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Scientific evidence underlying contraindications to the ketogenic diet: An update

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Summary

First identified as a feasible treatment for intractable epilepsy, the ketogenic diet (KD) has recently gained popularity thanks to growing evidence on applications such as weight loss, most importantly, but also NAFLD, cancer, neurologic conditions and chronic pain. As with any treatment, whether pharmacologic or not, the KD might not be an appropriate intervention for every individual, and a number of contraindications have been proposed, now deeply rooted into clinical practice, excluding de facto many patients that could benefit from its use. However, many of these concerns were expressed due to the absence of clinical studies conducted on fragile populations, and an assessment of lately emerged evidence relative to KD safety is currently lacking and much needed. We herein provide a critical revision of the literature behind each safety alert, in order to guide through the treatment options in the case of subjects with an indication to the KD and a borderline safe situation. Based on available evidence, the possible use of this diet as a therapeutic intervention should be assessed on a patient-to-patient basis by adequately skilled medical doctors, keeping in mind current recommendations, but reading them through the knowledge of the current state of the art.

KEYWORDS

low-carbohydrate diet, safety, very low-calorie diet, VLCKD

1 | INTRODUCTION

The ketogenic diet (KD) is defined as a dietary manipulation characterized by a very low carbohydrate content (5%–10% of total daily calorie intake, or 20–50 g per day[1,2]), but the macronutrient composition may vary, defining different ways to reach nutritional ketosis. High-fat ketogenic diets (HFKD) are characterized by a restriction of carbohydrates <50 g/day, with ad libitum fat and calorie intake. Despite their initial introduction as a treatment for refractory epilepsy, they are currently the most widespread weight loss oriented KD. The very low-calorie KD (VLCKD) is a subtype of very low-calorie diet (VLCD), also referred as protein-sparing modified fast (PSMF), that usually relies on meal replacements based on protein derived from whey, soy, eggs and green peas. VLCDs are characterized by extreme energy restriction (400–800 kcal/daily), that, if not associated with major carbohydrate intake reduction, is not necessarily capable of inducing ketosis.[3] The European Food Safety Authority (EFSA) defined a VLCD to be ketogenic when carbohydrate content is below <30–50 g/day

and fats account for 15%–30% of total caloric intake.[3] However, it should be noted that the carbohydrate and calorie intake under which an individual enters ketosis is subjective, making the line between starvation and nutritional ketosis subtle.

Dietary manipulation does not usually recognize specific contraindications as pharmacological interventions do, hence the lack of a 'drug facts label' for the KD. However, ketone bodies are now proven to be signalling, drug-like, mediators.[4] Moreover, the VLCKD is a fairly extreme dietary manipulation possibly leading to serious adverse events when not medically supervised. A recent Italian consensus has therefore updated indications and contraindications to the VLCKD,[5] implementing those proposed initially,[6] similar to what reported by other authors in the United States.[7]

The applications of the KD are now diverse and ever increasing, the most validated being obesity and refractory epilepsy, but with an emerging role in the treatment of neurological disorders, cancer, NAFLD, type 2 diabetes and chronic pain among many others.[5] With the prevalence of obesity steadily growing, and the several newly proposed fields of application, it is more and more frequent to face situations where the patient could benefit from a KD and also suffers from co-morbidities or conditions contraindicating its use according to the current recommendations.[5–7]

We herein aimed at providing an updated and critical revision on the evidence underlying each current safety concern (Table 1). We report that most studies are low quality, sample size often very small, and duration usually quite short, making no definitive conclusion possibly be drawn. However, based on current evidence, it seems reasonable to recommend that a patient-to-patient tailoring be made by experienced physicians, possibly reconsidering many alerts proven questionable (Table 2).

2 | MATERIALS AND METHODS

An updated literature review was conducted to investigate the safety profile of the KD in specific fragile populations. The research was conducted on MEDLINE, EMBASE and Cochrane Database by using the keywords reported in Table S1. We initially selected relevant studies meeting the following criteria: (1) case-reports, case series, case-control studies, cohort studies, observational prospective and retrospective studies, randomized clinical trials; (2) reported safety outcomes following any kind of KD; (3) no age limitation; (4) sufficient detail about nutritional intervention reported; and (5) studies written in English or Japanese or Italian. Case reports and case series were then excluded if higher quality data was available. Preclinical studies were occasionally included if no clinical study was retrieved or when the findings were of particular interest according to the authors.

A total of 1034 manuscripts were identified through database search and reference lists of retrieved articles. After removal of 821 studies based on title and abstract or for being duplicates, 213 full text articles were assessed and 52 included in the present study (Figure 1).

3 | REPORTED CONTRAINDICATIONS TO THE KETOGENIC DIET

3.1 | Liver failure

Nonalcoholic fatty liver disease (NAFLD) is nowadays the second cause of liver transplant in the United States.[60] A relevant body of evidence suggests a protective role of KDs in its pathogenesis, possibly going beyond simple weight loss: virtually all studies assessing liver fat content report positive results after all kinds of KDs, including those with a high fat content.[9]

Noteworthy, malnutrition is a common issue in chronic liver disease.[61] The 2019 Guidelines of the European Association for the Study of the Liver therefore recommend consuming an adequate number of calories and protein. To avoid hepatic encephalopathy, it is suggested to privilege vegetable and dairy protein and decrease the amount of animal (meat) protein, with no reduction in total protein intake even when cirrhosis is present, unless directed by a health professional.[62] However, with the prevalence of obesity increasing all over the world, and NAFLD being now a common cause of cirrhosis, over 30% of liver transplant recipients are obese, and weight loss is strongly encouraged.[63] A case series reports that VLCKD treatment for obesity was well tolerated by two subjects with end stage liver disease (ESLD) effectively reducing weight with no adverse events, and possibly improving liver damage.[8]

Upon close medical monitoring, liver damage may not be exacerbated by the KD, that could conversely prove beneficial. An application might be retained up until ESLD, although further studies are needed to recommend it.

3.2 | Chronic kidney disease

Obesity is a well-established risk factor for chronic kidney disease (CKD),[64] and it is therefore common to encounter patients affected by both severe obesity and renal failure, whom the KD is not proposed due to its relative protein excess that could potentially harm the kidney. Guidelines are inconclusive on recommendations relative to protein intake in patients with CKD at early stages, with some suggesting .8 g/kg body weight,[65] and others recommending up to 1.4 g/kg body weight.[66] Renal function may be differentially affected by protein sources, with red meat proving potentially harmful in a dose dependent way, and other protein sources (fish, egg and dairies) being less noxious,[67] with vegetable derived protein possibly even playing a protective role.[68,69]

A systematic review assessing renal outcomes reports that the kidney seems scarcely affected by VLCDs, although the diets were heterogeneous in macronutrient composition, and the studies only included subjects with normal renal function, making the findings not applicable to those with baseline impaired function.[70] In our hands, kidney function is unaffected in obese individuals with normal glomerular filtration rate (GFR).[71] Moreover, we previously showed that kidney function is not altered by VLCKD in patients with mild chronic

TABLE 1 Summary of data available regarding each contraindication to the KD

Main contraindications	Summary of data
Liver failure	All KDs are beneficial towards NASH. Two patients with ESLD on a VLCKD lost weight with no adverse events.
Kidney disease	VLCDs seem not to affect the kidney in healthy patients. Mild CKD may be improved and is not worsened in obese patients undergoing a VLCKD. 10 patients with obesity and advanced nephropathy lost weight on a VLCKD with no major safety concern.
Type 1 diabetes	One retrospective and one prospective study report that 23 patients with T1D on an HFKD had an improvement in glycaemic variability with a small increase in the hypoglycaemia risk.
Concomitant use of SGLT-2 inhibitors	Several case reports are available regarding the onset of euglycaemic DKA in those consuming HFKDs while on SGLT-2 treatment.
Pregnancy	A teratogenic effect of HFKD is suggested by a case series, and preclinical data partially support the hypothesis.
Breastfeeding	Lactation ketoacidosis is rarely described to happen spontaneously, but a few case reports show an increased risk when KD is a precipitating factor.
Cardiac arrhythmias	Cardiomyopathy and arrhythmias were occasionally reported in epileptic children undergoing an HFKD due to selenium deficiency. VLCDs caused fatal cardiac arrhythmias in the 1970s due to inadequate supplementation. A recent prospective study suggests that a low carbohydrate, high fat diet is associated with increased risk of atrial fibrillation, further studies are needed to confirm the hypothesis.
Recent stroke or myocardial infarction	Preclinical evidence suggests ketone bodies to be protective on ischaemic brain and heart damage. No clinical data are available yet.
Heart failure	The human failing heart uses ketone bodies as a fuel source. One report shows that ketones infusion was harmless and increased cardiac output significantly in those at an NYHA II-III stage.
Respiratory failure	A study in lean subjects with COPD on LCD reports significant improvement and no adverse events. Unreplicated small studies from the 1980s showed that an HFKD was beneficial in patients with respiratory failure or on mechanical ventilation.
Active/severe infections	Clinical studies on KDs do not report a clear immunosuppressive effect. Preclinical data suggest a possible protection towards viral infections.
Frail elderly patients, history of mental disorders and substance abuse	No studies or reports are available.
Elective surgery or invasive procedures	Fasting related perioperative ketosis seems not to increase acidosis risk. Preoperative VLCD may induce hypovolaemia possibly increasing the risk of perioperative complications. Adverse events were not reported when a VLCKD was interrupted 24 h before surgery.
Malignancy	KD does not cause major adverse events around cancer treatment.
Increased serum uric acid and abnormal lipid profile	KDs might induce mild worsening short term, with following improvement or no change in patients with obesity. Sustained dyslipidaemia is observed in lean epileptic subjects on HFKD.
Rare disorders	No studies or reports are available.

Abbreviations: T1D, type 1 diabetes; DKA, diabetic ketoacidosis; ESLD, end stage liver disease; NASH, nonalcoholic steatohepatitis; CKD, chronic kidney disease; NYHA, New York heart association functional classification; COPD, chronic obstructive pulmonary disease; VLCKD, very low-calorie ketogenic diet; HFKD, high fat ketogenic diet; LCD, low carbohydrate diet.

kidney disease (GFR > 60), with almost one third even presenting GFR normalization after the dietary intervention.[10] Noteworthy, VLCKDs rely on meal replacements whose protein source is whey and plant derived, and, when gradual reintroduction of other protein sources occurs, fish, poultry and dairy are strongly recommended over red meat, with total protein intake being always equal to or lower than 1.5 g/kg/ideal body weight. Taken together, available evidence suggests that a VLCKD, with the profound weight loss usually obtained, might be an effective tool to manage patients with obesity and mild kidney failure.

Conversely, very little evidence is available relative to the safety profile in patients with more prominent kidney function impairment. A small 12-week study conducted on five patients with obesity and advanced diabetic nephropathy reported significant improvement in kidney function together with weight loss after a VLCKD intervention.[11] Pointing in the same direction, five patients on haemodialysis underwent a low-calorie, low carbohydrate diet for a median time of 364 days with no major safety concern and prominent weight loss.[12]

While considering the use of KD on patients with end stage CKD, it is crucial to keep in mind that this condition is characterized by limited capacity to handle acid loads and partial impairment of ketones urinary excretion. Moreover, in the initial phase of a KD, increased diuresis will require careful monitoring of goal dry weight if the patient is on haemodialysis treatment. Another possible side effect is

TABLE 2 Summary of reported contraindication to the KD with theoretical reason in support to each, population where safety outcome was evaluated, type of dietary intervention, and critical revision based on available evidence

Main contraindications	Main arguments in support of contraindications	Population	Diet	Critical revision of the contraindications
Liver failure	Exacerbation of liver damage	Obesity with ESLD[8] and NASH[9]	VLCKD,[8,9] HFKD[9]	Skilled hepatologist to evaluate in ESLD, safe and therapeutic in NASH
Chronic kidney disease	Exacerbation of kidney damage	Obesity with mild[10] and severe CKD[11,12]	VLCKD[10–12]	Safe in mild disease, skilled nephrologist to evaluate in end stage disease
T1D	Hypoglycaemia and DKA	Lean T1D[13,14]	HFKD[13,14]	Skilled diabetologist to evaluate, continuous glucose monitoring
Concomitant use of SGLT-2 inhibitors	Euglycaemic DKA	T2D[15–19]	HFKD[15–19]	Not recommended
Pregnancy and breastfeeding	Ketoacidosis	Epilepsy and pregnancy,[20] breastfeeding[21]	HFKD,[20,21] VLCKD[21]	Not recommended
Cardiac arrhythmias	Sudden death and cardiomyopathy	Obesity,[22–25] paediatric epilepsy,[26–28] general population[29]	VLCKD,[22–25] HFKD,[26–28] LCD[25,29]	Skilled cardiologist to evaluate
Recent stroke or myocardial infarction	Increased risk of arrhythmia	Preclinical[30–37]		Skilled cardiologist to evaluate
Heart failure	Increased risk of arrhythmia, hydroelectrolitic alterations	NYHA II-III[38]	bOHb infusion[38]	Avoid in NYHA IV, skilled cardiologist to evaluate in other cases
Respiratory failure	Acidosis	Lean COPD,[39] mechanical ventilation,[40,41] respiratory failure[42–44]	LCD,[39] HFKD,[40–42,44] VLCKD[43]	Skilled pneumologist to evaluate
Active/severe infections	Immunosuppression	Cancer,[45] general population,[46] paediatric epilepsy,[47] obesity,[48,49] preclinical[50]	HFKD,[45–47] VLCKD[48,49]	Generally not recommended
Frail elderly patients, history of mental disorders and substance abuse	Reduced compliance, increased risk of adverse events	n/a	n/a	Only consider if adequate support and monitoring available
Elective surgery or invasive procedures	Ketoacidosis	Obesity,[51,52] adult undergoing surgery[53]	VLCKD,[51,52] 12 h fasting[53]	Not recommended
Malignancy	Malnutrition, exacerbation of common side effects	Cancer,[54] preclinical[55]	HFKD[54]	Avoid in kidney cancer and melanoma, avoid VLCKD
Increased serum uric acid and abnormal lipid profile	Exacerbation of metabolic abnormality	Obesity,[56–58] lean paediatric epilepsy[59]	VLCKD,[56,57] HFKD[58,59]	Extra caution if lean subject with baseline abnormalities or when long term treatment is foreseen
Rare disorders	Impaired ketogenesis, increased risk of relapse	n/a	n/a	n/a

Abbreviations: T1D, type 1 diabetes; DKA, diabetic ketoacidosis; ESLD, end stage liver disease; NASH, nonalcoholic steatohepatitis; CKD, chronic kidney disease; T2D, type 2 diabetes; NYHA, New York heart association functional classification; COPD, chronic obstructive pulmonary disease; VLCKD, very low-calorie ketogenic diet; HFKD, high fat ketogenic diet; LCD, low carbohydrate diet; bOHb, beta hydroxy butyrate.

electrolyte imbalance, and most commonly hyperkalaemia; hence, repeat testing is warranted for an early diagnosis.

Given the scanty—although promising—evidence, with a total of only 10 patients being studied, it is of utmost importance to accurately assess pros and cons of such dietary intervention in advanced stage renal failure.

3.3 | Type 1 diabetes

Type 1 diabetes (T1D) is possibly the most well-described contraindication to the KD due to the increased risk of diabetic ketoacidosis and possible hypoglycaemia. However, it is more and more common to encounter patients affected by both T1D and weight excess, where a

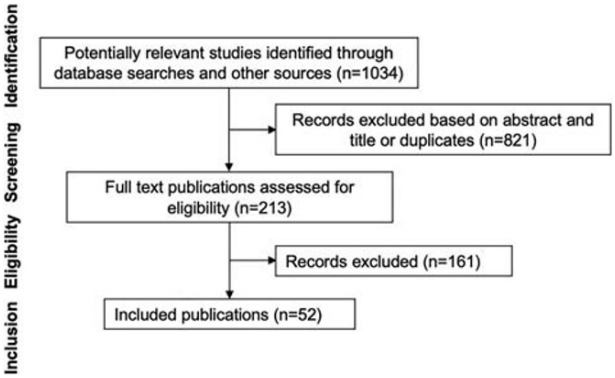

FIGURE 1 Flow chart of publications selection

change in dietary habits is necessary. The latest American Diabetes Association (ADA) guidelines do not support one eating plan over another, but education on carbohydrate counting is highly encouraged.[72]

In a retrospective study investigating the safety of an HFKD together with its efficacy in improving glucose control, 12 subjects with T1D followed an intense glucose monitoring (>4 times daily) and strictly titrated insulin regimen (<7 IU) while dieting. No severe hypoglycaemic events and a significant A1C reduction after 18 months of treatment were reported.[13] Pointing in the same direction, a recent report on 11 subjects with T1D on continuous glucose monitoring consuming an HFKD suggests glycaemic benefits in the form of decreased variability, a well-established cardiovascular risk factor.[73,74] However, in this case, it came at the cost of increased risk of hypoglycaemia.[14] Because of the heterogeneity of the studies and the lack of high-quality prospective trials, it is not possible to finally conclude whether KDs can be safely used in patients with T1D. Moreover, current evidence aimed at assessing a possible application of the KD to improve glucose control in T1D, rather than investigating its safety in those with T1D consuming it for other purposes such as weight loss. Overall, the scanty literature available suggests that its application might be considered in very selected cases, such as the concomitant presence of T1D and obesity or wide prandial excursions, always in the hands of experienced health professionals and with the aid of continuous glucose monitoring. It should be kept in mind that the cost-to-benefit ratio might be unfavourable in some individuals, and further testing is needed to better identify those possibly candidate to its use.

3.4 | Concomitant use of SGLT-2 inhibitors

Since the introduction of the glucose lowering class of drugs sodium–glucose cotransporter-2 inhibitors (SGLT2-i), several reports have been published regarding the risk of euglycaemic diabetic ketoacidosis (DKA) in those consuming HFKDs while on SGLT-2 treatment for type 2 diabetes.[15–19] SGLT2-i increase glucose urinary excretion by inhibiting the sodium and glucose reuptake in the kidney. In addition to the daily loss of ~60–70 g/day,[75] SGLT2-i also decrease insulin secretion and hyperglucagonaemia promoting lipolysis and ketogenesis.[76] As SGLT2-i facilitate ketosis, concomitant severe insulin impairment or significant dietary carbohydrate restriction might lead to DKA.

The reportedly normal glucose levels make such a diagnosis difficult to be formulated unless suspected. As this is a life-threatening condition, it seems advisable to strongly recommend against the concomitant use of this class of medications while on any kind of KD.

3.5 | Pregnancy and breastfeeding

Unsurprisingly, no clinical study is available relative to the use of KDs in pregnant women, with one case-series on two women suggesting a possible teratogenic effect of an HFKD as a treatment to refractory epilepsy.[20] Preclinical studies report a significant reduction in the cerebral blood flow, reduced glucose utilization similar to metabolic encephalopathies, and embryonic growth retardation,[77] but it should be noted that the KD given to rodent models is highly insufficient in protein and not comparable to a KD usually prescribed to human beings, making results scarcely translational.[78]

Lactation ketoacidosis is a well-described condition in cows, and it occurs as the high demand of glucose leads to fat mobilization, ketosis and ultimately acidosis under certain circumstances. Lactation ketoacidosis is rarely described to happen spontaneously in women, but a few case reports show an increased risk when KD is a precipitating factor.[21]

Given the potentially serious adverse events and the limited time that these conditions make KD not recommendable, it is reasonable to conclude that the KD should never be suggested in pregnant and breastfeeding women.

3.6 | Cardiac arrhythmias

VLCDs became very popular in the 1970s thanks to the rapid weight loss obtained, but soon, several fatal cardiac arrhythmias were reported in association with their use.[22] The absence of appropriate electrolyte supplementation and the use of low quality protein led to

such dramatic consequences, and nowadays, these complications are anecdotal.[79] However, the presence of baseline EKG abnormalities might potentially pose at increased risk of malignant arrhythmias upon KD consumption, although the little available evidence suggests it not being a common precipitating factor[23,26] unless accompanied by other concurring conditions.[24] Noteworthy, obesity is itself a risk factor for prolonged QT,[80] and it has been shown that weight loss in general, and both a low carbohydrate and a VLCD diet, in particular, are able to shorten the QT interval significantly.[25,80] Some cases of children undergoing an HFKD to treat refractory epilepsy and incurring in selenium deficiency are reported, causing cardiomyopathy and prolonged QT interval, with lethal outcomes on some occasions. It is therefore of particular importance to make sure that selenium supplementation is appropriate while following a ketogenic diet.[27,28] A recent prospective cohort study demonstrated that a low carbohydrate, high fat diet is associated with increased risk of incident atrial fibrillation. The authors suggest a possible link with reduced vegetables and fruit intake with subsequent increase in oxidative stress. Nevertheless, the association, proposed for the first time, seems to be controversial at the very least, and further studies are needed to confirm or reject the hypothesis.[29]

Overall, the cost-to-benefit ratio of KDs in patients with obesity might be favourable even in those with baseline prolonged QT interval, provided the patient is accurately monitored, and strict compliance with multivitamin, mineral and electrolyte supplementation is ensured. However, very low-calorie dietary manipulations are reasonably safer to be avoided, especially when protein quality and adequate supplementation cannot be guaranteed, with less calorie restricted options to be preferred, always in the hands of skilled cardiologists.

3.7 | Recent stroke or myocardial infarction

Obesity, diabetes, NAFLD and the metabolic syndrome are all strictly linked and represent major risk factors for cardio- and cerebrovascular accidents. It is therefore unsurprising to observe the concomitant presence of these conditions, possibly benefiting from KD treatment, in those with a recent history of stroke or myocardial infarction, absolute contraindications to such dietary intervention. Interestingly, preclinical evidence suggests a protective role played by nutritional ketosis and ketone body β hydroxy-butyrate (βOHb) infusion on ischaemia induced brain and heart damage.[30–36] The authors suggest that ketone bodies may inhibit excitotoxicity, oxidative stress and apoptosis, avoiding further cellular loss in the penumbra zone around the necrotic core.

It should be noted that some evidence, upon superficial evaluation, seems to suggest opposite effects. For example, Liu et al. report increased mortality and greater myocardial injury in rats undergoing ischaemia reperfusion injury and previously fed a normal protein, high fat, low carbohydrate diet similar in composition to the Atkins diet commonly consumed as a form of HFKD in human subjects.[37,81,82] If it has been proven that dietary protein has little contribution to endogenous glucose production in human subjects,[83] making the Atkins Diet a feasible option to induce nutritional ketosis, the physiology of rodents is different, and the same macronutrient ratio leads to obesity and insulin resistance.[84] In fact, nutritional ketosis and weight loss are only observed in rats and mice when both protein and carbohydrate intake are reduced to less than 10%.[78] Therefore, despite the low carbohydrate content, the dietary model applied by Liu et al. is not comparable to an HFKD for human purposes, and the results should not lead to the conclusion that ketone bodies are harmful to the ischaemic heart.

Current evidence on the effect of ketone bodies on ischaemia-reperfusion injury outcomes is promising overall but only present at a preclinical level. It is therefore still not possible to infer on the safety of a KD in those suffering from recent myocardial infarction or stroke, even when other co-morbidities could significantly improve following its use.

3.8 | Heart failure

Obesity is a strong predictor of cardiac insufficiency as seen for acute cardiovascular accidents.[85] However, it is currently recommended against the induction of nutritional ketosis in patients with heart failure NYHA III-IV. Noteworthy, it has been proven that the human failing heart shifts to ketone bodies as a significant fuel source,[86] and myocardial lipid analysis conducted on hearts of nondiabetic, lean, advanced heart failure patients undergoing cardiac transplant confirmed increased ketone utilization.[87] Infusion of βOHb was harmless, and even increased cardiac output significantly in 34 patients at an NYHA II-III stage,[38] suggesting that the present contraindication should be at least reduced to those with NYHA stage IV, for which no safety evidence is available to date.

Altogether, it seems reasonable to foresee that more studies will become available in the next years, possibly confirming a beneficial effect of ketone bodies on all stages of cardiac failure, thus shortening the list of contraindications to the KD.

3.9 | Respiratory failure

Excess fat is known to be associated with several respiratory conditions,[88] as obesity is characterized by low-grade systemic inflammation,[89] possibly playing a major role in the pathogenesis of pulmonary disease.[88] Furthermore, fat accumulates within the alveolar interstitium in obese diabetic rats,[90] and recent evidence confirms accumulation of adipose tissue within the lung of subjects with obesity, its presence correlating with inflammatory infiltrate.[91] Therefore, an intervention leading to weight loss might in theory ameliorate respiratory failure in subjects with obesity and respiratory failure.

Interestingly, a study conducted in 60 lean individuals with COPD consuming a low carbohydrate diet (75 g/die, an amount possibly leading to ketosis in lean individuals, although this was not confirmed in the study) reports significant improvements as measured by increase in Forced Expiratory Volume 1 (FEV1) levels and reduction of

airway resistance.[39] Studies from the 1980s showed that an HFKD was beneficial in 35 patients undergoing artificial ventilation, with a significant reduction of the time where ventilation was required.[40,41] In the same years, some authors suggested that a VLCKD was able to ameliorate respiratory failure in a total of 22 subjects.[42–44] However, extreme caution should be paid as the sample size was always very small, and the results were never replicated.

Current evidence is insufficient to determine whether patients with respiratory failure may safely consume a KD, but an unexpected, beneficial effect both in lean and obese patients has been suggested.

3.10 | Active/severe infections

Bovine peripartum ketosis can impair leukocyte localization to infections, increase the risk of mastitis and impair leukocyte function.[92,93] However, clinical studies investigating inflammation markers and/or white blood cell number or function report variable and contrasting results, overall pointing towards a neutral effect or even possible improvement in subjects with obesity undergoing weight loss while following a KD.[45–49] Interestingly, a recent preclinical report suggests that the KD could even protect against certain viral infections through activation of protective δ γ T lymphocytes.[50]

Further studies are needed to be conclusive on the role possibly played by the KD in active or severe infections, and a cost-to-benefit ratio should be assessed on a patient-to patient basis until clearer evidence is reported.

3.11 | Frail elderly patients, history of mental disorders and substance abuse

Elderly patients are frequently affected by sarcopenic obesity,[94] and those with mental disorders are often on medications known to prevent weight loss.[95] However, administration of a KD to frail and/or elderly subjects might not be advisable due to several reasons. First, the KD induces increased urination with possible hypotension and dehydration, leading to an increase in the risk of falls. Second, some KDs, such as VLCKDs, require the use of supplements. Elderly patients might find remembering these challenging, especially when impaired cognitive ability is present, possibly posing at risk of cardiac arrhythmias and vitamin deficiencies. Finally, elderly subjects with limited mobility are at increased risk of decubitus, and some evidence suggests that wound healing might be impaired during KD consumption.[96]

Severe mental illness, similar to impaired cognitive ability and aging, may lead to reduced compliance in adequate water consumption and constant use of prescribed electrolyte and vitamin supplement crucial to maintain a good safety profile especially during a VLCKD among all KDs, thus increasing the risk of side effects. Unless properly assisted and monitored, fragile subjects at increased risk of poor compliance should avoid the use of VLCKDs.

A separate chapter should be opened for eating disorders such as Bulimia and Anorexia Nervosa (AN). Carbohydrate counting typical of KDs may theoretically trigger eating disorders in predisposed subjects. However, it has been proposed that the KD might be a possible bridge treatment for those with AN in order to avoid starvation and increase patient compliance,[9] although no clinical evidence has been reported to support this hypothesis to date.

Finally, abuse of alcohol and some substances increase the risk of metabolic acidosis under certain circumstances.[97] The concomitant consumption of a KD exacerbates the risk, and it is therefore to be recommend against the prescription of a KD to those with a history of alcohol and substance abuse where relapse seems possible, especially in the absence of adequate support. Noteworthy, a ketogenic diet seems to be effective in suppressing alcohol cravings both at a preclinical level and in subjects with obesity,[98,99] although it should be kept in mind that the physiology underlying such association might be very different across species, as the link in rodent models seems to be an elevation in Fibroblast Growth Factor 21 levels,[78,100] whereas such elevation following a ketogenic diet is not observed in human beings.[101]

3.12 | Elective surgery or invasive procedures

The theoretical basis to the recommendation of avoiding ketosis within 48 h of elective surgery and in the immediate perioperative period is that acute stress is characterized by the use of large amounts of glucose, possibly posing at increased risk of ketoacidosis. However, fasting related perioperative ketosis seems not to pose at increased risk of acidosis.[53] A recent study reports a VLCKD to be interrupted the day before surgery in 44 prebariatric patients, but no safety outcomes are shown.[51] Of note, a recent case report showed that the concomitant use of SGLT-2 inhibitors and VLCKD consumption in a diabetic patient undergoing surgery led to recurrent intraoperative *torsade de pointes*.[24] Moreover, preoperative VLCD has been shown to induce hypovolaemia possibly increasing the risk of perioperative complications in a study including 28 prebariatric patients.[52] However, data relative to the treatment intervention and timing are insufficient to draw conclusions on such outcome.

Although there is not enough evidence to confirm reduced safety outcomes in this particular situation, it is reasonable to conclude that a KD should be interrupted for some time while foreseeing elective surgery or invasive procedures, and adequate fluid repletion has to be ensured.

3.13 | Malignancy

Obesity is a well-established risk factor for many cancer types,[102] and long-term survival following tumour resection/treatment is increasingly observed. However, a diagnosis of malignancy is listed as a contraindication to KDs according to some[7] but not all recommendations.[5] This is possibly due to the growing evidence emerged in

between suggesting a beneficial effect of nutritional ketosis during, before and after cancer treatment, without significant adverse events being reported.[54] Of note, the KD stands in line with current nutritional recommendations of the American Institute for cancer Research (AIRC) and the American Cancer Society regarding the avoidance of refined grains, alcohol, and sugary drinks, and not in line relative to the consumption of fresh fruits, whole grain and legumes.[103] It should be acknowledged that preclinical evidence suggests a possible detrimental effect of an HFKD on melanoma and kidney cancer outcomes.[55] Therefore, KD consumption should be discouraged in those affected by these solid tumours until further evidence emerges. For other cancer types, ad libitum KD rather than VLCKD is usually best, unless rapid weight loss is advisable for specific reasons.

3.14 | Increased serum uric acid and abnormal lipid profile

Hyperuricaemia and dyslipidaemia are co-morbidities commonly seen in subjects seeking a KD for weight loss purposes, but they may be exacerbated by it due to the relative increase in protein intake and the variable dietary fat depending on the approach to achieve nutritional ketosis, despite not being listed as absolute contraindications according to available recommendations. However, it has been reported that both HFKD and VLCKD might lead to mild worsening short term, progressing to significant improvement or no change in most patients, possibly due to subsequent weight loss and insulin resistance amelioration in those with overweight or obesity,[56–58] whereas sustained hypercholesterolaemia and hypertriglyceridaemia are observed in lean subjects undergoing an HFKD for the treatment of refractory epilepsy.[59] Overall, extra caution should be paid when considering this nutritional intervention not for weight loss purposes in those with baseline metabolic abnormalities and no weight excess, or in the case of refractory epilepsy, where treatment might be considered long-term and macronutrient ratio is strongly hyper lipidic.

3.15 | Rare disorders

Carnitine deficiency, carnitine palmitoyl-transferase deficiency, carnitine-acylcarnitine translocase deficiency, mitochondrial fatty acid β-oxidation disorders and pyruvate carboxylase deficiency are conditions characterized by defective ketogenesis. Where individuals with no such disorder, under frank reduction of carbohydrate intake would mobilize fat depots leading to ketogenesis, patients affected by these rare disorders would eventually experience hypoglycaemia, coma and ultimately death.[104–106]

Finally, subjects with acute intermittent porphyria should avoid the KD as the lack of carbohydrates in is a well-known precipitating factor causing relapse of the condition.[107]

4 | DISCUSSION

Nutritional ketosis, although long known to be an effective treatment for refractory epilepsy, has only recently gained broad attention thanks to the several emerging applications ranging from obesity to type 2 diabetes and neurologic disorders.[5] However, its absolute contraindications according to the currently available scientific societies consensus and position papers may make patients potentially receiving significant benefit from it not candidate to such dietary intervention[5–7] (Table 2).

Some of these, such as pregnancy, breastfeeding and perioperative timing, find no reason in not being followed, given the short non-applicable time and the potential major adverse events that could develop. The presence of co-morbidities such as liver, kidney and respiratory failure, together with type 1 diabetes, should be addressed by specialists of the relative discipline and the patient be accurately assessed and monitored, with eventual treatment tailored and characterized by favourable cost-to-benefit ratio. The KD might ultimately find an indication in the treatment of cardio- and cerebrovascular injury within a few years should current evidence be confirmed, despite these conditions being at present defined as absolute contraindications to the KD. Up until then, an adequately experienced cardiologist/neurologist should take the lead deciding on a patient-to-patient basis. The application to fragile subjects such as the elderly, those with a history of mental disorder, eating behaviour or substance abuse must benefit from an appropriate support in the daily routine for the KD to be potentially considered as a feasible treatment for concomitant conditions. Finally, further, specifically targeted studies are needed to assess whether KD consumption may influence wound healing, infections resolution or chronic organ damage, to better understand if its use might not be contraindicated in these frail patients.

Upon critical revision of the current state of the art, it emerges that most studies are low quality, sample size often very small, and duration usually quite short, making no definitive conclusion possibly be drawn. However, it seems reasonable to say that many alerts are cautionary in the attempt of protecting fragile populations, rather than being based on actual evidence supporting the risk of inducing serious adverse events, or recent evidence has proven them questionable. Overall, as the KD is comparable in efficacy to pharmacological interventions, and is similarly not devoid of adverse events if not coupled with proper care, it deserves very careful management, and its prescription should therefore be in the hands of adequately skilled medical doctors, who, while keeping in mind current recommendations, possess the necessary knowledge to putting them into the context of the single individual being evaluated.

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CONFLICT OF INTEREST

The authors declare no competing interest.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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