the 24 h. These methodological differences do not allow a direct comparison between studies and definitive conclusions regarding the role of KD on energy metabolism.

Overall, it has been hypothesized [77] that during the first phase of KDs, when glucose utilization is still prevalent, an increase in EE may occur possibly due to increased hepatic oxygen consumption, proportional to the rate of ketogenesis and consequent to a raise in the energy request for gluconeogenic pathways and for triglyceride-fatty acid recycling [81–83]. Later on, a reduction of gluconeogenesis caused by the shifting from glucose to ketone bodies oxidation by the brain, a decrease in the respiratory quotient, and the possible direct action of additional hormonal signals (i.e., thyroid hormone, adipokines and catecholamines) might lead to a reduction in EE [84–87] (Figure 1). KDs might also act on long-lasting adaptations, by attenuating the decline of REE, which would occur following a reduction of body mass, but the lack of long-term follow-up studies in this regard does not allow us to speculate on this possibility.

6. Conclusions

Several lines of evidence support the efficacy of KDs as a strategy for fat loss. Studies so far reported do not show a clear EE response to extreme carbohydrate limitation. Minor changes in EE may occur in various phases of KD intervention due to the shift to different metabolic processes. A lack of long term follow up studies does not allow to shed light on the long-lasting adaptations (lower EE, reduced fat oxidation, changes in body composition, and greater appetite signals) to KD restrictions, which may occur following weight loss and might expose individuals to weight regain over time.

Author Contributions: Conceptualization, A.B., F.S. and G.C.; writing—original draft, A.B.; writing—review and editing, A.B., S.M., F.S. and G.C. All authors have read and agreed to the published version of the manuscript.

Funding: A.B. was funded by the Italian Ministry of the University, Project code 2017L8Z2EM: “Mechanisms of adipose tissue dysfunction in obesity: a target of future weight loss strategies for the prevention of diabetes and cardiovascular diseases.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Conflicts of Interest: The authors declare no conflict of interest.

Abbreviations

KD: ketogenic diet; LCD: Low-carbohydrate diet; VLCD: very-low-carbohydrate diets; LF: low fat diet; LCKD: low-calorie ketogenic diet; VLCKD: very low-calorie ketogenic diet; EI: energy intake; EE: energy expenditure; PA; physical activity; RMR: resting metabolic rate; TEF: thermic effect of food.

References

1. World Health Organization. Obesity and Overweight Fact Sheet. 2016. Available online: <https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight> (accessed on 21 March 2022).
2. Hall, K.D.; Heymsfield, S.B.; Kemnitz, J.W.; Klein, S.; Schoeller, D.A.; Speakman, J.R. Energy balance and its components: Implications for body weight regulation. *Am. J. Clin. Nutr.* **2012**, *95*, 989–994. [CrossRef] [PubMed]
3. Piaggi, P.; Vinales, K.L.; Basolo, A.; Santini, F.; Krakoff, J. Energy expenditure in the etiology of human obesity: Spendthrift and thrifty metabolic phenotypes and energy-sensing mechanisms. *J. Endocrinol. Invest.* **2018**, *41*, 83–89. [CrossRef] [PubMed]
4. Basolo, A.; Bechi Genzano, S.; Piaggi, P.; Krakoff, J.; Santini, F. Energy Balance and Control of Body Weight: Possible Effects of Meal Timing and Circadian Rhythm Dysregulation. *Nutrients* **2021**, *13*, 3276. [CrossRef] [PubMed]
5. Weyer, C.; Snitker, S.; Rising, R.; Bogardus, C.; Ravussin, E. Determinants of energy expenditure and fuel utilization in man: Effects of body composition, age, sex, ethnicity and glucose tolerance in 916 subjects. *Int. J. Obes. Relat. Metab. Disord.* **1999**, *23*, 715–722. [CrossRef] [PubMed]
6. Ludwig, D.S.; Friedman, M.I. Increasing adiposity: Consequence or cause of overeating? *JAMA* **2014**, *311*, 2167–2168. [CrossRef] [PubMed]

7. Wells, J.C.; Siervo, M. Obesity and energy balance: Is the tail wagging the dog? *Eur. J. Clin. Nutr.* **2011**, *65*, 1173–1189. [[CrossRef](#)]
8. Hall, K.D.; Farooqi, I.S.; Friedman, J.M.; Klein, S.; Loos, R.J.F.; Mangelsdorf, D.J.; O'Rahilly, S.; Ravussin, E.; Redman, L.M.; Ryan, D.H.; et al. The energy balance model of obesity: Beyond calories in, calories out. *Am. J. Clin. Nutr.* **2022**. *Online ahead of print.* [[CrossRef](#)]
9. Carpentier, A.C. 100(th) anniversary of the discovery of insulin perspective: Insulin and adipose tissue fatty acid metabolism. *Am. J. Physiol. Endocrinol. Metab.* **2021**, *320*, E653–E670. [[CrossRef](#)]
10. Evans, K.; Clark, M.L.; Frayn, K.N. Effects of an oral and intravenous fat load on adipose tissue and forearm lipid metabolism. *Am. J. Physiol.* **1999**, *276*, E241–E248. [[CrossRef](#)]
11. Corkey, B.E.; Deeney, J.T.; Merrins, M.J. What Regulates Basal Insulin Secretion and Causes Hyperinsulinemia? *Diabetes* **2021**, *70*, 2174–2182. [[CrossRef](#)]
12. Henquin, J.C. Non-glucose modulators of insulin secretion in healthy humans: (dis)similarities between islet and in vivo studies. *Metabolism* **2021**, *122*, 154821. [[CrossRef](#)] [[PubMed](#)]
13. Di Lorenzo, C.; Ballerini, G.; Barbanti, P.; Bernardini, A.; D'Arrigo, G.; Egeo, G.; Frediani, F.; Garbo, R.; Pierangeli, G.; Prudeniano, M.P.; et al. Applications of Ketogenic Diets in Patients with Headache: Clinical Recommendations. *Nutrients* **2021**, *13*, 2307. [[CrossRef](#)] [[PubMed](#)]
14. Di Lorenzo, C.; Pinto, A.; Ienca, R.; Coppola, G.; Sirianni, G.; Di Lorenzo, G.; Parisi, V.; Serrao, M.; Spagnoli, A.; Vestri, A.; et al. A Randomized Double-Blind, Cross-Over Trial of very Low-Calorie Diet in Overweight Migraine Patients: A Possible Role for Ketones? *Nutrients* **2019**, *11*, 1742. [[CrossRef](#)] [[PubMed](#)]
15. Bongiovanni, D.; Benedetto, C.; Corvisieri, S.; Del Favero, C.; Orlandi, F.; Allais, G.; Sinigaglia, S.; Fadda, M. Effectiveness of ketogenic diet in treatment of patients with refractory chronic migraine. *Neurol. Sci.* **2021**, *42*, 3865–3870. [[CrossRef](#)] [[PubMed](#)]
16. Paoli, A.; Mancin, L.; Giacona, M.C.; Bianco, A.; Caprio, M. Effects of a ketogenic diet in overweight women with polycystic ovary syndrome. *J. Transl. Med.* **2020**, *18*, 104. [[CrossRef](#)]
17. Weber, D.D.; Aminzadeh-Gohari, S.; Tulipan, J.; Catalano, L.; Feichtinger, R.G.; Kofler, B. Ketogenic diet in the treatment of cancer—Where do we stand? *Mol. Metab.* **2020**, *33*, 102–121. [[CrossRef](#)]
18. Włodarek, D. Role of Ketogenic Diets in Neurodegenerative Diseases (Alzheimer's Disease and Parkinson's Disease). *Nutrients* **2019**, *11*, 169. [[CrossRef](#)]
19. Broom, G.M.; Shaw, I.C.; Rucklidge, J.J. The ketogenic diet as a potential treatment and prevention strategy for Alzheimer's disease. *Nutrition* **2019**, *60*, 118–121. [[CrossRef](#)]
20. Tillery, E.E.; Ellis, K.D.; Threatt, T.B.; Reyes, H.A.; Plummer, C.S.; Barney, L.R. The use of the ketogenic diet in the treatment of psychiatric disorders. *Ment. Health Clin.* **2021**, *11*, 211–219. [[CrossRef](#)]
21. Liu, H.; Yang, Y.; Wang, Y.; Tang, H.; Zhang, F.; Zhang, Y.; Zhao, Y. Ketogenic diet for treatment of intractable epilepsy in adults: A meta-analysis of observational studies. *Epilepsia Open* **2018**, *3*, 9–17. [[CrossRef](#)]
22. Masi, D.; Spoltore, M.E.; Rossetti, R.; Watanabe, M.; Tozzi, R.; Caputi, A.; Risi, R.; Balena, A.; Gandini, O.; Mariani, S.; et al. The Influence of Ketone Bodies on Circadian Processes Regarding Appetite, Sleep and Hormone Release: A Systematic Review of the Literature. *Nutrients* **2022**, *14*, 1410. [[CrossRef](#)] [[PubMed](#)]
23. Sebastián, D.; Palacín, M.; Zorzano, A. Mitochondrial Dynamics: Coupling Mitochondrial Fitness with Healthy Aging. *Trends Mol. Med.* **2017**, *23*, 201–215. [[CrossRef](#)] [[PubMed](#)]
24. Miller, V.J.; Villamena, F.A.; Volek, J.S. Nutritional Ketosis and Mitohormesis: Potential Implications for Mitochondrial Function and Human Health. *J. Nutr. Metab.* **2018**, *2018*, 5157645. [[CrossRef](#)] [[PubMed](#)]
25. Atkins, C. *Dr. Atkins' New Diet Revolution: The High Calorie Way to Stay Thin Forever*; David McKay Inc. Publishers: New York, NY, USA, 1972.
26. Freire, R. Scientific evidence of diets for weight loss: Different macronutrient composition, intermittent fasting, and popular diets. *Nutrition* **2020**, *69*, 110549. [[CrossRef](#)] [[PubMed](#)]
27. Moreno, B.; Bellido, D.; Sajoux, I.; Goday, A.; Saavedra, D.; Crujeiras, A.B.; Casanueva, F.F. Comparison of a very low-calorie-ketogenic diet with a standard low-calorie diet in the treatment of obesity. *Endocrine* **2014**, *47*, 793–805. [[CrossRef](#)] [[PubMed](#)]
28. Muscogiuri, G.; Barrea, L.; Laudisio, D.; Pugliese, G.; Salzano, C.; Savastano, S.; Colao, A. The management of very low-calorie ketogenic diet in obesity outpatient clinic: A practical guide. *J. Transl. Med.* **2019**, *17*, 356. [[CrossRef](#)]
29. Caprio, M.; Infante, M.; Moriconi, E.; Armani, A.; Fabbri, A.; Mantovani, G.; Mariani, S.; Lubrano, C.; Poggiogalle, E.; Migliaccio, S.; et al. Very-low-calorie ketogenic diet (VLCKD) in the management of metabolic diseases: Systematic review and consensus statement from the Italian Society of Endocrinology (SIE). *J. Endocrinol. Invest.* **2019**, *42*, 1365–1386. [[CrossRef](#)]
30. Sukkar, S.G.; Muscaritoli, M. A Clinical Perspective of Low Carbohydrate Ketogenic Diets: A Narrative Review. *Front. Nutr.* **2021**, *8*, 642628. [[CrossRef](#)]
31. Sumithran, P.; Proietto, J. Ketogenic diets for weight loss: A review of their principles, safety and efficacy. *Obes. Res. Clin. Pract.* **2008**, *2*, I–II. [[CrossRef](#)]
32. Mullins, G.; Hallam, C.; Broom, I. Ketosis, ketoacidosis and very-low-calorie diets: Putting the record straight. *Nutr. Bull.* **2011**, *36*, 397–402. [[CrossRef](#)]
33. Dimitriadis, G.; Mitrou, P.; Lambadiari, V.; Maratou, E.; Raptis, S.A. Insulin effects in muscle and adipose tissue. *Diabetes Res. Clin. Pract.* **2011**, *93* (Suppl. 1), S52–S59. [[CrossRef](#)]

34. Petersen, M.C.; Vatner, D.F.; Shulman, G.I. Regulation of hepatic glucose metabolism in health and disease. *Nat. Rev. Endocrinol.* **2017**, *13*, 572–587. [[CrossRef](#)] [[PubMed](#)]
35. Grabner, G.F.; Xie, H.; Schweiger, M.; Zechner, R. Lipolysis: Cellular mechanisms for lipid mobilization from fat stores. *Nat. Metab.* **2021**, *3*, 1445–1465. [[CrossRef](#)] [[PubMed](#)]
36. Laffel, L. Ketone bodies: A review of physiology, pathophysiology and application of monitoring to diabetes. *Diabetes Metab. Res. Rev.* **1999**, *15*, 412–426. [[CrossRef](#)]
37. Robinson, A.M.; Williamson, D.H. Physiological roles of ketone bodies as substrates and signals in mammalian tissues. *Physiol. Rev.* **1980**, *60*, 143–187. [[CrossRef](#)]
38. Koutnik, A.P.; D’Agostino, D.P.; Egan, B. Anticatabolic Effects of Ketone Bodies in Skeletal Muscle. *Trends Endocrinol. Metab.* **2019**, *30*, 227–229. [[CrossRef](#)]
39. Paoli, A. Ketogenic diet for obesity: Friend or foe? *Int. J. Environ. Res. Public Health* **2014**, *11*, 2092–2107. [[CrossRef](#)]
40. Lam, Y.Y.; Ravussin, E. Indirect calorimetry: An indispensable tool to understand and predict obesity. *Eur. J. Clin. Nutr.* **2017**, *71*, 318–322. [[CrossRef](#)]
41. Schoffelen, P.F.M.; Plasqui, G. Classical experiments in whole-body metabolism: Open-circuit respirometry-diluted flow chamber, hood, or facemask systems. *Eur. J. Appl. Physiol.* **2018**, *118*, 33–49. [[CrossRef](#)]
42. Ravussin, E.; Lillioja, S.; Anderson, T.E.; Christin, L.; Bogardus, C. Determinants of 24-hour energy expenditure in man. Methods and results using a respiratory chamber. *J. Clin. Investig.* **1986**, *78*, 1568–1578. [[CrossRef](#)]
43. Ravussin, E.; Bogardus, C. A brief overview of human energy metabolism and its relationship to essential obesity. *Am. J. Clin. Nutr.* **1992**, *55*, 242s–245s. [[CrossRef](#)] [[PubMed](#)]
44. Bogardus, C.; Lillioja, S.; Ravussin, E.; Abbott, W.; Zawadzki, J.K.; Young, A.; Knowler, W.C.; Jacobowitz, R.; Moll, P.P. Familial dependence of the resting metabolic rate. *N. Engl. J. Med.* **1986**, *315*, 96–100. [[CrossRef](#)] [[PubMed](#)]
45. Secor, S.M. Specific dynamic action: A review of the postprandial metabolic response. *J. Comp. Physiol. B* **2009**, *179*, 1–56. [[CrossRef](#)] [[PubMed](#)]
46. de Jonge, L.; Bray, G.A. The thermic effect of food and obesity: A critical review. *Obes. Res.* **1997**, *5*, 622–631. [[CrossRef](#)]
47. Thearle, M.S.; Pannacciulli, N.; Bonfiglio, S.; Pacak, K.; Krakoff, J. Extent and determinants of thermogenic responses to 24 hours of fasting, energy balance, and five different overfeeding diets in humans. *J. Clin. Endocrinol. Metab.* **2013**, *98*, 2791–2799. [[CrossRef](#)]
48. Levine, J.A. Non-exercise activity thermogenesis (NEAT). *Nutr. Rev.* **2004**, *62*, S82–97. [[CrossRef](#)]
49. Timper, K.; Brüning, J.C. Hypothalamic circuits regulating appetite and energy homeostasis: Pathways to obesity. *Dis. Models Mech.* **2017**, *10*, 679–689. [[CrossRef](#)]
50. Ceccarini, G.; Maffei, M.; Vitti, P.; Santini, F. Fuel homeostasis and locomotor behavior: Role of leptin and melanocortin pathways. *J. Endocrinol. Invest.* **2015**, *38*, 125–131. [[CrossRef](#)]
51. Weyer, C.; Vozarova, B.; Ravussin, E.; Tataranni, P.A. Changes in energy metabolism in response to 48 h of overfeeding and fasting in Caucasians and Pima Indians. *Int. J. Obes. Relat. Metab. Disord.* **2001**, *25*, 593–600. [[CrossRef](#)]
52. Heinitz, S.; Hollstein, T.; Ando, T.; Walter, M.; Basolo, A.; Krakoff, J.; Votruba, S.B.; Piaggi, P. Early adaptive thermogenesis is a determinant of weight loss after six weeks of caloric restriction in overweight subjects. *Metabolism* **2020**, *110*, 154303. [[CrossRef](#)]
53. Reinhardt, M.; Schlögl, M.; Bonfiglio, S.; Votruba, S.B.; Krakoff, J.; Thearle, M.S. Lower core body temperature and greater body fat are components of a human thrifty phenotype. *Int. J. Obes.* **2016**, *40*, 754–760. [[CrossRef](#)] [[PubMed](#)]
54. Schlögl, M.; Piaggi, P.; Pannacciulli, N.; Bonfiglio, S.M.; Krakoff, J.; Thearle, M.S. Energy Expenditure Responses to Fasting and Overfeeding Identify Phenotypes Associated With Weight Change. *Diabetes* **2015**, *64*, 3680–3689. [[CrossRef](#)] [[PubMed](#)]
55. Basolo, A.; Heinitz, S.; Stinson, E.J.; Begaye, B.; Hohenadel, M.; Piaggi, P.; Krakoff, J.; Votruba, S.B. Fasting glucagon-like peptide 1 concentration is associated with lower carbohydrate intake and increases with overeating. *J. Endocrinol. Invest.* **2019**, *42*, 557–566. [[CrossRef](#)] [[PubMed](#)]
56. Basolo, A.; Begaye, B.; Hollstein, T.; Vinales, K.L.; Walter, M.; Santini, F.; Krakoff, J.; Piaggi, P. Effects of Short-Term Fasting and Different Overfeeding Diets on Thyroid Hormones in Healthy Humans. *Thyroid* **2019**, *29*, 1209–1219. [[CrossRef](#)]
57. Basolo, A.; Hollstein, T.; Walter, M.; Krakoff, J.; Piaggi, P. Urinary Dopamine Excretion Rate Decreases during Acute Dietary Protein Deprivation and Is Associated with Increased Plasma Pancreatic Polypeptide Concentration. *Nutrients* **2021**, *13*, 1234. [[CrossRef](#)]
58. Basolo, A.; Hollstein, T.; Shah, M.H.; Walter, M.; Krakoff, J.; Votruba, S.B.; Piaggi, P. Higher fasting plasma FGF21 concentration is associated with lower ad libitum soda consumption in humans. *Am. J. Clin. Nutr.* **2021**, *114*, 1518–1522. [[CrossRef](#)]
59. Hollstein, T.; Vinales, K.; Chen, K.Y.; Cypess, A.M.; Basolo, A.; Schlögl, M.; Krakoff, J.; Piaggi, P. Reduced brown adipose tissue activity during cold exposure is a metabolic feature of the human thrifty phenotype. *Metabolism* **2021**, *117*, 154709. [[CrossRef](#)]
60. Hollstein, T.; Heinitz, S.; Ando, T.; Rodzevik, T.L.; Basolo, A.; Walter, M.; Chang, D.C.; Krakoff, J.; Piaggi, P. Metabolic Responses to 24-Hour Fasting and Mild Cold Exposure in Overweight Individuals Are Correlated and Accompanied by Changes in FGF21 Concentration. *Diabetes* **2020**, *69*, 1382–1388. [[CrossRef](#)]
61. Basolo, A.; Ando, T.; Hollstein, T.; Votruba, S.B.; Krakoff, J.; Piaggi, P. Higher Urinary Dopamine Concentration is Associated with Greater Ad Libitum Energy Intake in Humans. *Obesity* **2020**, *28*, 953–961. [[CrossRef](#)]

62. Heinitz, S.; Basolo, A.; Piaggi, P.; Piomelli, D.; Jumpertz von Schwartzberg, R.; Krakoff, J. Peripheral Endocannabinoids Associated With Energy Expenditure in Native Americans of Southwestern Heritage. *J. Clin. Endocrinol. Metab.* **2018**, *103*, 1077–1087. [[CrossRef](#)]
63. Vinales, K.L.; Schlögl, M.; Piaggi, P.; Hohenadel, M.; Graham, A.; Bonfiglio, S.; Krakoff, J.; Thearle, M.S. The Consistency in Macronutrient Oxidation and the Role for Epinephrine in the Response to Fasting and Overfeeding. *J. Clin. Endocrinol. Metab.* **2017**, *102*, 279–289. [[CrossRef](#)] [[PubMed](#)]
64. Ravussin, E.; Smith, S.R.; Ferrante, A.W., Jr. Physiology of Energy Expenditure in the Weight-Reduced State. *Obesity* **2021**, *29* (Suppl. 1), S31–S38. [[CrossRef](#)] [[PubMed](#)]
65. Leibel, R.L.; Rosenbaum, M.; Hirsch, J. Changes in energy expenditure resulting from altered body weight. *N. Engl. J. Med.* **1995**, *332*, 621–628. [[CrossRef](#)] [[PubMed](#)]
66. Rosenbaum, M.; Hirsch, J.; Gallagher, D.A.; Leibel, R.L. Long-term persistence of adaptive thermogenesis in subjects who have maintained a reduced body weight. *Am. J. Clin. Nutr.* **2008**, *88*, 906–912. [[CrossRef](#)]
67. Johannsen, D.L.; Knuth, N.D.; Huizenga, R.; Rood, J.C.; Ravussin, E.; Hall, K.D. Metabolic slowing with massive weight loss despite preservation of fat-free mass. *J. Clin. Endocrinol. Metab.* **2012**, *97*, 2489–2496. [[CrossRef](#)]
68. Fothergill, E.; Guo, J.; Howard, L.; Kerns, J.C.; Knuth, N.D.; Brychta, R.; Chen, K.Y.; Skarulis, M.C.; Walter, M.; Walter, P.J.; et al. Persistent metabolic adaptation 6 years after “The Biggest Loser” competition. *Obesity* **2016**, *24*, 1612–1619. [[CrossRef](#)]
69. Ravussin, E.; Ryan, D.H. Energy expenditure and weight control: Is the biggest loser the best loser? *Obesity* **2016**, *24*, 1607–1608. [[CrossRef](#)]
70. Wing, R.R.; Hill, J.O. Successful weight loss maintenance. *Annu. Rev. Nutr.* **2001**, *21*, 323–341. [[CrossRef](#)]
71. Koliaki, C.; Liatis, S.; Dalamaga, M.; Kokkinos, A. The Implication of Gut Hormones in the Regulation of Energy Homeostasis and Their Role in the Pathophysiology of Obesity. *Curr. Obes. Rep.* **2020**, *9*, 255–271. [[CrossRef](#)]
72. Hollstein, T.; Piaggi, P. Metabolic Factors Determining the Susceptibility to Weight Gain: Current Evidence. *Curr. Obes. Rep.* **2020**, *9*, 121–135. [[CrossRef](#)]
73. Moreno, B.; Crujeiras, A.B.; Bellido, D.; Sajoux, I.; Casanueva, F.F. Obesity treatment by very low-calorie-ketogenic diet at two years: Reduction in visceral fat and on the burden of disease. *Endocrine* **2016**, *54*, 681–690. [[CrossRef](#)] [[PubMed](#)]
74. Urbain, P.; Strom, L.; Morawski, L.; Wehrle, A.; Deibert, P.; Bertz, H. Impact of a 6-week non-energy-restricted ketogenic diet on physical fitness, body composition and biochemical parameters in healthy adults. *Nutr. Metab.* **2017**, *14*, 17. [[CrossRef](#)] [[PubMed](#)]
75. Gomez-Arbelaiz, D.; Bellido, D.; Castro, A.I.; Ordoñez-Mayan, L.; Carreira, J.; Galban, C.; Martinez-Olmos, M.A.; Crujeiras, A.B.; Sajoux, I.; Casanueva, F.F. Body Composition Changes After Very-Low-Calorie Ketogenic Diet in Obesity Evaluated by 3 Standardized Methods. *J. Clin. Endocrinol. Metab.* **2017**, *102*, 488–498. [[CrossRef](#)]
76. Ebbeling, C.B.; Swain, J.F.; Feldman, H.A.; Wong, W.W.; Hachey, D.L.; Garcia-Lago, E.; Ludwig, D.S. Effects of dietary composition on energy expenditure during weight-loss maintenance. *JAMA* **2012**, *307*, 2627–2634. [[CrossRef](#)] [[PubMed](#)]
77. Hall, K.D.; Chen, K.Y.; Guo, J.; Lam, Y.Y.; Leibel, R.L.; Mayer, L.E.; Reitman, M.L.; Rosenbaum, M.; Smith, S.R.; Walsh, B.T.; et al. Energy expenditure and body composition changes after an isocaloric ketogenic diet in overweight and obese men. *Am. J. Clin. Nutr.* **2016**, *104*, 324–333. [[CrossRef](#)]
78. Brehm, B.J.; Spang, S.E.; Lattin, B.L.; Seeley, R.J.; Daniels, S.R.; D’Alessio, D.A. The role of energy expenditure in the differential weight loss in obese women on low-fat and low-carbohydrate diets. *J. Clin. Endocrinol. Metab.* **2005**, *90*, 1475–1482. [[CrossRef](#)]
79. Rubini, A.; Bosco, G.; Lodi, A.; Cenci, L.; Parmagnani, A.; Grimaldi, K.; Zhongjin, Y.; Paoli, A. Effects of Twenty Days of the Ketogenic Diet on Metabolic and Respiratory Parameters in Healthy Subjects. *Lung* **2015**, *193*, 939–945. [[CrossRef](#)]
80. Antonio Paoli, A.; Mancin, L.; Caprio, M.; Monti, E.; Narici, M.V.; Cenci, L.; Piccini, F.; Pincella, M.; Grigoletto, D.; Marcolin, G. Effects of 30 days of ketogenic diet on body composition, muscle strength, muscle area, metabolism, and performance in semi-professional soccer players. *J. Int. Soc. Sports Nutr.* **2021**, *18*, 62. [[CrossRef](#)]
81. Scholz, R.; Schwabe, U.; Soboll, S. Influence of fatty acids on energy metabolism. 1. Stimulation of oxygen consumption, ketogenesis and CO₂ production following addition of octanoate and oleate in perfused rat liver. *Eur. J. Biochem.* **1984**, *141*, 223–230. [[CrossRef](#)]
82. Elia, M.; Zed, C.; Neale, G.; Livesey, G. The energy cost of triglyceride-fatty acid recycling in nonobese subjects after an overnight fast and four days of starvation. *Metabolism* **1987**, *36*, 251–255. [[CrossRef](#)]
83. Veldhorst, M.A.; Westerterp-Plantenga, M.S.; Westerterp, K.R. Gluconeogenesis and energy expenditure after a high-protein, carbohydrate-free diet. *Am. J. Clin. Nutr.* **2009**, *90*, 519–526. [[CrossRef](#)] [[PubMed](#)]
84. Balasse, E.O.; Féry, F. Ketone body production and disposal: Effects of fasting, diabetes, and exercise. *Diabetes Metab. Rev.* **1989**, *5*, 247–270. [[CrossRef](#)] [[PubMed](#)]
85. Cahill, G.F., Jr. Starvation in man. *N. Engl. J. Med.* **1970**, *282*, 668–675. [[CrossRef](#)]
86. Cahill, G.F., Jr. Fuel metabolism in starvation. *Annu. Rev. Nutr.* **2006**, *26*, 1–22. [[CrossRef](#)] [[PubMed](#)]
87. Müller, M.J.; Enderle, J.; Pourhassan, M.; Braun, W.; Eggeling, B.; Lagerpusch, M.; Glüer, C.C.; Kehayias, J.J.; Kiosz, D.; Bosp-Westphal, A. Metabolic adaptation to caloric restriction and subsequent refeeding: The Minnesota Starvation Experiment revisited. *Am. J. Clin. Nutr.* **2015**, *102*, 807–819. [[CrossRef](#)]