Ketogenic Diet plus Resistance Training Applied to Physio-Pathological Conditions: A Brief Review

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Abstract: The ketogenic diet (KD) is a nutritional strategy characterized by a reduced intake of carbohydrates (between 30 and 45 g per day or ≈5% of one’s total calories from this macronutrient). The regimen induces physiological ketosis in which serum levels of ketone bodies increase from 0.5 to 3.0 mM, becoming an essential contributor to energy production. The popularity of using the KD to lose weight and its application in specific physio-pathological conditions, such as epilepsy, lipedema, and polycystic ovary syndrome, which is maintained over extended periods, gave us the impulse to write this brief review. In these types of physio-pathological conditions, subjects can achieve favorable training outcomes even if adhering to a KD. Therefore, performing resistance training under the KD to enhance muscle status and quality of life could be possible. It is important to note that, while some statements here suggest potential future directions, they are hypotheses that require experimental validation, even if they are supported by the independent benefits reported from the KD and resistance training and represent a promising area for future research.

Keywords: ketogenic diet; muscle hypertrophy; resistance training; creatine; ketone bodies

1. Introduction to Ketogenic Diet

The ketogenic diet (KD) is a nutritional regimen characterized by a reduced carbohydrate intake, typically less than 30–45 g per day or ≈5% of total calories. A small amount of carbohydrates is included in the diet because red blood cells, lacking mitochondria, rely exclusively on glucose as an energy source (which can also come from the glycerol of triglycerides or gluconeogenesis) [1,2]. The decreased carbohydrate intake induces a physiological ketogenesis, resulting in serum ketone bodies (β-hydroxybutyrate, acetoacetate, and acetone) ranging from 0.5 to 3.0 mM. These molecules are synthesized in the liver, but they serve as energy substrates in other cells, such as neurons in the central nervous system (CNS). Unlike fatty acids, which are not capable of crossing the blood–brain barrier (BBB), the ketone bodies, particularly β-hydroxybutyrate (BHB), can do so via monocarboxylate transporters [3]. Overall, this leads to a shift in the body’s energy substrate from glucose to ketone bodies (Figure 1), with this as the main
Before reaching ketosis, the KD triggers glycogenolysis, reducing liver and muscle glycogen concentrations within the initial 3–6 days [5]. This can result in body mass reductions of one to four kilograms, considering that glycogen is stored with three to five times its mass in water [6]. Throughout this dietary-induced ketogenesis, common side effects described as “keto flu” may arise, including headache, difficulty concentrating, and nausea. These symptoms typically subside once a stable ketonemia level (>0.4 mmol/L) is maintained, generally after 5–7 days [7].

Figure 1. Scheme of cell during ketogenic diet vs normal diet: (A) Increase in ketone body level as a result of fatty acid oxidation, thus enhancing level of acetyl-CoA in mitochondria to compensate for the ATP needed. (B) Glucose is fully oxidized through glycolysis followed by the mitochondrial Krebs cycle coupled to oxidative phosphorylation. Created with BioRender.

2. Ketogenic Diet Applied to Physio-Pathological Conditions Not Cancer Related

It is noteworthy to mention that older phenotypes might experience a slower glycogen depletion and ketogenesis rate [8], possibly due to an impairment of metabolic switching [9]. Even if using urine strips to assess ketosis is a common practice, practitioners and consumers should be cautious of potential false negatives [10]. For instance, BHB, one of the major ketoacids, does not react with nitroprusside in dipsticks. Hence, using self-blood monitoring for ketoacids is recommended. About one hundred years since its first application for the management of epilepsy [11], the KD has undergone numerous developments [12]. It is frequently employed as a non-pharmacological therapy in various physio-pathological conditions, such as, first of all, neurological disorders [13,14], polycystic ovary syndrome (PCOS) [15], obesity and lipedema [13,16,17], and, importantly, as a supportive measure for metabolic disorders [13,18]. It should be noted that the KD and other low-carbohydrate configurations are frequently used during a hypoenergetic diet to promote weight loss and improve body composition [19]. Several studies as part of the Curves Women’s Health & Fitness Initiative at the Exercise & Sport
Nutrition Laboratory (Texas A&M University) have demonstrated that a carbohydrate-restricted diet promoted more favorable changes in weight loss, fat loss, and markers of health in obese women who initiated a circuit-style resistance training program compared with a diet higher in carbohydrate [20–22]. In fact, it seems that greater improvements in body composition are achieved when carbohydrates are replaced in the diet with protein, in general [23]. Similarly, the KD involves a high fat intake, accounting for up to 80% of total calories. Importantly, the protein/fat ratio varies based on the intended goal; for example, a 4:1 ratio for fat/protein intake has been discussed for pediatric epilepsy [24], and our research group has applied the 2.5:1 ratio to manage lipedema [16]. Its clinical use as well as short- and long-term non-desired effects [16,25–43] are listed in Table 1.

<table>
<thead>
<tr>
<th>Disorder Type</th>
<th>Disease</th>
<th>Non-Desired Effects</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurological disease</td>
<td>Refractory epilepsy</td>
<td>Nausea and vomiting</td>
<td>[29]</td>
</tr>
<tr>
<td></td>
<td>Myoclonic-astatic epilepsy</td>
<td>Constipation</td>
<td>[30]</td>
</tr>
<tr>
<td></td>
<td>Parkinson’s disease</td>
<td>Dehydration</td>
<td>[31]</td>
</tr>
<tr>
<td></td>
<td>Alzheimer’s disease</td>
<td>Anorexia</td>
<td>[32]</td>
</tr>
<tr>
<td></td>
<td>Multiple sclerosis</td>
<td>Lethargy</td>
<td>[33]</td>
</tr>
<tr>
<td></td>
<td>Migraine</td>
<td>Hypoglycaemia</td>
<td>[34]</td>
</tr>
<tr>
<td></td>
<td>Depression</td>
<td></td>
<td>[35]</td>
</tr>
<tr>
<td></td>
<td>Autism</td>
<td></td>
<td>[36]</td>
</tr>
<tr>
<td>Endocrine disorders</td>
<td>Diabetes</td>
<td></td>
<td>[37]</td>
</tr>
<tr>
<td></td>
<td>Obesity and Lipedema</td>
<td></td>
<td>[16]</td>
</tr>
<tr>
<td></td>
<td>Metabolic syndrome</td>
<td></td>
<td>[38]</td>
</tr>
<tr>
<td></td>
<td>PCOS</td>
<td>Abnormalities of lipid</td>
<td>[39]</td>
</tr>
<tr>
<td></td>
<td>Non-alcoholic fatty liver disease</td>
<td>metabolism Hepatic</td>
<td>[40]</td>
</tr>
<tr>
<td>Metabolic disorders</td>
<td>Glucose transporter type 1 deficiency</td>
<td>Hypoproteinaemia Mineral deficiencies</td>
<td>[41]</td>
</tr>
<tr>
<td></td>
<td>Pyruvate dehydrogenase complex deficiency</td>
<td>Myocardiopathy</td>
<td>[42]</td>
</tr>
<tr>
<td></td>
<td>Phosphofructokinase deficiency</td>
<td>Nephrolithiasis</td>
<td></td>
</tr>
</tbody>
</table>

Hence, despite its popularity, the KD should not be selected only under hypoenergetic conditions and the isocaloric ketogenic diet (ICKD) might be preferable if the aim is to support seizures, immune function, PCOS, and muscle status [44]. Although there are still relatively few studies on this topic, it seems that the ICKD could serve as a viable alternative to traditional diets, particularly in pathological conditions. For instance, Kim et al. [45] demonstrated that just three days of the ICKD led to improvements in inflammation-related parameters, particularly in regulating the inflammasome. This is of particular importance, if we consider the anti-inflammatory action through the modulation of nuclear factor-κB (NFκB) and the nuclear factor erythroid 2-related factor 2 (NFE2L2, also known as Nrf2) [45]. Also, in a systematic review, Erickson et al. concluded that the ICKD could be beneficial in supporting the treatment of various types of tumors [46]. This is probably because cancer cells, known to use glucose preferentially as a substrate for growth, with a mechanism known as the Warburg effect, are delayed in their progression because of this metabolic alteration. In any case, here we want to discuss more regarding the KD applied to decreasing cancer levels.
Based on a meta-study which employed the meta-analysis model, it was found that the KD controls fasting blood glucose, and improves lipid metabolism in type 2 patients [47]. During the KD, the absence of glycemic and insulin fluctuations might have important biochemical implications, although energy balance remains the key factor for the KD in health promotion and disease therapeutics. For example, the very low-calorie KD (VLCKD), which provides a highly restricted caloric intake (less than 800 kcal per day), has been studied [48,49]. In subjects treated with the VLCKD, glycemic stability is guaranteed by hepatic neo-glucogenesis which induces the basal secretion of the insulin; this is also evident in obese sarcopenia patients [50]. Preserved insulin secretion prevents the onset of pathological ketoacidosis. Moreover, the level of insulin was maintained at about 7 to 9 mU/L [51]. Biochemical blood parameters under physiological ketosis are listed in Table 2.

### Table 2. The impact of physiological ketosis on metabolic profile.

<table>
<thead>
<tr>
<th>Markers</th>
<th>KD</th>
<th>ICKD</th>
<th>VLCKD</th>
<th>VLCKD + Exercise</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c</td>
<td>Decrease</td>
<td>NR</td>
<td>Decrease</td>
<td>NR</td>
</tr>
<tr>
<td>TG</td>
<td>Decrease</td>
<td>No changes</td>
<td>Decrease</td>
<td>Decrease</td>
</tr>
<tr>
<td>HDL</td>
<td>Increase</td>
<td>No changes</td>
<td>No changes</td>
<td>Increase</td>
</tr>
<tr>
<td>LDL</td>
<td>Decrease</td>
<td>Increase</td>
<td>No changes</td>
<td>Decrease</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>NR</td>
<td>Increase</td>
<td>NR</td>
<td>Decrease</td>
</tr>
<tr>
<td>Fasting glucose</td>
<td>Decrease</td>
<td>Decrease</td>
<td>Decrease</td>
<td>Decrease</td>
</tr>
<tr>
<td>Insulin</td>
<td>NR</td>
<td>Decrease</td>
<td>NR</td>
<td>Decrease</td>
</tr>
</tbody>
</table>

NR: Not Reported.

3. Insulin-Dependent and -Independent Responses to Resistance Training

The musculoskeletal system represents a unique structure in which bones, muscles, ligaments, soft tissues, and tendons are intricately interconnected [52] and coordinated by neuromuscular junctions [53]. As a type of strength training, resistance exercise is characterized by the physical effort exerted when skeletal muscles work against a given weight or external force. Numerous positive health and physical performance adaptations have been reported when the stressful stimulus of resistance exercise is administered with appropriate time intervals and optimal recovery time in different phenotypes [54–59]. This remarkable plasticity is responsible for adaptations in physiological and pathophysiological conditions [60–63]. This ability of muscles to adapt to external stimuli relies on different signaling pathways and secondary messengers, which are responsible for maintaining muscle status. The concept of muscle status is encouraged, given that it encompasses not only quantity (skeletal muscle mass) but also gives relevance to intramuscular structural features (muscle quality), endocrine activity (insulin), and movement functionality. In particular, the mechanistic Target of Rapamycin complex 1 (mTORC1) pathway [52], strongly activated by insulin, and the mitogen-activated protein kinase (MAPK) pathway [64] seem to play an essential role in resistance exercise-induced adaptations of musculoskeletal tissue.

Besides the insulin-mediated response, other biochemical signalers also contribute to muscular plasticity, including the mechano growth factor (MGF), testosterone, and the Protein Kinase B (PKB or AKT), which inhibits the Forkhead Box 1/3 FoxO1/3 pathway, providing an anticaatabolic stimulus [65]. Additionally, nitric oxide (NO) and amino acids, particularly glutamine and leucine, are involved in these processes. Although leucine directly activates mTORC1 [66,67], muscle protein synthesis strongly relies on essential amino acids, so focusing on the amino acid profile rather than leucine content alone would be a recommended approach [68]. Interestingly, a recent study in a murine model showed that (D)-3-hydroxybutyrate, the main component of ketone bodies, has positive effects on muscle atrophy and beneficial metabolic reprogramming effects in healthy muscle [69]. Other non-dependent insulin biochemical mechanisms contributing to exercise-induced
adaptations include the NFκB, which is downregulated by inflammation and reactive oxygen species (ROS), and the peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α), whose activation is particularly beneficial for mitochondrial health, but more responsive to endurance training [60] (Figure 2). These findings suggest that, even in the absence of continuous peaks of insulin stimulation, increased strength and/or hypertrophy can be achieved due to the intricate mechanisms and alternative pathways that characterize the human physiology’s flexibility.

Figure 2. Skeletal muscle signaling pathways activated after mechanical loading. (Source: the authors are using the software at BioRender.com accessed on 1 January 2024).

4. Allostatic Load in Resistance Training

Notably, when human physiology is subjected to intermittently repeated chronic stressors (such as resistance training, hypoenergetic conditions, and sleep deprivation), several biochemical regulators consistently operate outside their normal ranges, causing the entire biological system to suffer before adaptation. The adaptation can be achieved over time, and it is known as allostatic load [70]. In exercise sciences, this adaptation process is commonly elucidated by the principle of supercompensation, which suggests that following a stressor (such as resistance workload) there is a need for energy (nutrition) and time (rest) to compensate for the decline in performance and facilitate muscle recovery [71,72]. If the organism is placed under optimal conditions, it might result in functional overreaching, leading to positive adaptations (e.g., greater muscle strength or hypertrophy). However, if optimal conditions are not met, the body may experience non-functional over-reaching, resulting in a decline in performance that, if not properly managed, can progress to a pseudopathological state known as overtraining syndrome [73]. This syndrome serves as a prime example of allostatic overload in human physiology [74]. Considering the aforementioned remarks, it is worth noting that individualized and expert supervision, along with workload periodization, are crucial for a successful intervention [71,75]. This ensures that loads and workout intensity are properly adjusted. Generally, resistance exercise training, even with heavy loads, can be safely used in different pathological populations. For example, optimal interventions in postmenopausal women with
osteopenia and osteoporosis, as well as in individuals with knee osteoarthritis [76–78] or older adults [79,80], result in favorable outcomes for both the overall health and management of the underlying conditions.

5. Ketogenic Diet plus Resistance Training

It is well established that increasing dietary protein intake alongside an exercise intervention, especially resistance training, attenuates the body mass loss-induced reduction in muscle mass. Participants adhering to a KD consumed significantly higher amounts of dietary protein than those adhering to a non-KD. Nevertheless, the KD produces an unpleasant impact on muscle mass, which is lost in resistance-trained individuals, as is evidenced in a recent meta-analysis [81]. It also evidenced significant fluctuations of thyroid-stimulating hormone (TSH) reported during the VLCKD, as we demonstrated with our research group after only three days of it [82]. On the other hand, recently, Chiarello et al. (28) conducted a study on altitude performance, showing that despite the absence of carbohydrates, the ICKD led to an improvement in cardiorespiratory fitness (VO2max). Carbohydrate restriction leads to decreases in blood glucose, and it is possible that increased gluconeogenic activity could promote muscle mass loss to provide an amino acidic substrate to replenish the glucose and dietary protein intake’s small contribution to gluconeogenesis [83]. It is worth mentioning that a given resistance training workload (stimulus) requires special nutritional needs (e.g., energy, protein, creatine monohydrate) and recovery time (e.g., sleep quality, rest days, tapering). Following the 4Rs framework proposed by Bonilla et al., nutritional strategies to optimize post-exercise recovery encompass rehydration, refueling, repairing, and rest—pre-sleep nutrition [84]. If these are fulfilled by means of nutritional adherence and compliance, exercise-targeted adaptations might be achieved. Although it is suggested that the KD could lead to a more efficient utilization of energy substrates during exercise (enhancing oxidative metabolism), the impact of cardiac or muscle status for health and disease is not well understood [85]. Currently, the scientific community of exercise and sports agrees that carbohydrates (5–8 g/kg/day) are crucial for achieving improvements in muscle strength and hypertrophy [86]. Indeed, recent studies by several authors have demonstrated that the net effect of the KD on strength and/or hypertrophy is likely to be diminished in most cases [81,87–89]. For most individuals engaged in moderate-to-high volume resistance training, emphasizing moderate-to-high intensity exercise performance, or primarily aiming to increase lean mass, KDs may not be the most optimal choice [90]. A recent systematic review with a Bayesian meta-analysis by Koerich et al. concluded that while the KD can be a useful strategy for total and body fat losses, a small negative effect on fat-free mass has been observed among the analyzed clinical trials; thus, the KD might not be suitable for enhancing 1-RM strength or high-intensity cyclic performances in trained individuals [91]. This suggests that those persons looking to maximize resistance training adaptations should consider a more balanced or traditional macronutrient distribution that allows for adequate carbohydrate intake, especially if they are unfamiliar with, do not enjoy, or do not adhere to the KD. In this regard, our research group recently demonstrated that resistance-trained individuals following a KD may experience performance declines and higher perceived effort in the early weeks as they adapt to reduced carbohydrate consumption. However, the KD did not influence resistance exercise performance in terms of the volume load, number of repetitions, or velocity loss at the end of the intervention [92]. Similarly, LaFountain et al. (2019) reported improvements in body composition with no significant changes in strength performance after high adherence to the KD in US military personnel [93]. Some studies have also shown that the KD might not impair body composition or performance in CrossTrainers who meet the energy requirements, protein intake, and adhere to the KD [94,95]. Based on the available evidence, we encourage the recommendations of conventional macronutrient distribution when performing a strength-based exercise program; however, if the individual, fitness enthusiast, or patient prefers and adheres to a KD regimen, current findings do not imply that progress is unattainable while following this diet, or that results
are significantly different when compared to conventional high-carbohydrate diets once ketosis is reached and maintained over time.

6. Practical Recommendations to Combine Ketogenic Diet and Resistance Training

In 2020, the “keto diet” ranked as the most searched diet on Google in the United States of America [96]. Recent data further confirm the popularity of the KD, high-fat, and low-carbohydrate diets in the United States, as reported by the International Food Information Council (2023) [97]. Aware that ketone bodies constitute a double-edged sword for mammalian life spans [98], we also recognize that one nutritional intervention, such as a carbohydrate-rich diet, is not the sole option and it should be adjusted on an individual basis. In any case, it should be understood that any intervention cannot overlook the improvement in muscle status, and clinical evidence shows that individuals who adhere to a KD might achieve similar results compared to other conventional macronutrient distributions (see above). Additionally, it is well known that physical exercise, especially resistance training, should be incorporated into daily activities to enhance well-being, quality of life, and cardiometabolic health in patients with chronic diseases. Likewise, individuals who benefit from following a KD regimen, such as those with epilepsy [24,99], lipedema [16,84,85], GLUT1 deficiency [100–102], and PCOS [15,103], may also experience an improved quality of life by combining the nutritional strategy with a resistance exercise program. It is possible that the combination of a KD and resistance training results in fewer pathological symptoms, lower drug concentrations, and, consequently, fewer side effects, but further research is needed to consolidate clinical applications. It is relevant to consider the following points:

- Ensure the energy balance or caloric surplus (if needed) to properly manage the pathological condition. In this sense, practitioners should pay attention to higher satiety due to high fat and protein intake.
- Ensure an adequate daily protein intake of at least 1.5–1.6 g per kg of body mass. Physicians should consider the restrictions in protein intake for certain pathologies (e.g., kidney diseases). Protein of high biological value is recommended, including a combination of plant-based proteins, in order to ensure 8–10 g of essential amino acids and 2–3 g of leucine [68] are consumed.
- Administer creatine monohydrate as a safe, effective, and conditionally essential nutrient (with vast evidence) to improve muscle strength and hypertrophy, as well as quality of life, cognitive function, and metabolic health when combined with resistance training. A daily dosage of 0.1 g per kilogram of body mass is recommended [104,105].
- Consider vitamin C, N-acetylcysteine, and/or polyphenol supplementation. The KD program is limited to fruit and some vegetables; therefore, optimizing the antioxidant status could contribute to post-training recovery and overall health [106,107].
- Nutritionists and dietitians should develop intervention strategies to improve adherence to the KD, since this is a key factor to have successful results [108].
- Establish a low-load power-based training program based on objectives, population, and following non-linear (undulating) periodization focused on multi-joint exercises [71]. It should be noted that high-speed resistance training using a cluster set configuration might be suitable to avoid high fatigue levels, even in frail populations [80].
- Prescribe and adjust resistance training workload (2–3 days/week) using the OMNI-RES perception scale, repetitions in reserve, and movement velocity (actual or perceived) [92].
- Monitor the stress-response process and overall adaptation process using the allostatic load index as a composite of ten well-established biomarkers that correspond to four primary domains: the cardiovascular, endocrine, inflammatory, and metabolic systems. Readers are encouraged to refer to Beese et al. (2022) for recommendations to measure allostatic load [109].
Researchers studying these interventions are encouraged to follow the Preferred Reporting Items for Resistance Exercise Studies (PRIRES) to increase transparency, quality, and reproducibility [110].

7. Concluding Remarks

The KD plus resistance training combination is an underexplored area of research; it could be essential to understand the combination’s effects. The current evidence suggests that a KD regimen might have similar results compared to carbohydrate diets; that is, once ketosis is achieved and maintained over time for physio-pathological conditions in which a KD is a non-pharmacological therapy to be maintained for a long period of time. Developing protocols that incorporate the training outcomes of resistance workload with its management, including unconventional biomarkers like the allostatic load index or microRNAs, holds potential for advancing the understanding and application of KDs in resistance training. Given the popularity of the KD and its current application in specific physio-pathological conditions, integrating it with resistance training could improve muscle status and quality of life.

Author Contributions: Conceptualization, R.C., E.C. and D.A.B.; Writing—original draft preparation, R.C., E.C. and D.A.B.; Writing—review and editing, J.L.P., D.M.A.-G., M.C.C. and R.B.K. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Conflicts of Interest: R.C. receives honoraria for personalized nutrition services including the application of the ketogenic diet. R.B.K. has conducted industry-sponsored research, received financial support for presenting about dietary supplements at industry-sponsored scientific conferences, and has served as an expert witness on cases related to exercise physiology and nutrition. Additionally, R.B.K. serves as the chair of the “Creatine for Health” scientific advisory board sponsored by Creapure® & Creavitalis®—Alzchem Group AG (Germany), while D.A.B. serves as a scientific affiliate of this board. D.A.B. has also acted as a scientific consultant for MTX Corporation®, MET-Rx® and Healthy Sports, and has received honoraria for speaking about nutrient supplements at private courses. The other authors declare no conflicts of interest. All authors are responsible for the content of the article.

References


