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Review

Nutritional Studies Evaluating Ketogenic Diets as a Treatment for Obesity and Obesity-Associated Morbidities: Underlying Mechanisms and Potential for Clinical Implementation

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Abstract: Background: The ketogenic diet (KD), characterized by high-fat content, virtually no carbohydrates, and adequate protein intake, induces a metabolic state resembling fasting, as the absence of carbohydrates forces the body to rely on the energetic supply from hepatically produced ketone bodies using free fatty acids as substrate. While the KD is clinically used in pharmacologically refractory epilepsy and specific genetic conditions such as GLUT1 deficiency, recent research suggests that, due to its "fasting mimicking" properties, the KD may also beneficially affect obesity and obesity-associated metabolic diseases. Results: Here, we present a narrative review discussing completed and ongoing nutritional studies in human volunteers specifically addressing the potential of the ketogenic diet as an anti-obesity approach and, from a larger perspective, as an intervention to ameliorate the metabolic state in conditions such as type 1 and 2 diabetes and polycystic ovary syndrome (PCOS). Published studies as well as ongoing clinical trials will be discussed. Efficacy and safety considerations will be discussed, as well as the potential physiological mechanisms mediating the effects of the KD in humans in the context of the (i) energy balance model (EBM) and (ii) carbohydrate–insulin model (CIM) of body weight control. Conclusion: Ketogenic diets may be beneficial to attenuate obesity and improve obesity-related metabolic disease, and here, we try, based on current evidence, to define the boundaries of the KD's nutritional and clinical usefulness.

Keywords: ketogenic diet; metabolic disease; type 2 diabetes; polycystic ovary syndrome (PCOS); type 1 diabetes; carbohydrate–insulin model (CIM); energy balance model (EBM)

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1. Introduction

1.1. Incidence and Underlying Mechanisms of Obesity and Metabolic Diseases

Obesity is a predisposing condition to cancer and metabolic disease, and these two medical conditions are, within the WHO statistics, among the major causes of morbidity and mortality worldwide [1]. A sedentary lifestyle, stress, and an unbalanced diet all contribute to switching metabolism toward the development of obesity. Research in recent years has shown the persistence of the adverse effects of early metabolic insults, such as exposure to hyperglycemia, and obesity, even after such metabolic states have been normalized [2]. Such a phenomenon has been termed glycemic or metabolic memory [3]. The installment, and persistence, of metabolic memory may be based on long-lasting epigenetic alterations [4], and their reversal may contribute normalizing the body's metabolic state.

Dietary patterns favoring metabolic normalization and weight loss have been the object of intense scrutiny in recent decades, with the aim of bringing benefits to the general obese population, or in specific groups at risk. Among others, the ketogenic diet (KD)

is proposed to be an effective nutritional approach to curb the incidence of obesity with associated morbidities (insulin resistance, hypertension, diabetes, and increased incidence of specific cancers). In general terms, the KD induces the body to rely on hepatically produced β-hydroxybutyrate (BHB) as a major source of energy [5]. The importance of the balance between carbohydrates and lipids in nutritional strategies, particularly focusing on the recent nutritional model of the KD, which is high in fat and essentially devoid of carbohydrates, has been under intense analysis for neurological conditions such as pharmacologically refractory epilepsy and GLUT1 deficiency syndromes [6]. Importantly, BHB has also emerged as a beneficial regulator of the metabolic state, possibly via a direct effect on the epigenome through histone hydroxybutyrylation [7] or, more controversially, the inhibition of histone deacetylases (HDACs) [8,9].

In mouse models, chronic administration of a ketogenic diet reduced midlife mortality, improved cognitive functions of aging animals [10], and normalized glycemia in mice previously fed a high-fat diet [11]. KD metabolism may also alleviate cardiovascular disease [12], but the assertion should be considered cautiously as the KD has also been shown to promote cardiac fibrosis [13]. The putative beneficial effects of the circulating ketone body BHB would occur in the low mM range, as hyperketonemia states, with BHB concentration levels exceeding 10 mMol/L, are indicative of diabetic ketoacidosis, a life-threatening condition of ill-controlled diabetes [14]. In this context, a parallel can be drawn with respect to blood glucose levels in diabetes, in which hyperglycemia is the pathological manifestation of unmet glycemic control.

The feasibility of ketogenic nutrition in humans has supported the notion that this nutritional pattern may usefully serve the purpose of inducing weight loss and associated metabolic normalizations. In this review, we will critically survey the existing literature in support of—or critical against—this notion, and discuss the side effects and compliance issues that have been reported. Besides the existing published literature, we will also briefly survey the existing and ongoing clinical trials addressing the use of the ketogenic diet in obesity and obesity-related conditions.

Finally, the potential of the ketogenic diet to combat obesity will be discussed in the framework of the two current theories of weight control: the energy balance model (EBM) [15] and the carbohydrate–insulin model (CIM) [16].

1.2. Setting the Boundaries to Define the Ketogenic Diet

As the term KD is loosely applied to dietary schemes enriched in fat and deprived in carbohydrates, and given the intrinsic variability in nutritional patterns, a standardized universal composition for the KD is impossible to define. As a general feature, the KD is highly reduced in carbohydrates, and in parallel, the contribution of fat and proteins becomes prominent [17]. The KD initially emerged almost a century ago as an effective treatment in rarely occurring clinical situations, such as epilepsy refractory to pharmacological treatment [18]. The initial appreciation for the metabolic effects, and by extension, the effects on body weight, of the KD can be dated back to pioneering studies in the 1960s, with previous knowledge of the usefulness of the KD in the treatment of epilepsy dating back to the 1930s. Reported KDs include the "traditional ketogenic diet", described a few decades ago for use in pharmacologically intractable epilepsy [19,20]. A variation consists of the medium-chain triglycerides (MCT)-based KD, in which approximately 50% of the calories are provided by oil. In the MCT KD, triglycerides of a shorter length are energetically less dense and more ketogenic and are more easily oxidized than long-chain triglycerides [21]. Finally, a modified Atkins diet can also be considered as a KD and has been explored in several clinical trials against intractable epilepsy [22].

Beyond the treatment of epilepsy, initial evidence indicates that the KD may bring benefits as a nutritional approach against type 2 diabetes (T2D) [23], cardiovascular diseases (CVDs) [24], and polycystic ovary syndrome (PCOS) [25], which are all medical conditions with tight links to obesity. Even cancer is considered a disease on which the KD may exert beneficial effects, due to the propensity of cancer cells to preferentially utilize glucose, but

some caution must be exerted and, at best, the available research suggests that further well-designed and sufficiently powered clinical trials are necessary to definitely adjudicate or refute this assertion [26]. As the KD relies on the deficiency of one of the three major macronutrients, carbohydrates, concerns about possible side effects including micronutrient deficiencies, dyslipidemia, modification of the appetite, and general unhealthiness (nausea, constipation, and chronic fatigue) should not be discounted [27]. On the other hand, the KD, by reducing systemic inflammation and improving metabolism, may in the longer term improve the quality of life (QOL) of patients by reducing chronic pain and inflammation and improving metabolic parameters through multiple mechanisms [5]. Below, we summarize the evidence from randomized controlled trials (RCTs) supporting the effects of KDs on the management of obesity. Here, we examine clinical nutrition studies that have evaluated the effectiveness of ketogenic diets in the treatment of obesity and metabolic diseases. Based on the current evidence, we will discuss the limitations of the nutritional and clinical utility of the ketogenic diet.

2. Search Methodology

Here, we examine clinical nutrition studies that have evaluated the effectiveness of ketogenic diets in the treatment of obesity and metabolic diseases, as well as in PCOS, pregnancy, and type 1 diabetes. Based on the current evidence, we will discuss the potential and limitations of the nutritional and clinical utility of the ketogenic diet. PubMed and ClinicalTrials.gov databases were searched. Specifically, we targeted randomized controlled trials (RCTs) that investigated and evaluated the effects of a ketogenic diet on changes in body weight, glycemic control, and lipid profiles. To identify relevant studies, the following search terms were used, alone or in combination: ketogenic diet, obesity, overweight, metabolic syndrome, cardiovascular disease. Bibliographies of previous relevant reviews were also examined. A ketogenic diet was defined as a dietary approach characterized by a high fat content, moderate protein content, and low carbohydrate content.

3. On the Need for Nutritional RCTs Evaluating the Ketogenic Diet as a Treatment for Obesity and Metabolic Diseases

The increase in the prevalence of obesity worldwide is accompanied by an increase in cardiovascular disease levels. Obesity is also a significant risk factor in terms of insulin resistance and the development of type 2 diabetes (T2D). Insulin resistance is often associated with abnormal hepatic lipid accumulation and adipose tissue hypertrophy [28]. It is common for obesity and diabetes to coexist in the same individual [29]. Clear links have been established between obesity and increased risks of cardiovascular diseases such as hypertension, coronary heart disease, heart failure, and sudden death. Many individuals with insulin resistance, the main cause of type 2 diabetes, have high triglyceride levels and low high-density lipoprotein levels. Obesity, diabetes, and dyslipidemia are all risk factors for cardiovascular diseases.

The use of diet as a therapeutic strategy cannot be underestimated in the management and prevention of chronic diseases. To control blood glucose, weight, and abnormal factors, the recommendations of the American Diabetes Association (www.diabetes.org) include adopting a balanced diet, engaging in physical activity, and taking medications.

Several previous studies have proposed various dietary approaches, including low-carbohydrate ketogenic diets that contain approximately 60% fat, 25% protein, and 15% carbohydrates, but without calorie restriction [30].

These diets can mimic a fasting state in the body, leading to ketosis and replacing the glucose-based energy pattern with one based on ketone bodies. This process promotes fat catabolism and reduces fat synthesis, thereby increasing energy expenditure [31].

Low-carbohydrate diets are considered effective for weight loss and glycemic control. Studies have shown that ketogenic diets improve metabolic parameters in overweight or obese patients, particularly related to blood glucose, weight, and lipid control in patients with pre-existing diabetes [32]. However, other studies have shown that these diets may

potentially exacerbate lipid profiles in obese patients [33]. The current evidence for the use of these diets is limited, and the potential risks associated with their use are real. Therefore, it is necessary to study the clinical effects of ketogenic diets in overweight or obese patients compared to non-ketogenic diets to evaluate their impact on cardiovascular risk factors related to blood glucose, weight, glycated hemoglobin, blood pressure, and lipid levels (Figure 1).

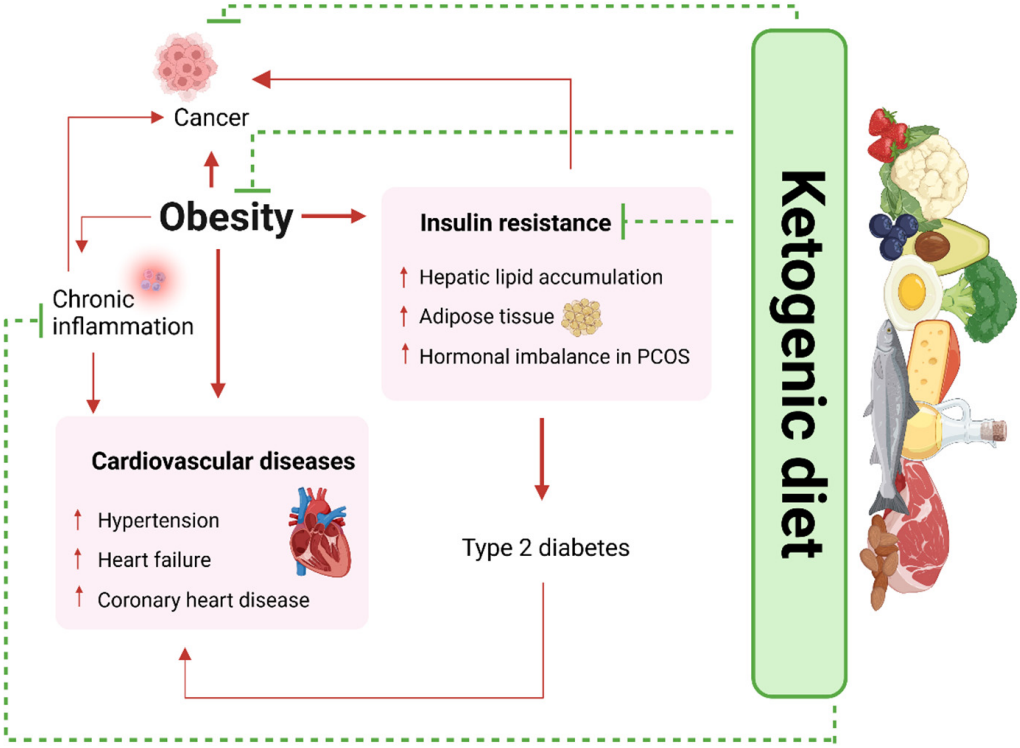

Figure 1. Therapeutic aspects of ketogenic diets in obesity and obesity-associated morbidities. Obesity predisposes to various diseases stemming from reprogrammed metabolism, creating a vicious cycle (red arrows). Adherence to ketogenic diets may promote weight loss and glycemic normalization, successfully alleviating many of the obesity-related features, such as insulin resistance, systemic inflammation, and the occurrence of certain types of cancer (green arrows). Created with biorender.com, accessed on 13 November 2024.

4. Study Findings on the Ketogenic Diet for Managing Obesity and Metabolic Diseases

To date, several nutritional clinical trials have studied the potential benefits of the ketogenic diet to promote weight loss and ameliorate glycemic control (Table 1). Among the earliest RCTs exploring the usefulness of the KD, Yancy et al. [34] compared a low-carbohydrate KD versus a low-fat diet to treat obesity in an outpatient cohort. Lipid levels were also evaluated. Compared with a low-fat diet, the low-carbohydrate KD showed better compliance and greater weight loss. In addition, during the study period, serum triglycerides decreased more and HDL cholesterol levels increased more in the low-carbohydrate KD than with the low-fat diet. Nonetheless, although the study supported the efficacy and relative safety of the low-carbohydrate KD, the study participants, although obese (BMI > 30), had an overall good health status. In addition, issues of adherence to the diet, in both study arms, and the relatively short duration of the study—24 weeks—called for studies with longer durations and with larger cohorts.

In a very small cohort of diabetic (n = 13) and non-diabetic (n = 13) obese subjects (BMI > 35), a low-carbohydrate diet (<40 g/day, approximating a KD) induced higher body weight reduction than "healthy eating" in both the diabetic and non-diabetic subjects over a period of 3 months. In this nutritional protocol, however, no differences in changes in glycated hemoglobin, circulating ketone bodies, or lipid profiles were observed [35].

In a well-controlled study, including weekly counseling for the first 12 weeks, followed by sessions every other week until the end of the 24-week study duration, Westman et al. found that a low-carbohydrate diet (<20/day), compared with a low-glycemic, low-calorie diet, resulted in significantly greater weight loss (−11.1 kg vs. −6.9 kg) and better improvements in glycated hemoglobin (−1.5% vs. −0.5%) [36]. To expand on this study, with a larger cohort of type 2 diabetic obese subjects subjected to less intensive counseling, to be closer to a real-life outpatient practice, and for a longer study period (24 months), Iqubal et al. [37] failed to demonstrate differences in body weight loss or glycemic changes in low-carbohydrate versus low-fat diet participants. These findings, summarized in Table 2, demonstrate that either a low-carbohydrate or a low-fat diet dietary scheme may be beneficial. A caveat, however, exists, as these diets can be difficult to follow continuously in the absence of constant behavioral and nutritional recommendations. This underscores the very general problem that weight loss interventions, to be effective in the long term, must be accompanied by continuous counseling [38].

Table 1. Ketogenic diet benefits to weight loss, glycemic control, and lipid profiles in overweight patients with or without type 2 diabetes mellitus.

Study Reference	Country	Study Period	Dietary Intervention
Goday et al. [39]	Spain	4 months	VLCKD: <50 g/day arbohydrates
Saslow et al. [40]	USA	3 months	LCKD: 20–50 g/day carbohydrates
Saslow et al. [41]	USA	12 months	LCKD: 20–50 g/day carbohydrates
Saslow et al. [42]	USA	32 weeks	LCKD: 20–50 g/day carbohydrates
Tay et al. [43]	Australia	52 weeks	LCD: carbohydrates (<50 g/day), 28% protein, 58% fat (35% monounsaturated, 13% polyunsaturated)
Tay et al. [44]	Australia	2 years	LCD: 14% carbohydrates (<50 g/day), 28% protein, 58% fat
Makenzie et al. [45]	USA	10 weeks	Very low calorie diets (VLCDs): <30 g/day carbohydrate, 1.5 g/kg protein, incorporate dietary fats to satiety.
Yancy [34]	USA	16 months	Low-carbohydrate, ketogenic diet (LCKD): ≤20 g/day carbohydrate
Dashti et al. [46]	Kuwait	56 weeks	Low-carbohydrate, ketogenic diet (LCKD): <20 g/day carbohydrates, 80–100 g/day proteins, additional 20 g/day carbohydrates after 12 weeks.
Myette-Cote et al. [47]	Canada	4 days	Low-carbohydrate, high-fat diet (LC): 10% carbohydrate, 25% protein, 65% fat.
Leonetti et al. [48]	Italy	4 months	Very low calorie ketogenic diet (VLCKD): 15 g/day carbohydrates, 72–80 g/day proteins, 23–24 g/day lipids
Walton et al. [49]	USA	13 months	Low-carbohydrate (LC) ketogenic diet: 5% carbohydrate (carbohydrate < 30 g/day), 20−25% protein, 70−75% fat
Iqbal et al. [37]	USA	24 months	Low-carbohydrate diet (<30 g/day)
Dyson et al. [35]	United Kingdom	3 months	Ketogenic diet (carbohydrate ≤ 40 g/day)

Obesity is associated with the establishment of a permanent low-grade inflammatory state, with the continuous release of pro-inflammatory mediators such as interleukins or tumor necrosis factor α, but also the reduced production of anti-inflammatory adiponectin. This inflammatory state favors the development of obesity-associated morbidities [50]. In this respect, the ketogenic diet has also been administered in studies addressing obesity-related conditions such as chronic kidney disease, cancer, or cardiovascular diseases and analyzed in multiple clinical trials, as presented in Table 2.

Table 2. Investigating metabolic disorders through ketone body intervention: overview of clinical studies and trials.

Medical Condition	Target Group (Sex, Age)	Cohort Size	Intervention	Examined Factors	Phase	Clinical Trial Registration Number
Diabetes	Both genders, 35–70	18	BHB infused intravenously	Composite cognitive score	Phase I	NCT03657537
Diabetes	Both genders, 18–60	19	Different insulin therapy after positive blood ketones	Glucose metabolism, time course of ketone body production	N/D	NCT00970567
Diabetes	Both genders, >18	10	Dietary supplement: ketone ester	Variation in lipolysis rate and glucose kinetic	N/D	NCT05159570
Cardiovascular disorder	Both genders, >18	24	Dietary supplement: KetoneAid ketone ester	Cardiac output (power), left ventricular filling pressure, ejection fraction, hourly urinary output, mixed venous saturation, renal and peripheral perfusion	N/D	NCT04642768
Cardiovascular disorder	Both genders, >18	10	Dietary supplement: ketone monoester	Changes in lipolysis rate, protein metabolism, glucose kinetics	Phase II	NCT05161676
Cardiovascular disorder	Both genders, >18	16	Drug: BHB ester	Measurements of blood concentrations of BHB, insulin, and bicarbonate; left ventricular ejection fraction; cardiac output	Phase I	NCT04370600
Acute ketosis	Men, 18–40	6	Drink of ketone bodies	Measurement of BHB concentration in blood, glucose kinetics, free fatty acid accumulation	N/D	NCT02917252
Obesity	Both genders, 18–45	10	6 h morning fasting	Mobilization of adipose tissue and gut peptides, degree of appetite suppression, and induction of satiety	N/D	NCT04293003
Obesity	Women, 20–40	100	Calorie-reduced, intermittent fasting diet (time-restricted eating: 16 h fasting and 8 h eating	Measurements of serum levels of dopamine and serotonin, diagnosis of food addiction disorder and binge eating disorder	N/D	NCT04873648
PCOS	Women, 16–35	20	Starvation for 48 h	Alterations in androgen metabolism and steroid profiles	N/D	NCT03573063
PCOS	Women, 18–45	14	Low-calorie Mediterranean ketogenic diet with phytoextracts (KEMEPHY)	Measurements of body weight, fat mass, total testosterone, progesterone, estradiol, ketone bodies, total cholesterol, triglycerides	N/D [51]	NCT04163120
Cancer	Both genders, >18	18	Bevacizumab and the modified Atkins diet (high fat, unlimited protein, low carbohydrates (<20 g/day)	Correlation of blood sugar levels and ketosis values based on compliance level, correlation of blood sugar levels and ketosis values based on tumor response	Early Phase 1	NCT02768389
Cancer	Both genders, >18	101	Fasting mimicking diet: (5-day plant-based, low-calorie (600 Kcal on day 1, followed by 300 KCal/day on days 2 to 5), low-protein, low-carbohydrate)	Alterations in blood cell counts; weight changes; measurements of glucose, cholesterol, and triglycerides in blood; measurement of urinary ketone bodies	N/D [52]	NCT03340935
Cancer	Women, >19	57	Ketogenic diet	Changes in fasting glucose, insulin, and BHB; total and regional body fat; food cravings; perceived hunger	N/D [53–55]	NCT03171506

N/D: not determined, research studies.

5. Ketogenic Diets in Polycystic Ovary Syndrome

Polycystic ovary syndrome (PCOS) is a common endocrine disorder in women of reproductive age, typically characterized by and diagnosed based on two out of three criteria: (i) oligomenorrhea or amenorrhea (accompanied by either oligo-ovulation or anovulation) (ii) hyper-androgenism, and (iii) the presence of polycystic ovaries [51]. PCOS is often associated, but not univocally, with obesity, type 2 diabetes and, to a lesser extent, cardiovascular disorders [56]. At present, the etiology of PCOS remains unknown; however, the onset of PCOS has been associated with several hereditary and environmental factors, also including an altered fetal environment [57], mtDNA point mutations or mtDNA deletions [58], and microbial dysbiosis [59].

In women with PCOS, hormonal disturbances lead to a lack of ovulation and hyperandrogenism steam from an increased ratio of luteinizing hormone (LH) to follicle stimulating hormone (FSH), which, as a consequence, prompt excessive androgen production due to the inadequate stimulation of ovarian follicle maturation and estrogen secretion by FSH [60]. Moreover, insufficient FSH levels also contribute to the decreased activity of aromatase, the enzyme responsible for the conversion of androgens into estrogens. Nevertheless, it is believed that insulin resistance may play a crucial pathogenic role, since insulin can additionally fuel the production of androgens by negatively influencing the hepatic synthesis of the main testosterone-binding protein, thereby resulting in testosterone circulating in the unbound active form. Moreover, the majority of women with PCOS eventually develop insulin resistance [61]. This is why among strategies to alleviate symptoms of the disease, typically including combined oral contraceptives [62] or metformin [63], there is a raising interest in curbing PCOS with adequate dietary interventions [64].

Among the diets currently being investigated to manage the symptoms of PCOS, the spotlight belongs to the ketogenic diet, mainly due its significant improvement in insulin signaling [65], promotion of weight loss [60] and amelioration of the patient's hormonal balance [66] with restoration of a proper LH/FSH ratio with a subsequent reduction in total free testosterone levels [51]. Moreover, the KD induces a decrease in blood glucose levels and improvements in insulin sensitivity, also leading to reduced androgen production [25].

In a recent study, 84 obese/overweight PCOS patients planning to receive in vitro fertilization were assigned to either a very low calorie ketogenic diet (VLCKD) or a Mediterranean diet (MD). In comparison to the MD, the VLCKD proved to be more effective in the promotion of weight loss, restoration of insulin sensitivity and, importantly, IVF successfulness [67]. Hence, this study suggests that the KD could be a promising nutritional therapy supporting, indirectly, patient fertility or receptivity towards in vitro fertilization procedures. Other independent studies reported that implementation of a ketogenic diet prior to IVF significantly increased embryo implantation and pregnancy rates [68,69], also with additional metabolic beneficial effects, including improved liver function and insulin sensitivity [70]. While ketogenic diets can improve fertility in PCOS patients, the question of whether keeping the ketogenic regimen during pregnancy and post-partum is safe remains, in light of currently available data, elusive. Below, we discuss the potential applicability of the KD during pregnancy and post-partum, with emphasis on clinical situations, such as epilepsy or GLUT1 deficiency, in which the KD is the main, or unique, option.

6. Efficacy of Ketogenic Diets During Pregnancy and Breastfeeding

The safety of following a ketogenic diet regimen during the pregnancy and post-partum period must be benchmarked against potential risks both to the mother and the fetus/newborn. When considering both the benefits and risks of implementing the ketogenic diet during pregnancy, epilepsy treatment through a ketogenic diet during pregnancy stands as a therapeutically actionable option [71]. Similarly, the risk of developing ketoacidosis during the breastfeeding period is also to be considered prior to adhering to the ketogenic regimen [72].

Over the years, the ketogenic diet has been proven to be an effective treatment for various types of drug-resistant epilepsies in infants, children, and adults. Implementing the

dietary intervention in epilepsy therapy might pose a promising prospect during pregnancy, since some of the currently available anticonvulsant drugs, such as valproic acid (VPA) and carbamazepine (CBZ), are teratogenic, and their use during certain stages of fetal development may lead to various malformations such as neural tube defects and cardiac anomalies [73,74]. At present, however, there is still a lack of data on whether a ketogenic regimen adhered to by epileptic pregnant women and women with glucose transporter type 1 deficiency syndrome (Glut1DS) may affect fetal and neonatal development, although the few existing publications seem to suggest the absence of any contraindication [71,75].

In a case series study, van der Louw et al. [71] suggest that a ketogenic diet during pregnancy could be used as a nonpharmacological alternative in epileptic patients; however, they also advocate for further research to potentially identify the long-term effects of this nutritional approach, as some patients (e.g., a 27-year-old epileptic study participant) presented low vitamin levels and mild hyperlipidemia. Moreover, both van der Louw et al. [71] and Kramer and Smith [75] observed decreased serum carnitine levels in their patients. Carnitine deficiency can be a result of primary carnitine deficiency or related to the use of antiepileptic drugs (VPA), malnutrition, or a vegetarian diet. Because fetal and maternal carnitine concentrations are correlated, due to the ability of carnitine to cross the placenta, it is important to monitor its levels [76].

Cautionary data on the use of the ketogenic diet during pregnancy have also been raised in rodent models, pointing towards the threating effects of a maternal ketogenic regimen on the nervous system of the fetus, which may put into question the safety of the KD in pregnant epileptic women. In these studies, prenatal exposure to ketogenic diet caused alterations in the embryonic organ growth of mice [77] as well as altered brain structures in neonatal mice [78]. It may be probable that the aforementioned changes could affect postnatal life, potentially influencing behavior, which is consistent with research claiming that a ketogenic diet, administered to dams, may increase susceptibility to depression and anxiety in the adult mouse offspring [79]. Also, the KD was proven to suppress neuroinflammation in a rat model of spinal cord injury via the downregulation of NLRP3 [80]; however, prenatal ketogenic diet has also been shown to induce neuronal defects, with lower neuronal densities in selected brain regions such as the prefrontal cortex dentate gyrus [81].

Further threating effects of following the ketogenic diet during breastfeeding may also arise due to the higher risk of ketoacidosis [82]. In general, adherence to either a ketogenic or a low-carbohydrate diet carries an inherent risk of developing ketoacidosis. Furthermore, the additional energy demands of lactation may potentially exacerbate this risk, particularly when combined with the aforementioned dietary patterns. Increased glucose utilization may result in the dysregulation of the compensatory mechanism regulating normal ketone levels in lactating women on a ketogenic diet [72]. Similarly to starvation ketoacidosis, an increase in catabolic hormones including catecholamines and glucagon could be observed, accompanied with lower insulin levels, which overall can contribute to increased ketone body production [83]. Moreover, so-called "lactation ketoacidosis" may lead to the depletion of the glycogen stores, forcing the body into using gluconeogenesis as an energy substrate for the production of breast milk [84].

Given the increased popularity of the KD, also as a strategy used to achieve weight loss, it would be of value to educate both mothers and clinicians regarding the potential adverse effects of the KD during the lactation period, especially to raise awareness against following self-planned ketogenic diets, and even more so considering that the prospect of weight loss after the pregnancy is a potential main motivation for women to start a KD in several reported cases (Table 3).

Table 3. Overview of case reports presenting ketoacidosis incidents while adhering to KD during breastfeeding by non-diabetic women.

Patient	Symptoms at Admission	Details of the Diet	Management of the Symptoms	Ref.
32-year-old	Nausea, vomiting, serum pH of 7.20	Carbohydrate intake estimated as less than 20 g/day	Intravenous administration of fluids and insulin. Recovery after 3 days.	[85]
24-year-old	Nausea, vomiting, episodes of diarrhea	Adherence to strict KD with adequate calorie intake (2200 Kcals per day) since the birth of her 18-week-old son	Administration of fluids, insulin, and glucose, followed by the introduction of oral carbohydrate diet.	[72]
31-year-old	Shortness of breath, epigastric pain, blood glucose of 79 mg/dL (within normal range), blood ketones of 7.0 mmol/L (exceeding beyond normal range)	Self-managed KD with restricted variety of food products over the past 3 weeks	Administration of insulin, non-invasive ventilatory support (due to respiratory distress from severe acidosis), and monitoring in ICU. Full recovery after 4 days.	[82]
32-year-old	Glycemia, 89 mg/dL; ketonuria, 80 mg/dL	Limitation of carbohydrate intake to 25 g/day approximately for the period of 1–2 months	Administration of fluids, followed by the re-introduction of standard diet.	[86]

7. Ketogenic Diets as Adjuvant Measures in Type 1 and Type 2 Diabetes

Although ketogenic diets were the only slightly effective treatments for T1D before the discovery of insulin, to date, and because of the insulin standard care, type 1 diabetes has been found to be an important contraindication to the ketogenic diet [87]. A recent report of 11 patients with type 1 diabetes and following a ketogenic diet suggests a reduction in glycemic variability in the development of cardiovascular complications in diabetes. However, lowered glycemic variability comes at the cost of an increased risk of hypoglycemia [88]. As shown, the ketone bodies—especially BHB—in type 1 diabetes can act as a double-edged sword. At present, it is not possible to draw a final conclusion as to whether the ketogenic diet can be safely used in patients with type 1 diabetes, as high-quality prospective studies are lacking. In some selected cases, such as the simultaneous presence of type 1 diabetes and obesity, this application may be considered, but always under the supervision of an experienced physician and with continuous blood glucose monitoring [87].

In case of type 2 diabetes, the application of the ketogenic diet, and thus an increase in ketone bodies, is not recommended when the sodium-glucose co-transporter-2 (SGLT2) inhibitors (e.g., dapagliflozin, empagliflozin, canagliflozin) are used [87]. The SGLT2 inhibitors primarily increase the urinary excretion of glucose and reduce insulin secretion and hyperglucagonemia by facilitating lipolysis and ketogenesis, which, when combined with severe insulin impairment or severe dietary carbohydrate restriction, can lead to diabetic ketoacidosis [89]. Interestingly, in type 2 diabetic patients at high risk of cardiovascular disease, the use of SGLT2 inhibitors showed cardioprotective behavior potentially associated with an increase in BHB production [90]. When type T2D is treated without SGLT2 inhibitors, increasing ketone levels can be a beneficial adjunctive nutritional strategy as it allows the body to keep glucose levels relatively low. Low carbohydrate intake can help eliminate high blood sugar spikes while reducing insulin requirements. However, this approach requires further research as there is no information on the long-term maintenance of higher levels of ketone bodies [91].

8. In T2D, Ketogenic Diets Modulate the Microbiome

In the case of diabetes, the microbiome, which responds to changes in the diet composition, plays a key role in the development of the disease. The gut microbiota plays

a chief role in the production of short-chain fatty acids (SCFAs), branched-chain amino acids (BCAAs), and other crucial metabolites [92]. Numerous studies have established that disturbances in normal gut microbiome composition (dysbiosis) are often associated with the development of various pathological conditions, such as type 2 diabetes, or some types of cancer. Nevertheless, in the case of type 2 diabetes, data regarding the influence of the ketogenic diet regimen on the microbiome are limited and often restricted only to populations of obese individuals with or without type 2 diabetes [93]. According to Louis et al. [94], implementation of the VLCKD in obese individuals is accompanied with an increased fecal expression of *Akkermansia*, and since *Akkermansia* is enriched in individuals without metabolic morbidities, this advocates for the positive impact of the VLCKD in obesity. Similarly, the VLCKD was associated with a decrease in gut-microbiota-driven inflammation markers [95]. Moreover, high-protein/low-carbohydrate diets reduce *Roseburia* spp. and *Eubacterium rectale* in gut microbiota, resulting in a potentially unfavorable gut environment [96]. Overall, clear evidence of the impact of ketogenic diets on the microbiome in type 2 diabetic individuals still needs to be firmly established. Nevertheless, improving the outcomes of diabetes via microbiome-directed dietary approaches is worth exploring further.

9. Concluding Remarks

If we consider an organism, including a human subject, as a thermodynamic system, then, according to the first law of thermodynamics, describing the conservation of energy, body weight is the result of the difference between energy intakes versus energy expenditure. In this context, the proposed energy balance model (EBM) to describe body weight applies as a direct application of the thermodynamics laws [15], and any weight loss of organisms caused by a diet would be independent from the macronutrient composition of the diet [97], but only dependent on the negative caloric balance. Yet, in contrast to this thermodynamic view, studies exist showing that nutrition schemes on a low-carbohydrate diet lead to higher weight loss in the first 3–6 months of diet in comparison to a balanced diet [98–100]. Arguably, changing patterns of nutrition, favoring one of the three macronutrients over the others, leading to low-carbohydrate (and high-fat) or low-fat (and higher-carbohydrate-content) diets, will lead to endocrine and physiological changes so that the "sensing" of the body on a calorie differs. If viewed from this perspective, then the carbohydrate–insulin model (CIM) provides a credible physiological explanation for accrued adiposity upon the continuous uptake of excessive carbohydrates [101], and, indirectly, supports from a theoretical point of view the validity of KD-based nutritional approaches. Irrespective of the biochemical changes ensuing upon adherence to a ketogenic diet, a key feature is evident in the clinical trials exploring ketogenic nutrition: as the blinding of participants to the intervention arm is not possible, as a nutritional scheme is clearly recognizable, it may be surmised that the benefits of a KD may be amplified by the fact that a study participant in the KD arm may be favored by closer interaction with the investigator through consultations and follow-up and by a sense of proactive involvement in the study.

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